Treatment of Inflammatory Bowel Disease with Biologics

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Preface

In the last number of years, the treatments for inflammatory bowel disease have been rapidly evolving. With the emergence of biologic therapies as the more effective medications for the treatment of moderate to severe ulcerative colitis and Crohn's disease, understanding the best methods to effectively utilize them to induce and maintain remission is critical for the practicing gastroenterologist. In addition to antitumor necrosis (anti-TNF) agents (infliximab, adalimumab, golimumab, certolizumab) and anti-integrins (vedolizumab and natalizumab), the FDA has recently approved biosimilar anti-TNF agents and ustekinumab, an anti-IL12/IL23 inhibitor.

We are excited that this book, *Treatment of Inflammatory Bowel Disease with Biologics*, provides the reader with expert reviews on important topics pertaining to the use of biologics in inflammatory bowel disease as well their potential complications. The authors were carefully chosen for their expertise in the management of inflammatory bowel disease and their ability to summarize the important concepts.

Drs Alan Moss, Scott Lee, and Byron Vaughn provide expert summaries on the mechanisms of action of the various biologics and the use of anti-TNF therapy in ulcerative colitis and Crohn's disease. Drs Sarah Flier, Miguel Regueiro, Sunandra Kane, and Bret Lashner review the use anti-TNF in special circumstances when managing IBD: extraintestinal manifestations, postoperative Crohn's disease, pregnancy and lactation, and the perioperative setting.

Drs Corey Siegel, Mark Osterman, and Cynthia Seow examine the critical topics on the role of combination therapy, therapeutic drug monitoring, and the possible discontinuation of biologics. Complications of biologic therapy are expertly summarized by Drs Joshua Korzenik, Millie Long, and Raymond Cross.

Newer agents, including biosimilars, anti-integrins, and novel therapies, are reviewed by Drs Asher Kornbluth, Francis Farraye, and Fernando Velayos. Finally, Drs Gil Melmed and Jennifer Strople evaluate the quality of care and safety of biologic therapy and use of biologics in pediatrics.

We believe that this book will provide the reader with a thorough review of biologic therapies in inflammatory bowel disease and inform the reader on how to optimize patient care on these medications.

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Chapter 1
Mechanism of Action and Pharmacokinetics of Biologics

Alan C. Moss

Introduction

The pathological features of inflammatory bowel diseases (IBD) are characterized by an infiltration of the lamina propria with lymphocytes, macrophages, and neutrophils [1]. The cytokines released by these cells trigger a process of local cell death and matrix damage, leading to the endoscopic appearance of ulcers, friability, and exudates. The biologic agents approved, or in development, for IBD target specific steps in this process. These mechanisms of action not only resolve local inflammation but also account for some of the adverse events associated with the use of biologics. In this chapter we will review the pharmacodynamics (physiological effects of drugs and their mechanisms of their actions) and the pharmacokinetics (the fate of a drug within the body) of currently approved biologics. Since the anti-TNFs were been the only biologic class for 15 years, most of the independent laboratory data has tested these agents, whereas published data on vedolizumab and ustekinumab is more limited.

Anti-TNFs

Role of Tumor Necrosis Factor (TNF) in IBD

Tumor necrosis factor (TNF) is an important mediator of inflammation in human diseases. It is initially a transmembrane protein (mTNF) expressed by activated

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T lymphocytes, monocytes/macrophages, and natural killer (NK) cells but also non-immune cells such as endothelial cells and fibroblasts [2]. In patients with IBD, an increase in TNF-positive cells has been noted throughout the intestinal mucosa, and high levels of TNF can be found in patients' feces [3]. In the ileum of patients with active Crohn's disease, Paneth cells strongly express TNF, unlike Paneth cells in normal tissue [4]. TNF on the surface of cells can be cleaved by a metalloprotease to release soluble TNF (sTNF) into the circulation. Both forms of TNF exhibit their destructive effects in the intestinal tract in IBD by their ability to induce cell death (apoptosis) and cell activation (release of cytokines, chemokines, arachidonic acid, and leukotrienes) via the TNF receptors (TNFR1 and 2). Epithelial cells bear the brunt of this process, resulting in the characteristic mucosal ulceration, erythema, and exudates noted in IBD. Complementary to its pro-inflammatory effects, TNF is also directly cytotoxic to virus-infected cells, making it a potent antiviral molecule [5]. It is also highly effective in activating cells in response to bacterial infection, particularly B-cells and macrophages. Thus, the inhibition of TNF can be a double-edged sword, leading to the efficacy of anti-TNFs in IBD and their adverse effects.

Pharmacodynamics of Anti-TNFs

The anti-TNF antibodies currently FDA approved for IBD are infliximab (Remicade, Inflectra), adalimumab (Humira, Amjevita), certolizumab (Cimzia), and golimumab (Simponi). Laboratory studies over the last 20 years have provided evidence that the mechanism of action of these drugs in IBD is multifaceted and goes beyond simple "mopping up" of TNF in circulation (Table 1.1). Based on preclinical data, all these agents bind to soluble and membrane TNF with high affinity and specificity, thus preventing TNF from binding to TNF receptors (TNFRs) on surrounding cells. This mechanism of action is shared by all anti-TNFs but to a variable extent; certolizumab pegol binds to TNF with a higher affinity than adalimumab and infliximab, whereas etanercept has more potency in neutralizing soluble TNF-mediated signaling than infliximab, adalimumab, and certolizumab [6]. Preliminary data with biosimilar infliximab (CT-P13) and adalimumab (ABP501) also report comparable

Table 1.1 Comparative effects of anti-TNFs on molecular processes

	Infliximab	Adalimumab	Certolizumab	Golimumab	CT-P13	ABP501
sTNF binding	Y	Y	Y	Y	Y	Y
mTNF binding	Y	Y	Y	Y	Y	Y
mTNF reverse signaling	Y	Y	?	Y	Y	?
Inhibits cytokine production	Y	Y	Y	?	Y	Y
Fc-mediated ADCC/CDC	Y	Y	N	Y	Y	Y

TNF binding to their reference products [7]. Regardless of the extent of TNF binding, this step prevents TNF from binding to TNFRs, thus limiting the downstream expression of cytokines, including IL-6, IL-8, IL-1, and COX2, triggered by TNFRs [8]. Although there are clear differences in the relative binding of anti-TNFs to TNF in vitro, this has not translated to equivalent differences in clinical efficacy in vivo; etanercept failed to meet its primary end point in clinical trials in Crohn's disease, despite a higher binding affinity to soluble TNF [9, 10].

The net consequences of binding of anti-TNF antibodies to mTNF and sTNF are to limit their ongoing effects on immune responses on patients. Treatment with infliximab, for example, leads to a decrease in neutrophil growth factors (GM-CSF), lamina propria polymorphonuclear cells, and the pro-inflammatory cytokines IL-1 beta, IFN-γ, IL-13, IL-17A, IL-6, and MMP9 [11]. Anti-TNF treatment also alters the balance of pro- to anti-inflammatory cell phenotypes of the immune system. Infliximab has been shown to restore functional deficits in regulatory T-cells (Tregs), reflected in an increased expression of FoxP3 and in an increase in the suppressive activity of CD4+/CD25+ T-cells [12, 13]. Beyond T-cells, a range of beneficial effects have been reported in epithelial cells, regulator macrophages, and myofibroblasts in response to anti-TNF exposure [11].

When anti-TNF antibodies bind to membrane TNF (mTNF), they can also trigger "reverse signaling" via mTNF, which shuts down intracellular signaling pathways and induces apoptosis [14, 15]. Both infliximab and adalimumab induce apoptosis in peripheral blood cells, but etanercept and certolizumab do not [16]. Interestingly, infliximab and adalimumab have also been shown to induce cell cycle arrest, as a separate mechanism for suppression of immune cells [17]. The induction of apoptosis of T lymphocytes and $CD14^{+}$ macrophages in patients with IBD occurs via TNFR2 [18]. A related potential mechanism of action is the induction of antibody-dependent cell-mediated cytotoxicity (ADCC) by anti-TNFs that can engage with IgG Fc receptors (FcR). Lysis of mTNF-expressing cells and PBMCs could be induced by infliximab and adalimumab more potently than etanercept, whereas certolizumab pegol did not show any effect (it lacks the Fc domain) [6]. Complement-dependent cytotoxicity (CDC) of cell lines in vitro is a third mechanism though which anti-TNFs could disrupt pro-inflammatory cell populations in vivo [19]. It is unclear at this time if this pathway is relevant in their mechanism of action in patients with IBD [9]. Both currently approved biosimilars show similar ability to induce both ADCC and CDC in cell lines assays [7].

Despite these well-documented alterations in cytokines, cell survival, and phenotypes in response to anti-TNF treatment, their association with the typical measures of clinical response in patients has been lacking. This reflects the gaps between the artificial scenario of cell lines and transfected cells in vitro, the complex cellular matrix of the lamina propria in patients, and the disconnect between symptoms and objective indices of mucosal inflammation. Associations between baseline biomarkers and subsequent clinical outcomes of anti-TNF therapy have yet to be validated in prospective cohorts [20]. One promising approach requires quantification of mucosal mTNF-positive cells using a confocal laser endomicroscope but reported a 70% differential in clinical response rates based on baseline mTNF levels [18].

Pharmacokinetics of Anti-TNFs

Pharmacokinetics (pK) describes the effects of the body's physiological processes on an administered drug. For monoclonal antibodies (IgGs), adequate concentrations of the drug need to be achieved in the circulation for it to obtain its intended effects on circulating and intestinal mucosal cells. Individuals' differences in bioavailability and pK have been associated in IBD with lack of clinical response and mucosal healing. Intravenous administration of anti-TNFs, such as infliximab, allows for administration of large volumes, rapid central distribution, and low variability in bioavailability; peak serum concentrations are attained almost immediately post-infusion [21]. In contrast, subcutaneous anti-TNFs can only be given in low-volume doses and are taken up by lymphatic drainage and paracellular movement, leading to slower absorption into the vascular compartment. For adalimumab, peak serum concentrations are reached approximately 5 days after a single 40 mg dose, with average bioavailability around 65% [21]. Once in the circulation, extravasation of anti-TNFs occurs primarily via receptor-mediated endocytosis into vascular endothelial cells. The volume of distribution of anti-TNFs is ~0.1 L/kg, suggesting these drugs are mainly distributed within the extracellular fluid [22]. Preliminary data with biosimilar infliximab (CT-P13) and adalimumab (ABP501) also report comparable pK profiles to their reference products in rheumatological diseases [7].

Elimination of monoclonal antibodies occurs mostly via proteolytic catabolism by phagocytic cells of the reticuloendothelial system [23]. The reported serum half-life of infliximab ranges from 7 to 12 days in patients with Crohn's disease, in both those in remission and those with active disease [24, 25]. There is also the phenomenon of the "antigen sink" whereby internalization of anti-TNFs by their binding to mTNF can lead to their clearance from the extracellular space. This may explain the variability in clearance associated with inflammatory burden in patients with ulcerative colitis [26]. Balancing this process is the recycling of intact monoclonal antibodies back into the circulation, leading to the long serum half-life of IgGs (~23 days) and the slow systemic clearance of about 11–15 mL/h [25]. This system is disrupted by the presence of anti-drug antibodies (ADAs); ADAs congregate anti-TNFs into multimeric antibody complexes that are retained and degraded, but not recycled, by reticuloendothelial cells [27]. As an example of the impact of these ADAs on clearance, the clearance of infliximab increases threefold in patients with ADAs as compared with patients without ADAs [28]. The development of ADAs in patients with IBD is influenced by many factors, including genotype, trough drug levels, and concomitant medications [29]. Finally, fecal loss of anti-TNFs has been described as a particular problem to patients with active IBD. In patients with severe IBD, infliximab was noted in a greater proportion of patients failing therapy, compared to those with a clinical response [30]. It is unclear whether the drug leakage caused the loss of response or whether ongoing mucosal inflammation led to drug leakage.

Much study has been undertaken in recent years on the association between pK and clinical response to anti-TNFs and will be covered in detail in another chapter

of this book. For many drugs, response is dependent on drug concentrations or drug exposure (the AUC), and therefore drug concentration-guided individualized therapy can be important [24]. For infliximab, for example, a meta-analysis concluded that patients who achieved an infliximab level >2 μg/mL were more three times more likely to be in clinical remission or achieve endoscopic remission than patients with levels <2 μg/mL [31]. This concentration-effect relationship has also been described for adalimumab, certolizumab, and golimumab [21].

Anti-integrins

Two anti-integrins are currently FDA approved for use in IBD: natalizumab and vedolizumab. Natalizumab is a humanized monoclonal antibody against the cell adhesion molecule α4-integrin. Although approved to treat Crohn's disease, its association with progressive multifocal leukoencephalopathy (PML) has limited its use in IBD, particularly since the approval of vedolizumab. Vedolizumab is a humanized monoclonal antibody which acts against α4β7 integrin heterodimer and blocks the interaction of α4β7 integrin with MAdCAM-1. Other anti-integrins remain in clinical development, such as etrolizumab and the anti-MAdCAM antibody PF-00547659. Since vedolizumab is the only currently approved and widely used anti-integrin, this section will primarily discuss this agent.

Pharmacodynamics of Vedolizumab

Infiltration of the intestinal lamina propria by T lymphocytes is an established component of the pathogenic process in IBD, through molecular mechanisms unique to the intestinal tract [32]. Adhesion and signaling molecules on the surface of T lymphocytes (selectins, integrins, chemokine receptors) interact with ligands on the endothelium to instigate the migration process [33]. T lymphocytes utilize the α4β7 integrin to bind to mucosal addressin cell adhesion molecule 1 (MAdCAM-1) on endothelial cells [34]. Vedolizumab binds to the α4β7 integrin on peripheral blood lymphocytes and inhibits adhesion of the lymphocyte to MAdCAM-1. In addition to circulating mononuclear cells, vedolizumab also binds to mononuclear cells in the lymphoid tissues, intestinal tract, and bladder [35]. The highest level of binding by vedolizumab was observed on the α4β7+ population of memory CD45RO+ CD4+ T lymphocytes but also to B lymphocytes, naive CD8 T lymphocytes, Th17 cells, natural killer cells, and basophils. After administration of vedolizumab, almost 100% of MAdCAM-1-Fc receptors are saturated immediately, and this effect wears off around 20 weeks after the last dose [36, 37]. These data suggest potent inhibition of trafficking of a number of pro-inflammatory immune cells to the intestinal tract after vedolizumab is administered.

In addition to its effects on effector (pro-inflammatory) T-cells (Teff), β7 integrin is a component of migration of regulatory T-cells. Mice lacking β7 integrin exhibit depleted colonic regulatory T (Treg) cells and excessive macrophage infiltration in the colon, thereby exacerbating DSS-induced colitis [38]. Additionally, in patients with UC, Treg homing to the gut was suppressed significantly by vedolizumab, and this led to a decrease in the ratio between Teff and Treg cells in the peripheral circulation [39]. It is unclear whether this has implications for the protective role of Tregs and CD4+ cells in immune surveillance. Clinical trial data reported a greater risk of serious infections in patients treated with vedolizumab (6% vs. 3%), and a recent case series reported a significantly higher rate of surgical site infections with vedolizumab than in patients receiving anti-TNF agents [40, 41]. Further analysis of tissue T-cells will be required to determine the mucosal impact of limiting T-cell migration.

Pharmacokinetics of Vedolizumab

Like the anti-TNFs, vedolizumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody, and therefore it shares many pK properties with them. In patients with UC, serum concentrations increased linearly with increasing doses of vedolizumab and declined linearly after the last dose [36]. A population pharmacokinetic analysis that included data from phase II studies suggested that disease type (UC or CD) had no impact on the pharmacokinetics of vedolizumab [37]. Linear clearance was 0.15 L/day for patients with UC and CD, and the terminal elimination half-life (t1/2) was 26 days. Extreme low albumin concentrations (<3.2 g/dL) and extreme high weight values (>120 kg) were both associated with higher drug clearance of vedolizumab in these studies. In contrast, fecal calprotectin, CDAI score, disease activity scores, age, prior anti-TNF exposure, ADA status, and concomitant therapy use had no clinically relevant effects on vedolizumab clearance [37]. In this pK model, patients with an endoscopic subscore of 3 after induction therapy had on average 25% higher clearance than patients with an endoscopic subscore of 0, highlighting the importance of the "tissue sink" noted with anti-TNFs. Eleven (28%) vedolizumab-treated participants were persistently positive for ADAs, and clearance of vedolizumab was 12% greater than in participants in the same dose group who were not persistently ADA positive [42]. Surprisingly, α4β7 receptor saturation was maintained at vedolizumab concentrations considered subtherapeutic (1 μg/mL), raising the question of whether receptor saturation alone is sufficient for clinical efficacy (vedolizumab concentrations above 15 μg/mL) [37].

Anti-IL-12/23

The cytokines IL-12 and IL-23 are secreted heterodimeric cytokines, which both contain a p40 protein subunit. IL-12 is primarily produced by phagocytic and dendritic cells in response to microbial stimulation and drives cell-mediated immunity

by inducing lymphokine-activated killer cells and activation of natural killer (NK) cells and T lymphocytes, particularly Th1 populations [43]. IL-23 drives a population of T-cells (Th17) that produce IL-17, IL-6, and TNF [44]. In IBD, genome-wide association studies revealed that variants of the gene encoding the IL-23 receptor, and the p40 chain, conferred genetic risk for developing IBD. IL-17 mRNA expression is increased in the colon of patients with active UC and CD, correlating with the density of CD4+ T-cells [45]. IL-17 production by isolated lamina propria CD4+ T-cells from patients with UC is significantly increased by IL-23 [46]. IL-17 appears to play a role in IBD pathogenesis, as it can stimulate innate immune cells and epithelial cells to produce IL-1, IL-6, and IL-8, which induce increased neutrophil recruitment and other pro-inflammatory signals [47]. However, it should be noted that there is also evidence that IL-17 plays a role in mucosal homeostasis, with protective effects on the intestinal epithelium, and generation of antimicrobial peptides [13].

Pharmacodynamics of Ustekinumab

Ustekinumab is a human IgG1 monoclonal antibody developed to bind to IL-12 and later discovered to bind specifically to the p40 protein subunit of this cytokine [48]. After ustekinumab was developed, it was subsequently established that the cytokine IL-23 contains a p40 subunit, to which ustekinumab also binds. This dual specificity was unique in approved biologics but provides challenges by engaging an unintended pathway (IL-17). Ustekinumab binding to the p40 subunits of these cytokines prevents IL-12 and IL-23 from binding to the IL-12Rβ1 receptor and IL-23 (IL-12Rβ1/23R) receptor complexes on the surface of NK and T-cells [49]. It can only bind to free cytokines, not receptor-bound complexes, and is thus unlikely to mediate Fc effector functions, such as ADCC or CDC (see anti-TNFs). Binding to ustekinumab neutralizes IL-12/23-mediated responses, including production of IFNγ, IL-17A, IL-17F, and IL-22. It is important to note that while ustekinumab will effectively neutralize IL-12- and IL-23-mediated functional responses, it will not affect immune responses stimulated through other cytokines or cellular activities, e.g., Th2 cytokines.

Pharmacokinetics of Ustekinumab

Ustekinumab was FDA approved in two formulations for Crohn's disease: as an IV infusion for the loading dose and as a fixed-dose subcutaneous injection for maintenance therapy. The pharmacokinetic (PK) behavior of ustekinumab is typical of other IgG-based therapeutic monoclonal antibodies, such as anti-TNFs. It demonstrates linear pharmacokinetics following either single-dose intravenous (IV) administration (0.09–4.5 mg/kg) or subcutaneous (SC) administration (0.27–2.7 mg/kg) in patients with psoriasis [50]. Given its absolute bioavailability of

approximately 57%, the volume of distribution of ustekinumab is approximately 8.9 L, consistent with confinement to the circulatory system with limited extravascular tissue distribution. The median half-life (t1/2) of ustekinumab was estimated to be 22, supporting the infrequent dosing of every 8 weeks in patients with IBD [50]. Clearance in patients was increased modestly in patients with higher body weight, and those with diabetes, but no effect was seen from concomitant immunosuppresants in these studies. Exposure-efficacy modeling identified a trend of lower exposure to ustekinumab in partial responders and nonresponders compared with responders with psoriasis [51]. In the UNITI studies in Crohn's disease, median serum levels of ustekinumab were associated with clinical remission. The incidence of anti-drug antibodies at week 44 was low (2%) in these trials [52].

Conclusions

The data reviewed in this chapter provide an overview of the mechanisms of action, and pharmacokinetics, of currently approved biologics used to treat IBD. It should be apparent that many of the unintended immunological consequences of these antibodies have both contributed to their efficacy and their risks. An appreciation of the role of exposure-efficacy dynamics has led to a "late" adoption of therapeutic drug monitoring and individualized doses and schedules beyond the labeled ones. It is likely that novel biologics will benefit from these discoveries in both their clinical development and practical use in the clinic.

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Chapter 2
Antitumor Necrosis Factor Agents in Ulcerative Colitis

Kindra Clark-Snustad, Ives Hot, and Scott Lee

Introduction

Ulcerative colitis (UC) is an autoimmune inflammatory bowel disease (IBD) that results in ulceration of the colonic mucosa, resulting in symptoms that classically include abdominal pain, diarrhea, and hematochezia. UC has a relapsing, remitting natural history, and active UC increases the risk of stricture formation, dysplasia, colorectal cancer, and a poor quality of life when disease is not adequately controlled. While the majority of UC patients are managed with medical therapies, 20–30% of UC patients undergo colectomy for medically refractory disease [1, 2]. Treatment paradigms for UC are based on disease severity and the extent of disease involvement. Biologic therapies, including those that antagonize tumor necrosis factor alpha (anti-TNFα), are indicated to treat moderately to severely active UC. These therapies are frequently prescribed in combination with other medications with the goal of steroid-free clinical and endoscopic remission. Anti-TNFα therapies currently approved for the treatment of UC include infliximab (Remicade®), adalimumab (Humira®), and golimumab (Simponi®). Biosimilars are now available and FDA approved, and biologics with an alternative mechanism of action are available; however neither of these will be discussed in this chapter.

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Currently, biologic therapies including anti-TNFα agents, utilized with or without concomitant immunomodulators, are considered the most effective medical therapies for moderately to severely active UC. Clinical trials support the efficacy of anti-TNFα therapies, suggesting that approximately two thirds of patients achieve clinical response after treatment with the first anti-TNFα medication, one third attain clinical remission, and one third are refractory or intolerant to the medication [3]. Anti-TNFα therapies are generally well tolerated, but potential adverse effects include injection site and infusion reactions, infection, autoimmunity, neutropenia, cutaneous reactions, malignancy, and worsening of existing demyelinating disease or heart failure. This chapter will review the use of anti-TNFα therapies in UC including the indication, goals of therapy, and the safety and efficacy for individual agents. Also discussed will be the treatment of older adults, general monitoring for safety and efficacy, factors that influence choice of anti-TNFα agent, information regarding switching agents, and important topics for patient education.

Indication for Use of TNFα Therapy in Ulcerative Colitis

Approach to therapy in UC is based on the endoscopic extent and clinical severity of disease presentation. Endoscopic extent can include disease limited to the rectum (ulcerative proctitis), involvement of the entire colon (pan-colitis), or any extent between. Severity can be categorized as mild, moderate, severe, or fulminant and guides therapeutic intervention [4]. Anti-TNFα agents are reserved for those patients refractory to first-line therapies (discussed in another chapter) or who are systemically ill. Patients with mildly to moderately active extensive colitis who are steroid refractory and steroid dependent and/or those who have failed adequate mesalamine or thiopurine therapy are candidates for anti-TNFα therapy. If patients respond to the anti-TNFα induction regimen, then maintenance therapy with that agent is indicated to maintain remission. Anti-TNFα therapies are contraindicated for patients with active infection, untreated latent tuberculosis, moderate-to-severe congestive heart failure, demyelinating disorders, or malignancies.

Goals of TNFα Therapy

Goals of UC therapy include (1) inducing and maintaining steroid-free remission, (2) preventing disease-related complications, and (3) improving quality of life and minimizing adverse events [5]. However, goals in the treatment of UC have evolved

in recent years. While resolution of patient symptoms was historically utilized as a primary goal of therapy, recent studies suggest that achieving endoscopic or mucosal improvement is associated with higher rates of sustained clinical remission, corticosteroid-free clinical remission, decreased hospitalization, and improved quality of life [6–9]. A systematic review and meta-analysis suggests that mucosal healing is associated with higher rates of clinical remission, colectomy avoidance, sustained mucosal healing, and likely corticosteroid-free clinical remission [10]. While mucosal healing is considered an important goal of therapy for UC, the definition of this outcome is not standardized.

Anti-TNFα Agents

Introduction

TNFα, a key pro-inflammatory cytokine in the pathogenesis of Crohn's disease, is also found in increased concentrations in the blood, colonic tissue, and stool of patients with UC [11–13]. The mechanism of action for anti-TNFα agents is to bind free and membrane-bound TNFα, which prevents TNFα from binding to its receptor sites and neutralizes its biological activity. Three anti-TNFα agents to date have been studied for the induction and maintenance of clinical remission in UC (Tables 2.1 and 2.2). One of these agents, infliximab, is administered intravenously (IV), while adalimumab and golimumab are administered as subcutaneous (SC) injections. There are currently no head-to-head studies comparing the safety and efficacy of these agents; however, placebo-controlled trials have evaluated each therapy individually.

Infliximab

Induction and Maintenance Clinical Trials

Infliximab is an IV-administered, chimeric monoclonal antibody against TNFα for the treatment of UC, as well as rheumatoid arthritis, ankylosing spondylitis, plaque psoriasis, psoriatic arthritis, and Crohn's disease [14]. In the UC population, the Active Ulcerative Colitis Trials 1 and 2 (ACT 1 and ACT 2) found patients with moderately to severely active UC who received infliximab were more likely to have a clinical response than those receiving placebo. Each study was a double-blind, placebo-controlled trial evaluating infliximab at a dose of 5–10 mg/kg of body

Table 2.1 Summary of efficacy for induction and maintenance clinical trials of anti-TNFα medications in UC

Anti-TNFα medication	Authors, date	Study summary	Study population, sample size	Dosing information	Clinical response	Clinical remission and mucosal improvement
Infliximab	Rutgeerts et al. [15]	Induction (ACT 1)	364 TNF-naïve patients with moderate-to-severe active UC	Placebo or infliximab 5 mg/kg or 10 mg/kg IV at weeks 0, 2, and 6 and then every 8 weeks through week 46	Clinical response at week 8 occurred in 69% of patients on 5 mg/kg, 61% of patients on 10 mg/kg, and 37% of patients on placebo ($P < 0.001$ for both comparisons with placebo)	Clinical remission at week 8 occurred in 38.8% of patients on 5 mg/kg, 32% of patients on 10 mg/kg, and 14.9% of patients on placebo ($P < 0.001$, $P = 0.002$, respectively)
						Mucosal improvement at weeks 8, 30, and 54 occurred in significantly more patients in the infliximab groups than in the placebo groups ($P < 0.001$ for all comparisons)
		Induction (ACT 2)	364 TNF-naïve patients with moderate-to-severe active UC	Placebo or infliximab 5 mg/kg or 10 mg/kg IV at weeks 0, 2, and 6 and then every 8 weeks through week 22	Clinical response at week 8 occurred in 64% of patients on 5 mg/kg, 69% of patients on 10 mg/kg, and 29% of patients on placebo ($P < 0.001$ for both comparisons with placebo)	Clinical remission at week 8 occurred in 33.9% of patients on 5 mg/kg, 27.5% of 10 mg/kg, and 5.7% of patients on placebo ($P < 0.001$ for both comparisons to placebo)
						Mucosal improvement at weeks 8 and 30 occurred in significantly more patients in the infliximab groups than in the placebo groups ($P \leq 0.009$ for all comparisons)

Adalimumab	Reinisch et al. [18]	Induction (ULTRA-1)	576 patients with moderate-to-severe UC despite corticosteroids or immunosuppressants	Randomized 1:1:1 to 160 mg at week 0, 80 mg at week 2, 40 mg at weeks 4 and 6 (ADA160/80), 80 mg at week 0, 40 mg at weeks 2, 4, and 6 (ADA80/40), or placebo	Clinical response at week 8 achieved in 54.6% of the ADA160/80 group, 51.5% of the ADA80/40 group, and 44.6% of the placebo group	Clinical remission at week 8 achieved in 18.5% of patients in the ADA160/80 group ($P = 0.031$), 10.0% in the ADA80/40 group ($P = 0.833$), and 9.2% in the placebo group
			Study protocol amended and led to two analyses (ITT-A3, $N = 390$ and ITT-E, $N = 576$)[a]			Mucosal improvement occurred in 46.9% of the ADA160/80 group, 37.7% of the ADA80/40 group, and 41.5% of the placebo group
	Sandborn et al. [19]	Maintenance (ULTRA-2)	494 patients with moderate-to-severe UC who received concurrent treatment with oral corticosteroids or immunosuppressants, 40% of study population had prior TNF exposure	Adalimumab 160 mg at week 0, 80 mg at week 2, and then 40 mg every other week or placebo	Clinical response at week 8 occurred in 50.4% of adalimumab-treated patients and 34.6% of placebo-treated patients ($P < 0.001$)	Overall clinical remission at week 8 achieved in 16.5% of adalimumab-treated patients and 9.3% of placebo-treated patients ($P = 0.19$)
						Overall clinical remission at week 52 achieved in 17.3% of adalimumab-treated patients and 8.5% of placebo patients ($P = 0.004$)
					Clinical response at week 52 occurred in 30.2% of adalimumab-treated patients and 18.3% of placebo-treated patients ($P < 0.002$)	Mucosal improvement at week 8 achieved in 41.1% and 31.7%, respectively, for adalimumab and placebo groups ($P = 0.032$). Mucosal improvements at week 52 were 25.0% and 15.4%, respectively, for adalimumab and placebo groups ($P = 0.009$)

(continued)

Table 2.1 (continued)

Anti-TNFα medication	Authors, date	Study summary	Study population, sample size	Dosing information	Clinical response	Clinical remission and mucosal improvement
Golimumab	Sandborn et al. [28]	Induction with SC golimumab (PURSUIT-SC)	761 patients	Randomized to placebo, 200/100 mg, and 400/200 mg at weeks 0 and 2	Rates of clinical response at week 6 were 30.3%, 51.0%, and 54.9% for placebo, 200/100 mg, and 400/200 mg golimumab groups, respectively (both, $P \leq 0.0001$)	Rates of clinical remission at week 6 were 6.4%, 17.8%, and 17.9% for placebo, 200/100 mg, and 400/200 mg golimumab groups, respectively (both, $P < 0.0001$)
						Rates of mucosal improvement were 28.7%, 42.3%, and 45.1% for placebo, 200/100 mg, and 400/200 mg golimumab groups, respectively ($P = 0.0014$, $P < 0.0001$, respectively)
	Sandborn et al. [29]	Maintenance (PURSUIT-SC maintenance)	464 patients who responded to induction therapy with golimumab	Randomized to placebo, 50 mg, or 100 mg golimumab every 4 weeks	Clinical response maintained through week 54 in 31.2%, 47.0%, and 49.7% and of patients receiving placebo, 50 mg, and 100 mg golimumab, respectively ($P = 0.010$ and $P < 0.001$, respectively)	Rates for clinical remission and mucosal improvement at weeks 30 and 54 were 15.6% and 26.6% for placebo, 23.2% and 41.7% for golimumab 50 mg, and 27.8% and 42.4% for golimumab 100 mg ($P = 0.004$, P = 0.002, respectively)

[a]Clinical response, clinical remission, and mucosal improvement results are all for the ITT-A3 treatment group, which were patients in the amended study protocol

Table 2.2 Summary of FDA-approved induction and maintenance dosing for anti-TNFα medications for UC

Anti-TNFα medication	Induction dosing	Maintenance dosing
Infliximab	5 mg/kg IV weeks 0, 2, and 6	5–10 mg/kg IV q 8 weeks
Adalimumab	160 mg SC day 1 and 80 mg SC day 15 -OR- 80 mg SC day 1, day 2, and day 15	Day 29 initiate 40 mg SC q 2 weeks
Golimumab	200 mg SC day 1 and 100 mg SC day 15	100 mg SC q 4 weeks

weight or placebo administered at weeks 0, 2, and 6 and then every 8 weeks through week 22 in ACT 2 and week 46 in ACT 1 [15]. TNFα-naïve patients with active moderate-to-severe UC who had failed or were intolerant to conventional therapies were included. Concomitant medication remained stable throughout each study, except for corticosteroid therapy, which was tapered after week 8. The primary endpoint of each trial was clinical response at week 8.

In ACT 1, 69.4% of patients receiving 5 mg/kg (84 of 121) and 61.5% of patients receiving 10 mg/kg (75 of 122) had a clinical response at week 8, compared with 37.2% of patients receiving placebo (45 of 121, $P < 0.001$ for both comparisons). In ACT 2, 64.5% of patients receiving 5 mg/kg (78 of 121) and 69.2% of patients receiving 10 mg/kg (83 of 120) had a clinical response at week 8, compared with 29.3% of patients receiving placebo (36 of 123, $P < 0.001$ for both comparisons). Clinical remission and mucosal improvement occurred in a higher proportion of patients treated with infliximab compared with placebo in both ACT 1 and ACT 2 trials at weeks 8, 30, and 54 and weeks 8 and 30, respectively ($P \leq 0.009$ for all comparisons). Incidence of infliximab antibody formation at week 54 in ACT 1 was 6.1% (14 of 229 patients) and 6.4% (12 of 188 patients) at week 30 in ACT 2. In ACT 1, infusion reactions occurred in 10.7% (13 patients) in placebo group, 9.9% (12 patients) of 5 mg/kg group, and 12.3% (15 patients) of 10 mg/kg group ($P = 1.00$). In ACT 2, incidence of infusion reactions was 8.1% (10 patients) in placebo group, 11.6% (14 patients) in the 5 mg/kg group, and 11.7% (14 patients) of the 10 mg/kg group ($P = 0.37$). At week 54 in ACT 1, 35.4% of patients with anti-infliximab antibodies had an infusion reaction compared with 9.8% of patients with negative or inconclusive antibody testing (5 of 14 and 21 of 215, respectively). At week 30 in ACT 2, 50% of patients with anti-infliximab antibodies had an infusion reaction compared with 9.7% of patients with inconclusive or lack of antibodies (6 of 12 and 17 of 176, respectively), suggesting that patients with positive tests for antibodies were more likely to develop infusion reactions than those without antibodies. Infliximab was generally well tolerated, and incidence of adverse events and infections was similar for both patients treated with drug and placebo.

Long-Term Safety and Efficacy

Long-term infliximab maintenance therapy for UC was evaluated during the ACT 1 and ACT 2 extension studies, in which patients who achieved a benefit from infliximab continued to receive up to three additional years of therapy [16]. Of

484 infliximab-treated patients in ACT 1 and ACT 2, 229 patients continued to receive infliximab in the extension studies. Of the 229 patients in the infliximab group, 70 (30.6%) discontinued infusions: 24 (10.5%) due to an adverse event, 11 (4.8%) due to lack of efficacy, 1 (0.4%) required colectomy, and 34 (14.8%) for other reasons. The primary intent of the efficacy analysis was to evaluate maintenance of efficacy. At week 0 of the extension study, 42.4% (97 of 229 patients) had no disease activity, and at week 152, 54.6% (125 of 229 patients) had no disease activity. For patients with mild or no disease activity, the proportion was 76.9% (176 of 229 patients) at week 0 and 89.5% (205 of 229 patients) at week 152. Based on these results from the intention-to-treat analysis, efficacy was maintained in both subgroups. Of note, patients who discontinued the study due to trial termination or for other reasons had the last available observation carried forward.

Safety was reported as events per 100 patient-years, for any patient who received at least one infusion of infliximab ($N = 230$), with a mean treatment duration of 1.99 years in the extension studies. Overall rates of adverse events were 506 per 100 patient-years, and infliximab was discontinued secondary to an adverse event at a rate of 4.63 patients per 100 patient-years of therapy. Infusion reactions occurred at a rate of 7.25 patients per 100 patient-years (36 of 230 patients). Only three patients experienced serious infusion reactions. Five malignancies were diagnosed during the extension studies, including adenocarcinoma of the lung, breast cancer, prostate cancer, basal cell carcinoma, and skin cancer of the nose and forearm (1.01 patients per 100 patient-years of therapy). No new or unexpected safety data compared to previous data on safety of infliximab was reported during the extension studies.

Adalimumab

Induction and Maintenance Clinical Trials

Adalimumab is a SC-administered, recombinant human antibody against TNFα approved for the treatment of UC, in addition to rheumatoid arthritis, juvenile idiopathic arthritis, hidradenitis suppurativa, ankylosing spondylitis, plaque psoriasis, psoriatic arthritis, and Crohn's disease [17]. The first trial to evaluate the safety and efficacy of adalimumab in UC was the Ulcerative Colitis Long-Term Remission and Maintenance with Adalimumab (ULTRA 1). This 8-week, multicenter, randomized, double-blind, placebo-controlled study assessed adalimumab for the induction of clinical remission in anti-TNFα-naïve patients with moderate-to-severe UC despite concurrent therapy with corticosteroids and/or immunomodulators [18]. A second multicenter, randomized, double-blind, placebo-controlled clinical trial, ULTRA 2, was performed to further evaluate the efficacy and safety of adalimumab in patients with moderate-to-severe UC and gather long-term data [19].

The ULTRA 1 study protocol originally included one adalimumab group of patients receiving adalimumab 160 mg at week 0, 80 mg at week 2, 40 mg at weeks 4 and 6 (ADA160/80), and placebo. However, the study protocol was amended to include a second induction group of adalimumab 80 mg at week 0 and 40 mg at weeks 2, 4, and 6 (ADA80/40). Patients in the study continued to receive adalimumab 40 mg SC every 2 weeks through week 52 in an open-label phase. There were two intention-to-treat analyses, one including patients under the amended study protocol (ITT-A3, $N = 390$) and a second intention-to-treat population including all patients under the original protocol and amendments (ITT-E, $N = 575$). In the ITT-A3 population, 18.5% of patients in the ADA160/80 arm, 10% of patients in the ADA80/40 arm, and 9.2% of patients in placebo arm achieved primary efficacy endpoint of clinical remission at week 8 ($P = 0.031$, $P = 0.833$ versus placebo, respectively). Adalimumab treatment was generally well tolerated at both induction doses, and overall safety profile was comparable to placebo. The findings of ULTRA 1 trial demonstrated that ADA160/80 was safe and effective for induction of remission of moderate-to-severe UC.

The ULTRA 2 trial randomized 494 patients with moderate-to-severe active UC despite concurrent corticosteroid and/or immunomodulator therapy to adalimumab or placebo. Unlike ULTRA 1, prior treatment with infliximab was allowed if it had been discontinued due to loss of response or drug intolerance for greater than 8 weeks, and approximately 40% of the total study population had prior infliximab exposure. Patients were randomized 1:1 to ADA160/80 or placebo after stratification by prior anti-TNFα exposure. The primary efficacy endpoint was rate of clinical remission at weeks 8 and 52. At week 8, 16.5% of patients treated with adalimumab achieved clinical remission compared with 9.3% receiving placebo ($P = 0.019$). Similarly, at week 52 patients treated with adalimumab achieved a significantly higher rate of clinical remission (17.3% versus 8.5%, $P = 0.004$). At week 52, both anti-TNFα-naïve and experienced patients achieved clinical remission at significantly higher rates compared with placebo arms (22% versus 12.4%, $P = 0.029$ and 10.2% versus 3%, $P = 0.039$, respectively). Whereas, at week 8 only patients who were anti-TNFα naïve had a statistically significant rate of clinical remission compared with placebo group (21.3% versus 11%, $P = 0.017$). In secondary endpoint analyses, significantly more patients treated with adalimumab compared with placebo achieved clinical response at week 8 (50.4% versus 34.6%, $P < 0.001$) and week 52 (30.2% versus 18.3%, $P = 0.002$). Adalimumab-treated patients also achieved mucosal improvement more often than placebo-treated patients (week 8, 41.1% versus 31.7%, $P = 0.032$, and week 52, 25% versus 15.4%, $P = 0.009$). Overall, adalimumab treatment had a similar safety profile to placebo.

The ULTRA 2 trial was designed to permit patients with inadequate response to initial treatment to switch to open-label adalimumab 40 mg every other week at week 12 or later and weekly adalimumab 40 mg for patients who continued to demonstrate inadequate response. After week 12, 31.7% (39 of 123) of week 8 responders and 61.6% (77 of 125) of week 8 nonresponders switched to open-label adalimumab. Furthermore, 16.3% (20 of 123) and 38.4% (48 of 125) escalated to weekly adalimumab for responders and nonresponders, respectively [20]. Remission,

response, and mucosal improvement rates at week 52 for prior week 8 responders were 20%, 45%, and 45%, respectively, compared with 2.1%, 25%, and 29.2%, respectively, for prior week 8 nonresponders. These results indicate that escalation to weekly adalimumab dosing may be beneficial for both patients who initially respond to induction dosing and then lose response, as well as patients who are primary non-responders. Weekly dosing was not associated with a greater risk of adverse events.

Long-Term Safety and Efficacy

Efficacy and safety data for long-term use of adalimumab was reported for patients enrolled in the ULTRA 1 and 2 trials. Colombel et al. evaluated 600 of the 1094 patients enrolled in ULTRA 1 and 2 who received at least one dose of adalimumab (ADA Randomized Set) and found that 199 patients remained on adalimumab at week 208 [21]. Long-term remission rates and mucosal improvement rates over time were analyzed using nonresponder imputation (NRI), whereby patients with missing data were assumed not to have achieved the endpoint. For the ADA Randomized Set, rate of remission per partial Mayo score was 24.7% (148 of 600 (NRI)), and mucosal improvement was 27.7% (166 of 600 (NRI)) at year 4. Authors also evaluated the maintenance efficacy of adalimumab through week 156, for 588 patients who enrolled in the open-label extension, ULTRA 3, from ULTRA 1 and 2 (ADA Extension Set). Three hundred and sixty patients remained on adalimumab through week 156 in ULTRA 3. Long-term remission with mucosal improvement per partial Mayo score was 63.6% (NRI) at week 156 (of 242 patients who entered in remission) and 59.9% (NRI) at week 144 (of 409 patients who entered with mucosal improvement).

Safety data was reported for patients receiving at least one dose of adalimumab in ULTRA 1, 2, and 3 ($N = 1010$ patients or 2338 patient-years of exposure). Rates of serious adverse events per 100 patient-years of exposure were similar to or lower than that observed in prior studies. The overall rate was 30.7 events per 100 patient-years for week 52 of ADA 160/80/40 compared with a rate of 17.7 events per 100 patient-years for all ADA. During the ULTRA 3 study, three events of B-cell lymphoma occurred; however all patients had prior or current thiopurine use. Serious adverse events included, but were not limited to, two cases of cytomegalovirus colitis, one serious tuberculosis infection, one cardiorespiratory arrest, and one right ventricular failure. No new or unexpected safety data compared to previous data on safety of adalimumab was reported during the extension studies.

Golimumab

Induction and Maintenance Clinical Trials

Golimumab is a fully humanized, SC-administered antibody against TNFα that is approved for the treatment of UC and also for rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis [22–27]. In the UC population, the Program of

Ulcerative Colitis Research Studies Utilizing an Investigational Treatment-Subcutaneous (PURSUIT-SC) study evaluated the safety and efficacy of induction therapy with SC golimumab [28]. This multicenter, randomized, double-blind, placebo-controlled trial concluded that induction with SC golimumab 200/100 mg and 400/200 mg at weeks 0 and 2 was effective in inducing clinical response, clinical remission, and mucosal improvement in patients with moderately to severely active UC. The study also found that induction therapy was well tolerated with a safety profile consistent with other anti-TNFα therapies.

Specifically, this integrated phase 2 and 3 clinical trial enrolled patients with moderate-to-severe UC who were intolerant or refractory to oral 5-aminosalicylates, oral corticosteroids, azathioprine, and/or 6-mercaptopurine but naïve to anti-TNFα antagonists. In the phase 2 dose-finding portion of the trial, 169 subjects were randomized 1:1:1:1 to SC placebo or golimumab 100/50 mg, 200/100 mg, or 400/200 mg at weeks 0 and 2. In the phase 3 study, 774 subjects were randomized 1:1:1 to receive SC placebo, golimumab 200/100 mg, or 400/200 mg at weeks 0 and 2. At week 6, 51.0% and 54.9% of the golimumab 200/100 mg and 400/200 mg patients were in clinical response, compared to 30.3% of placebo patients. This result was statistically significant and met the primary endpoint of the study ($P < 0.0001$). Additionally, significantly more patients on golimumab 200/100 mg or 400/200 mg reached clinical remission as compared to placebo (17.8%, 17.9%, and 6.4% respectively, $P < 0.0001$). Significantly more patients on golimumab 200/100 mg or 400/200 mg also attained mucosal improvement. 42.3% on golimumab 200/100 mg ($P < 0.0014$), 45.1% on golimumab 400/200 mg ($P < 0.0001$), and 28.7% on placebo had mucosal improvement. Golimumab was generally well tolerated with an adverse event profile similar to placebo. Serious adverse events and serious infections were rare [28].

One thousand, two hundred and twenty eight patients completing one of two induction studies were then enrolled in a phase 3, multicenter, placebo-controlled, double-blind, and randomized-withdrawal study to evaluate SC golimumab maintenance therapy [29]. Patients received either golimumab 50 mg and 100 mg or placebo every 4 weeks through week 52. Results of the primary analysis population ($N = 456$) showed that significantly more patients treated with golimumab 100 mg or 50 mg maintained clinical response as compared to placebo (49.7%, 47.0%, 31.2%; $P < 0.001$ and $P = 0.010$, respectively); thus the study achieved the primary endpoint. For clinical response through week 52, the numbers needed to treat were 5 and 6, respectively, for the 100 mg and 50 mg golimumab groups. Significantly more patients on golimumab 100 mg were in clinical remission at weeks 30 and 54 compared to placebo (27.8%, 15.6%, respectively, $P = 0.004$). Clinical remission rates in the golimumab 50 mg SC group were numerically superior, but not statistically significant. The number needed to treat to attain clinical remission for the 100 mg group was 8. Analysis suggests that the incidence of anti-golimumab antibody formation is 2.9% after 54 weeks of therapy; subgroup analysis revealed those receiving concomitant immunomodulators had a 1.1% (4 of 362) incidence of antidrug antibody formation compared to 3.8% (28 of 741) of those receiving golimumab alone [29]. The overall safety profile in the maintenance clinical trial was consistent with the known safety profile of golimumab and included increased risk of rare serious infections, tuberculosis, malignancies, and antidrug antibodies [29].

Long-Term Safety and Efficacy Data

Authors published long-term safety and efficacy data on SC golimumab in 2016 [30]. 1240 anti-TNFα-naïve patients with moderate-to-severe UC from the phase 3 PURSUIT maintenance study were randomized to receive placebo or golimumab 50, 100, or 200 mg for 52 weeks in the maintenance study and then continued to receive treatment in the long-term extension study through week 104 [30]. At week 104 researchers noted that 86% of included patients had inactive or mildly active disease activity. Additionally, of the 174 patients who were corticosteroid-free at week 54, 88.5% remained corticosteroid-free at week 104.

For patients receiving at least one dose of golimumab (1664.0 patient-years), the safety profile was similar to that observed in earlier studies. Rates of serious adverse events per 100 patient-years of exposure were similar for exposure through weeks 54 and 104 (19.65% and 11.10%, respectively), as were adverse events that lead to discontinuation of golimumab (12.72% and 5.98%, respectively). Authors reported that tuberculosis, opportunistic infection, and malignancy rates were low; during the trial two nonmelanoma skin cancers, one metastatic colon cancer, and two deaths (biventricular heart dysfunction, sepsis) occurred between weeks 54 and 104 [30].

Treating Adults Over the Age of 60 with Anti-TNFα Therapy

In the United States, an estimated 10–15% of IBD patients are newly diagnosed after the age of 60, with an incidence of 6–8/100,000/year [31]. Additionally, aging patients who have been diagnosed earlier in life add to the growing population of older adults with IBD. While limited data exists to evaluate safety and efficacy of anti-TNFα biologics in older adults, the indication to use anti-TNFα medications in older populations is similar to that of younger patients [32]. Nonetheless, treatment decisions for older adults with UC are complicated by the lack of trials evaluating safety and efficacy of medications in this population. Additionally, older adults have a higher incidence of comorbid diseases and polypharmacy, complicating therapy. Furthermore, physiologic changes associated with aging increase the risk of morbidity and mortality; one study reports that 25% of IBD hospitalizations are for patients over the age of 65 [33].

Few studies have evaluated the safety and efficacy of anti-TNFα therapy in adults over the age of 65; in fact older adults are routinely excluded from clinical trial enrollment [5, 34]. In 2011, a retrospective study evaluated an Italian cohort of 95 IBD patients over the age of 65 of whom 78 patients (36 with UC and 58 with Crohn's disease) were treated with anti-TNFα agents with or without concomitant immunomodulators. Retrospective evaluation revealed 22 of 37 (59%) UC patients and 38 of 58 (65%) CD patients achieved clinical remission. Of patients receiving anti-TNFα therapy, 11% developed severe infections, 3% developed neoplasms, and 10% died, as compared to matched controls of whom 0.5% reported severe

infections, 2% developed neoplasms, and 2% died [33]. Although results suggest higher risk in older populations, the retrospective study design limited comparability, and patients treated with anti-TNFα therapy may have had more severe disease than the control group which may have significantly biased outcomes.

Another observational and retrospective study in 2015 compared 66 IBD patients over the age of 65 receiving anti-TNFα therapy, 112 IBD patients under the age of 65 receiving anti-TNFα therapy, and 61 anti-TNFα-naïve patients. Authors reported an increased risk of serious adverse events in the greater-than-65 anti-TNF-treated cohort as compared to those under the age of 65 treated with anti-TNFα therapy (RR = 4.7; $P < 0.001$). This risk was also higher as compared to those greater than 65 not treated with anti-TNFα therapies (RR = 3.09; $P = 0.0008$) [35]. Authors also reported that patients greater than 65 years old had significantly lower clinical response after 10 weeks of anti-TNFα therapy, as compared to patients less than 65 treated with anti-TNFα therapies; however, no difference in clinical response was noted between the groups after 6 months of therapy. Importantly, this assessment was limited by retrospective study design, and clinical response was based on clinical assessment only, not endoscopic evaluation [35].

Another consideration relevant to older populations with IBD treated with anti-TNFα therapies is the known risks of complications and adverse events. For example, anti-TNFα agents are contraindicated in moderate-to-severe New York Heart Association class III or IV heart failure [36], a comorbidity more common in older populations. Additionally, an increased risk of melanoma and nonmelanoma skin cancers has been associated with IBD. This will be discussed further in another chapter, but given the increased risk in older populations, appropriate screening is warranted [37]. Furthermore, the risk of lymphoproliferative disorders in the IBD population is thought to be similar to or slightly higher than the general population; however thiopurine therapy is associated with a four- to sixfold increased relative risk. The absolute risk is higher in adults over the age of 70 as compared to younger patients, with the absolute risk thought to be 1 in 4000–5000 for patients aged 20–29 and 1 in 300–400 in those over 70 [38]. While we feel that this risk is not an absolute contraindication to utilizing thiopurine therapy in conjunction with anti-TNFα therapy, this increased risk should be considered in this specific population. The true risk associated with anti-TNFα monotherapy is unclear as many patients treated with anti-TNF therapy are treated concomitantly with immunomodulators; this will be discussed further in a subsequent chapter.

While consideration should be given to potentially higher risk of complications, older adults with UC may present with severe disease, and, when indicated, these patients should be offered the most effective therapy, including anti-TNFα agents when appropriate. The assessment of risk in this population should compare the alternative therapies available including other classes of biologics, the inherent risk of patients being on steroids, and the risk of surgery which is also higher in the elderly population. Without the benefit of prospective controlled trials in this population, given a potential for higher rates of complications, it is important to try and reduce complications. Currently guidelines for any patient on anti-TNFα therapy, much less those at highest risk, include evaluation prior to initiation of therapy for

any infections or comorbid illness that would preclude use of anti-TNFα therapy. Additionally, guidelines recommend appropriate preventative care with immunizations and cancer screening when indicated. Evaluation of comorbid illness and performing appropriate immunizations and cancer screening are even more critical in older patients, as they appear to have the highest absolute risk for adverse events when on anti-TNFα therapy.

General Monitoring for Safety and Efficacy of Anti-TNFα Agents

Prior to initiation of anti-TNFα therapy, patients with UC should be screened for contraindications to therapy including tuberculosis, hepatitis B virus, and active infection. Other relative and absolute contraindications to therapy, including history of heart failure, demyelinating disease, the presence of current malignancy, and recent receipt of live vaccines, should be considered. Patients should be monitored throughout the therapy for signs and symptoms of infection, heart failure, hypersensitivity reaction, lupus-like syndrome, and malignancy. Safety laboratory monitoring at baseline and throughout treatment should include complete blood count and liver tests [39]. Therapeutic efficacy is generally evaluated with clinical assessment of symptomatic improvement, ability of patients to taper off of corticosteroids, and laboratory and endoscopic measures of improvement. Therapeutic drug monitoring is discussed in detail in a subsequent chapter.

Choice of Anti-TNFα Agent to Treat UC

The safety and efficacy of anti-TNFα therapies to treat moderately to severely active UC are in general similar among different agents. While each agent has been evaluated individually in double-blind, placebo-controlled clinical trials, no head-to-head studies comparing agents are currently available. However, without the benefit of head-to-head trials, when considering which anti-TNFα medication to utilize, factors that may influence the choice of therapy include the route of administration, the setting in which medications are administered, and cost [40].

Patient preference should be considered as therapies offer different routes of administration, either subcutaneous injection or intravenous infusion [40]. Also, maintenance dosing schedules vary, with infliximab typically administered intravenously every 8 weeks, adalimumab administered subcutaneously every 2 weeks, and golimumab administered subcutaneously every 4 weeks. Patient lifestyle is important to consider as the route or timing of doses may impact patient preference regarding therapy. For example, patients who live far from an infusion center or who have difficulty scheduling infusion appointments during clinic hours may prefer injectable agents that can be self-administered at home, while others may prefer the

infrequency of every 2 months of intravenous dosing. Furthermore ease of intravenous access is important to consider as patients with difficult IV access may prefer subcutaneous administration. Discomfort with self-injection may be a factor for other patients. Additionally, access to refrigeration is often required to store injectable medications, while intravenous medications are maintained at a clinical site and do not require patient storage of medications.

The location of administration may also impact choice of therapy. Intravenous medications are administered by a healthcare professional either in an infusion center or in the patient's home, which may be desirable for patients who prefer the presence of healthcare professionals during medication administration or in those who have difficulty adhering to a self-administered medication schedule. Additionally, intravenous administration facilitates laboratory monitoring without the need for additional clinic visits to arrange for ongoing blood draws.

Finally, given the expense of anti-TNFα therapies, insurance coverage often influences choice of first-line therapy in the absence of compelling indications for a particular therapy. Often this will be the primary factor regarding the choice of anti-TNFα therapy for patients. Without head-to-head trials, there is not compelling data to select a specific anti-TNFα therapy over another based on safety or efficacy.

Switching Anti-TNFα Therapies

Discontinuation of one anti-TNFα therapy and initiation of a subsequent anti-TNFα therapy may occur in the case of primary or secondary nonresponse to the previous agent, inadequate response, allergic reaction, patient nonadherence, or other interruption to therapy. Studies have suggested that response and remission rates are highest after treatment with the first therapy and lower with the second and third medication; however it appears that the reason for discontinuation of prior anti-TNFα therapies is a predictor of response to subsequent therapies. In general for patients who have responded to a specific anti-TNFα therapy, we do not advise "switching" to another anti-TNFα therapy, unless the patient loses response or has an adverse reaction.

In anti-TNFα-naïve patient populations, an estimated two thirds of patients with IBD have clinical response to the first anti-TNFα medication, one third achieve clinical remission, and one third are either intolerant or refractory to the medication [3]. Patients who do not respond to therapy are classified into primary nonresponders (those with no significant response to therapy), secondary nonresponders (those who initially respond to therapy and then subsequently lose response), and patients who are intolerant to the medication.

The response rate of patients treated with a second anti-TNFα therapy appears dependent on the reason for discontinuation of the first medication. A systematic review and meta-analysis suggest that of 61% of patients intolerant to the first anti-TNFα therapy, 45% of secondary nonresponders and 30% of primary nonresponders achieved remission with a second anti-TNFα agent [3]. However, response and

remission rates varied widely in retrospective studies, and currently only one placebo-controlled trial has evaluated the efficacy of a second anti-TNFα therapy in a Crohn's disease population [41]. In this study 301 patients who failed treatment with infliximab were randomized to receive induction with adalimumab or placebo. Twenty-one percent of adalimumab patients and 7% of placebo patients achieved remission after 4 weeks of treatment ($P < 0.001$). Statistically more adalimumab patients also achieved clinical response as compared to placebo (52%, 34%, respectively, $P < 0.001$). This suggests that patients with inadequate response or intolerance to infliximab can achieve remission with adalimumab, a second anti-TNFα medication [41].

Limited studies have evaluated the efficacy of treatment of IBD with a third anti-TNFα medication after failure of two previous anti-TNFα therapies, and the majority of the available data is in the Crohn's disease population [42]. One retrospective study evaluated 67 patients with Crohn's disease who were treated with a third anti-TNFα medication after intolerance or failure of two prior anti-TNFα therapies. This small retrospective study suggests that at weeks 6 and 20, 61% and 51% of patients, respectively, reported clinical response; however significant limitations of the study include small sample size, retrospective design, and lack of standardization of the definition of failure of prior anti-TNFα therapies [42, 43]. Another small retrospective study evaluating 63 patients with IBD treated with a third anti-TNFα therapy reports that 75% of patients achieved clinical response after 3 months of therapy, with 36% achieving remission [42, 44].

Patient Education

Patient education regarding anti-TNFα therapy is important for patient-centered shared decision-making to inform patients of the risks and benefits of therapy and to improve adherence. Education should include a discussion of goals of therapy, risk of adverse reactions, and the safety and efficacy monitoring plan. Patients should be instructed to notify healthcare professionals with signs or symptoms of infection or other adverse events. Patients should also be informed of the importance of contacting their healthcare team if they have planned surgery, as medication adjustment may be indicated. They should also inform their healthcare team if they are pregnant or considering conceiving, to discuss the role of therapy in pregnancy.

The importance of adherence to anti-TNFα medications to induce and maintain remission should be emphasized. Adherence is imperative to maintain response and to decrease the risk of developing antidrug antibodies that are associated with loss of response and increased risk of adverse reactions. Current treatment paradigms strongly encourage adherence to maintenance therapy to control active disease; the consequence of stopping therapy is discussed in a subsequent chapter.

Importantly, patients on immunosuppressant medications including anti-TNFα therapies should discuss age-appropriate healthcare maintenance recommendations

with their providers to consider the role of vaccines to reduce the risk of preventable illnesses [45, 46]. Patients should also be advised that receiving live vaccines while on immunosuppressant therapy is contraindicated. Age- and sex-appropriate cancer screening should be discussed. Additionally, patients should be informed about logistical issues related to insurance coverage of anti-TNFα therapies, including the need to notify healthcare providers about insurance changes to facilitate approval of medical therapy and to prevent dosing delays.

Conclusion

For those patients who have failed first-line therapy for UC, anti-TNFα agents can be utilized to induce and maintain remission. For the population that has failed first-line therapy, anti-TNFα therapy has been the most well-studied class of biologic therapy and has been proven to be relatively safe and effective for the treatment of UC. For those patients who initiate anti-TNFα therapy, prescribers should understand that the goals of therapy include improving the patient's quality of life and symptoms. However, other goals including achieving steroid-free remission, avoidance of hospitalization and complications from UC, and achieving improvement in the severity of disease based on endoscopic evaluation are of equal importance.

Currently there are three FDA-approved anti-TNFα therapies in the United States. This includes infliximab, adalimumab, and golimumab. In general, the safety profile and efficacy of the three available therapies are similar. There are no head-to-head trials to definitively show if one anti-TNFα therapy is superior to the others. The primary risks associated with anti-TNFα therapy are risk of infection, adverse reaction to the medication (infusion reaction or injection site reaction), and, while uncommon, an association with the development of other autoimmune reactions (lupus-like reaction, psoriasiform rash).

While therapy is generally tolerated very well, all patients and in particular adults over the age of 60 should be monitored carefully for signs of adverse reactions to the medication itself, infection, and malignancy. The primary contraindications to initiation of anti-TNFα therapy include evidence of active infection (e.g., tuberculosis, opportunistic infections, or hepatitis B), history of class III or IV heart failure, known demyelinating disease, known hypersensitivity reactions, or the presence of malignancy.

The initial choice of a specific anti-TNFα therapy, as there is no evidence that one is superior to another, has been primarily based on insurance authorization, patient's preference for infusion versus injection, and patient's out-of-pocket cost for any given therapy. For those patients with poor intravenous access, while infliximab is not contraindicated, adalimumab or golimumab may be a preferential first-line choice as they do not require intravenous access.

In general we do not recommend switching one anti-TNFα therapy to another for convenience or insurance factors. However, for those patients who have had intolerance or loss of response to a previous anti-TNFα therapy, it is reasonable to consider

trying a second anti-TNFα agent. We do not advocate switching unless the patient has lost response or been intolerant to a specific anti-TNFα therapy because this will increase the risk of the development of antibodies to the previous anti-TNFα therapy. Additionally, it has been shown that those patients started on a second anti-TNFα therapy generally have a lower response and remission rate compared to the first anti-TNFα agent. The utilization of concomitant immune suppression with anti-TNFα therapy will be discussed in detail in another chapter. However, in general we recommend that the majority of patients, unless there is intolerance or contraindication, should be on concomitant immune suppression when on an anti-TNFα therapy.

Patient education regarding the risks and benefits of anti-TNFα therapy is critical. It is also extremely important for patients to understand that interruption of therapy can result in antibody formation and loss of response. Therefore, adherence is an essential issue with regard to the long-term maintenance with anti-TNFα therapy.

In summary, for UC patients who have failed first-line therapy, anti-TNFα therapy can be utilized for the induction and maintenance of remission. Anti-TNFα therapy is relatively safe and effective for the treatment of UC provided patients are selected to ensure there are no treatment contraindications and that all patients are monitored carefully.

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Chapter 3
Antitumor Necrosis Factor Agents in Crohn's Disease

Byron P. Vaughn

Introduction

Antitumor necrosis factor (anti-TNF) agents revolutionized the treatment for Crohn's disease (CD). As discussed in the previous chapter, TNF is a key role in stimulating pro-inflammatory cytokines as well as the expression of adhesion molecules and fibroblast proliferation [1, 2]. Clinically, elevated fecal TNF concentrations correlate with disease activity, while inhibition of TNF prevents granuloma formation in vitro [3–5]. These associations led to the hypothesis that inhibiting TNF could be a therapeutic intervention in inflammatory diseases mediated by TNF. Developed at New York University, a murine monoclonal antibody (cA2) was constructed with a high affinity and specificity for human TNF [6]. This antibody eventually became infliximab (Remicade, Janssen) and was initially approved for Crohn's disease in 1998. Since that time, other anti-TNFs have been approved for the treatment of Crohn's disease including adalimumab (Humira, AbbVie) in 2007 and certolizumab pegol (Cimzia, UCB) in 2008. This chapter will review in detail each approved anti-TNF for Crohn's disease highlighting key efficacy data from major clinical trials.

Infliximab

Infliximab (IFX) is a chimeric, mouse-human monoclonal antibody against human-soluble and transmembrane-bound TNF [7]. The constant region of the antibody is human, while the variable regions are murine (approximately 25%). Clinical use of IFX was first described in a 12-year-old girl who failed therapy with prednisone,

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mesalazine, azathioprine, semi-elemental diet, and metronidazole [8]. After 2 years of CD-related symptoms and stunted growth, she received open-label IFX at a dose of 10 mg/kg for two infusions. She went into complete clinical and endoscopic remission for 3 months however, ultimately developed a symptomatic recurrence. This single experience led to a small open-label trial in ten patients with steroid-unresponsive CD [9]. Eight patients received a single infusion of IFX at 10 mg/kg, while two received 20 mg/kg to assess the safety of higher doses. Eight of the nine patients available for follow-up responded clinically measured via decrease in the Crohn's Disease Activity Index (CDAI).

Clinical Efficacy

Based on the remarkable open-label experience with IFX, a multicenter randomized controlled trial was designed to test the efficacy in moderately to severely active CD [10]. In this trial, 108 subjects were randomized to a single infusion of placebo, IFX at 5 mg/kg, 10 mg/kg, or 20 mg/kg. The primary end point of a 70-point reduction in CDAI score at 4 weeks was noted in 65% of those who received IFX versus 17% of those who received placebo ($p < 0.001$). More so 33% of those who received IFX were in clinical remission versus 4% on placebo ($p < 0.005$) (Fig. 3.1). No dose response was noted, although each arm only contained 25–28 subjects limiting the

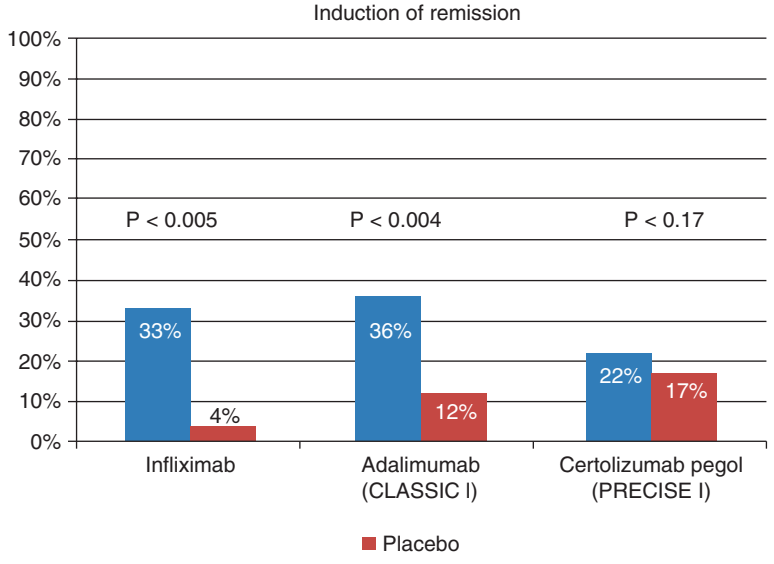

Fig. 3.1 Induction of remission with corresponding placebo rates from seminal clinical trials for each anti-TNF (note: trials had different inclusion criteria and end points and thus while presented on the same chart cannot be directly compared). Infliximab outcome: week 4 remission (defined as CDAI < 150), data pooled for doses of 5 mg/kg, 10 mg/kg, and 20 mg/kg [10]. Adalimumab outcome: week 4 remission (defined as CDAI < 150) following 160 mg/80 mg induction regimen [31]. Certolizumab pegol outcome: week 6 remission following 400 mg at weeks 0, 2, and 4 [48]

ability to detect subtle differences in dose response. Over 12 weeks, the difference in clinical response for IFX versus placebo remained significant (41% versus 12%, respectively, $p < 0.008$), while remission rates on the other hand were numerically better, but not statistically different (24% versus 8%, respectively, $p < 0.31$).

Given the early data demonstrating recurrence of disease weeks to months after a single infusion, patients who met the week 4 primary end point (70-point reduction in CDAI) were randomized to an extension study of IFX 10 mg/kg or placebo every 8 weeks for four infusions [11]. Seventy-three subjects were randomized, and at the end of 44 weeks, those on IFX were more likely to be in remission versus placebo (53% vs. 20%, respectively, $p < 0.013$). However, despite a significant difference for remission rates, the primary outcome of maintenance of clinical response was numerically superior and not statistically significant.

At this point in the early 2000s, IFX was being used on an intermittent basis for active CD given the mixed results for maintenance of remission. However it was hypothesized that this was an artifact from the small trials and thus ACCENT I (*A* *C*rohn's Disease *C*linical Trial *E*valuating Infliximab in a *N*ew Long-Term *T*reatment Regimen) was designed to assess the efficacy and safety of repeated infusions of IFX in those who responded to an initial infusion [12]. All participants received a single infusion of IFX 5 mg/kg and were randomized to one of three treatment groups (placebo, IFX 5 mg/kg or IFX 10mg/kg every 8 weeks) and then stratified by clinical response (defined as CDAI decrease of ≥70). The co-primary end points were clinical remission at week 30 and time to loss of response up to week 54. Five hundred and seventy-three patients were given IFX 5 mg/kg, and 335 (58%) had a week 2 clinical response. Subjects exposed to IFX were more likely to be in clinical remission at week 30 (OR: 2.7, 95% CI: 1.6, 4.6) and had a significantly longer time to loss of response versus those who received placebo. While no statistically significant differences were noted between IFX 5 mg/kg and 10 mg/kg, there was a numerical dose response for both remission and response at week 30 and week 54 favoring the higher dose. Additionally the median time to loss of response in the 5 mg/kg group was 38 weeks, while the 10 mg/kg group was >54 weeks. Among those initially randomized to the placebo group (including both responders and nonresponders at week 2), 49% crossed over to infliximab 5 mg/kg [13]. The episodic dosing arm (i.e., placebo arm) had higher CDAI scores and lower remission scores. These data from the ACCENT study group established the role of infliximab maintenance therapy following an initial response and additionally demonstrated the superiority of scheduled, rather than episodic, treatment.

A more extensive discussion of combination therapy with IFX and an immunomodulator is presented in a later chapter; however, the efficacy of IFX was confirmed in the SONIC trial (the *S*tudy of Biologic and *I*mmunomodulator *N*aïve Patients in *C*rohn's Disease) [14]. The SONIC trial remains one of the most informative trials for CD as it directly compared azathioprine monotherapy to IFX monotherapy to the combination of azathioprine and infliximab for patients with treatment-naïve, moderately to severely active CD. Forty-four percent of subjects on IFX monotherapy achieved steroid-free clinical remission at week 26 compared to 30% on azathioprine monotherapy ($p < 0.006$), although combination therapy was superior to both arms.

A key concern about IFX is the cost, given both the drug cost and infusion center cost. However numerous studies have evaluated the financial benefit of IFX when accounting for reduction of hospitalizations and surgery over 1 year [15–17]. Adhering to IFX maintenance therapy decreases hospital length of stay and lowers the overall cost of hospitalization versus nonadherence over the first year [18, 19].

Mucosal Healing

In addition to clinical response and remission, IFX is also successful at improving mucosal lesions. Subsets of the initial trials of IFX demonstrated that improvement of the Crohn's Disease Endoscopic Index of Severity (CDEIS) correlated with the improvement in clinical improvement [20]. An endoscopic sub-study of ACCENT I found those on schedule IFX had improved musical healing (defined as lack of mucosal ulceration) compared to a single dose at week 10 (31% vs. 0%, $p < 0.01$) and week 54 (50% vs. 7% in episodic group, $p < 0.007$) [21]. Similarly, mucosal healing was a secondary end point of the SONIC trial (defined as lack of mucosal ulcerations among those who had them at baseline) [14]. 30% of subjects in the IFX monotherapy arm and 43.9% in the combination arm achieved mucosal healing.

Fistula Healing

In an early study to determine the effectiveness of IFX for fistula healing, 94 were subjects randomized to placebo, IFX 5 mg/kg or 10 mg/kg, and fistula response (reduction by 50% or more in draining fistulas from baseline at two consecutive visits) was achieved in 68% of those on IFX 5mg/kg, 56% on IFX 10 mg/kg, and 26% on placebo ($p < 0.002$ and $p < 0.02$, respectively) [22]. Subsequently ACCENT II was designed to specifically evaluate the efficacy and safety of IFX for maintaining fistula closure [23]. In ACCENT II, subjects received IFX at 5 mg/kg at weeks 0, 2, and 6. Those with a response (reduction of draining fistulas by 50% at week 10 and 14) were randomized to receive scheduled IFX 5 mg/kg or placebo. The median time to loss of response among responders was 14 weeks in the placebo group and over 40 weeks in the IFX group ($p < 0.001$). At week 54, 19% of subjects receiving placebo had complete absence of draining fistulas compared to 36% of patients receiving scheduled IFX ($p < 0.009$). Patients on maintenance IFX in ACCENT II had significantly less hospitalization, surgeries, and procedures compared to placebo [24]. Combination IFX used with seton placement is also successful with complete healing in approximately two thirds of subjects in one single center study [25]. ACCENT II also had demonstrated improved closure for rectovaginal fistulas. Among responders, 72% of rectovaginal fistulas were not draining at 14 weeks [26].

One potential reason more fistulas do not heal is insufficient drug at the site of the fistula. Local injection of IFX into a fistula tract has been reported in a small study with success. Eleven patients had multiple IFX injections every four weeks

for up to 16 weeks. Seventy-three percent of subjects had an improvement in fistula symptoms with 36% in remission [27]. Additionally, very high trough concentrations of IFX are associated with fistula healing: in one study, an IFX trough >20.2 was associated with 86% fistula healing rate [28].

Adalimumab

In order to overcome the immunogenicity of IFX that was recognized as an important contributor to infusion reactions [29, 30], a recombinant humanized monoclonal antibody was developed, adalimumab (Humira, Abbott Laboratories, Chicago, IL). Adalimumab (ADA) has a high affinity for soluble TNF but, unlike IFX, is administered subcutaneously.

Clinical Efficacy

The clinical efficacy for induction of remission was established in the *C*linical Assessment of *A*dalimumab *S*afety and Efficacy *S*tudied as *I*nduction Therapy in *C*rohn's disease (CLASSIC I) [31]. This trial measured the effect of varying induction doses (time zero/week 2) on patients with moderate to severe CD naïve to anti-TNF therapy. Subjects were given a loading dose at time 0 and week 2, and the primary outcome was remission at week 4. The study met its primary end point with 36% of those receiving the highest dose (160 mg/80 mg) in remission at week 4 versus 24% of the lower dose (80 mg/40 mg) and 12% of placebo ($p < 0.004$) (Fig. 3.1). Over the 4-week induction course, antibodies to ADA were seen on only two subjects, one in the ADA treatment group and one in placebo. Following induction, a small phase II trial, CLASSIC II demonstrated that every other week ADA at 40 mg subcutaneously was superior to placebo for maintaining remission [32]. Given the strict remission criteria for CLASSIC II, only 55 subjects from CLASSIC I were randomized. However despite these small numbers, those on ADA were 1.5–2 times more likely to maintain remission at week 56 compared to placebo.

Given the positive signal for maintenance of remission in CLASSIC II, the *C*rohn's Trial of the Fully *H*uman Antibody *A*dalimumab for *R*emission *M*aintenance (CHARM) study was performed to determine the optimal dosing regimen for ADA for maintenance of remission in moderate to severe CD [33]. Subjects were given open-label ADA for induction at weeks 0 and 2 80 mg and 40 mg, respectively, and were randomized to ADA 40 mg every other week, ADA every week, or placebo. Notably, subjects did not have to be anti-TNF naïve. Eight hundred and fifty-four subjects were enrolled, and 499 (58%) responded to ADA at week 4 and were subsequently randomized. Those receiving ADA were statistically more likely to be in remission at weeks 26 and 56 compared to placebo (Fig. 3.2, week 26 data). Unfortunately ADA concentrations and antibodies to ADA were not measured in CHARM. Consistent with episodic versus scheduled IFX treatment, a larger analysis

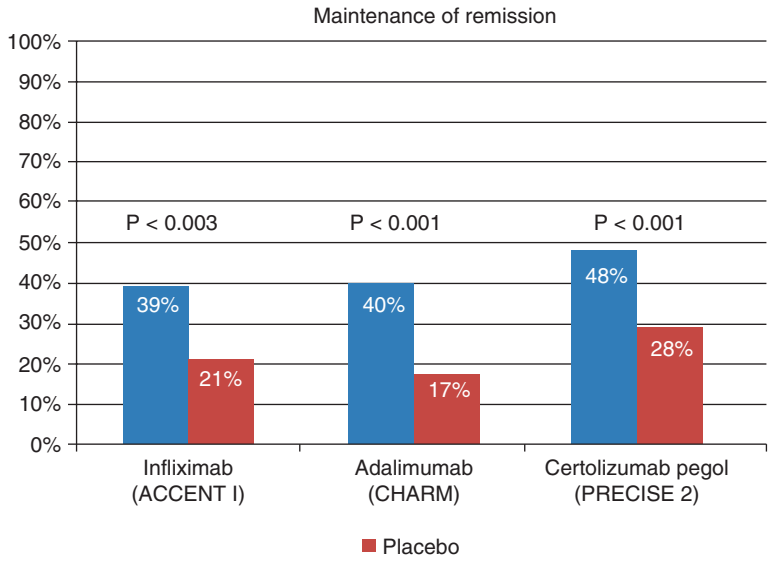

Fig. 3.2 Maintenance of remission with corresponding placebo rates from seminal clinical trials for each anti-TNF (note: trials had different inclusion criteria and end points and thus while presented on the same chart cannot be directly compared). Infliximab outcome: week 30 clinical remission dosed at 5 mg/kg [12]. Adalimumab outcome: week 26 remission dosed at 40 mg every other week [33]. Certolizumab pegol outcome: week 26 clinical remission dosed at 100 mg every 4 weeks [49]

of the entire CHARM cohort (including those who received open-label ADA) found that continuous ADA was a more effective treatment strategy versus induction dosing followed by retreatment for clinical flare [34].

Long-term follow-up studies of ADA from CHARM and the open-label extension, *A*dditional Long-Term *D*osing With *H*UMIRA to *E*valuate Sustained *R*emission and *E*fficacy in CD (ADHERE), demonstrated improved rates of steroid-free remission at 2, 3, and 4 years compared to placebo [35–37]. Additionally multiple analyses from these large randomized controlled trials demonstrate that ADA is effective at improving patient-reported outcomes for CD [38–40], reducing costs [38, 41], and reducing all-cause hospitalizations and surgery [42].

Mucosal Healing

The ability for ADA to induce and maintain mucosal healing was assessed in the EXTEND (*Ext*end the Safety and Efficacy of Adalimumab through *End*oscopic Healing) trial [43]. This study is notable in that it was the first prospective, randomized, placebo-controlled study with mucosal healing as an end point. All subjects were given open-label ADA for induction (160 mg at week 0 and 80 mg at week 2), and those with a clinical response (decrease in CDAI by at least 70 from baseline) were randomized to maintenance with ADA 40 mg every other week or placebo. Subjects who flared or were nonresponders were given open-label ADA. Ileocolonoscopy was

scored using the CDEIS, and while the initial assessment was study site specific, the final assessment was performed by a blinded central reviewer. In the intention to treat analysis, 27% of subjects in the ADA group achieved mucosal healing at week 12 versus 13% with placebo ($p < 0.056$). At week 52, the mucosal healing rate was 24% for those on ADA, while none of the subjects in the placebo group achieved mucosal healing ($p < 0.001$). Additionally, using clinical data from EXTEND, ADA was shown to improve a composite outcome including clinical remission and mucosal healing [44]. Similar to mucosal healing rates, no significant difference was noted at week 12, while 19% of those on ADA achieved deep remission at week 52 versus 0% on placebo ($p < 0.001$).

Fistula Healing

In the CLASSIC I trial, the rates of fistula improvement and remission for ADA and placebo groups were not significantly different, although only 11% of randomized patients had draining enterocutaneous fistulas [31]. Among those with fistulas at baseline, more patients in CHARM experience complete fistula closure at week 56 on ADA therapy (33%) versus placebo (13%) ($p < 0.016$) [33]. An open-label Canadian trial, *A*dalimumab in *C*anadian Subje*c*ts with Mod*e*rate to *S*evere Crohn's Disea*s*e (ACCESS), found that fistula healing rates at week 24 were as high as 60% for anti-TNF-naïve subjects and 28% for those previously treated with IFX [40]. In a randomized controlled trial of ADA plus ciprofloxacin versus ADA alone, those with ADA plus ciprofloxacin had a significantly higher reduction in fistula at 12 weeks versus ADA alone (71% versus 47%, $p < 0.047$) [45]. Complete fistula close was noted in 33% of ADA subjects at week 12 versus 65% of ADA plus ciprofloxacin ($p < 0.009$).

Certolizumab Pegol

Certolizumab pegol (CZP) is a humanized fragment of a monoclonal antibody that is a strong neutralizer of TNF but lacks the typical Fc portion of the parent IgG4 antibody and instead contains two molecules of polyethylene glycol [46]. The PEGylation of the antibody increases the plasma half-life and also prevents passage across the placenta during pregnancy [47].

Clinical Efficacy

The early randomized phase II placebo-controlled trial for CZP consisted of 92 adult subjects with moderate to severe CD who were randomized to CZP at varying doses and placebo [46]. The primary efficacy of clinical response at week 4 was similar for the three CZP treatment groups (5 mg/kg, 10 mg/kg, and 20 mg/kg) and

placebo with all ranging between 45% and 60% response (defined as decrease in CDAI ≥ 100). A post hoc analysis of the data revealed that the 10 mg/kg dose had a statistically significant week 2 remission rate versus placebo. Additionally, subjects treated with CZP 20 mg/kg had the lowest geometric mean of CRP at week 2. This trial was performed with an infusion of CZP in order to optimize the assessment of the pharmacokinetics. Overall the trial was thought to be negative due to the placebo response rate of 52–60% over the study period. Given this finding, a subsequent phase II trial was designed to assess efficacy and safety and dose response in a larger population [47]. Two hundred and sixty subjects were randomized into CZP 100 mg, 200 mg, 400 mg, or placebo. Similar to the initial phase II study, this study failed to reach its primary end point of clinical response (CDAI ≥ 100) at week 12. At every other time point, CZP at any dose was numerically superior to placebo; additionally CZP 400 mg was significantly superior to placebo at all time points aside from week 12. Week 4 remission rates were superior for all CZP treatment arms, and the higher doses of CZP suppressed CRP more although this was not statistically significant. Over the 12 weeks, 12.3% of subjects had at least one positive antidrug antibody. Similarly to the prior phase II study, this study had an unexpectedly high placebo response rate of 15–36% over the study period. Further post hoc assessments identified that the greatest benefit between CZP 400 mg and placebo was in those with a high baseline CRP.

Given the phase II experience with CZP and the high placebo response rate, the phase III induction trials for CZP were specifically designed to stratify for those with an elevated CRP. The *P*egylated Antibody F*r*agment *E*valuation in *C*rohn's D*i*sease: *S*afety and *E*fficacy (PRECISE 1 and 2) trials measured the efficacy for induction and maintenance of remission for moderate to severe CD [48, 49]. The PRECISE trials were unique from other anti-TNF trials in that they did not only randomize short-term responders but rather designed a 26-week induction/maintenance study. In PRECISE 1, the primary outcome of CDAI decrease by 100 or more in subjects with CRP > 10 mg/L was met in 37% of those on CZP 400 mg (0, 2, 4, then every 4 weeks) versus 26% of those on placebo ($p < 0.04$) [48]. Similar findings were noted in the entire population regardless of CRP level (clinical response of 35% for CZP and 27% for placebo, $p < 0.02$). The rates of remission at week 6 and remission at week 6 and 26 were similar for both CZP and placebo regardless of CRP strata (Fig. 3.1, week 6 data). When examining remission at every time point, significantly more patients on CZP were in remission at week 4 and week 26. PRECISE 2 evaluated maintenance CZP over 26 weeks as well as CZP withdraw among those with a clinical response to open-label CZP [49]. Following open-label induction with three doses of CZP 400 mg (weeks 0, 2, and 4), 64% had a clinical response (CDAI decrease of 100 or more) and 48% were in remission (CDAI < 150) (Fig. 3.2). Among week 6 responders who had a CRP > 10 mg/L, 62% had a clinical response at week 26 in the CZP arm, while only 34% had a response in the placebo arm ($p < 0.001$). Given the equivocal remission data from PRECISE 1, further data were needed for efficacy in induction. However, a subsequent trial of CZP versus placebo in 439 adults with moderate to severe CD failed to meet the

primary outcome of clinical remission at week 6 (32% and 25% for CZP and placebo, respectively, $p < 0.174$) [50]. However as with other CZP trials, when only looking at those with an elevated CRP (>5 mg/L), significant differences between CZP and placebo were noted. In PRECISE 1 and 2, the rates of antidrug antibody formation were 8 and 9%, respectively [48, 49].

PRECISE 3, an open-label extension including participants from PRECISE 1 and 2, demonstrated efficacy for CZP over a longer period as well as established that continuous therapy was superior to interrupted therapy [51]. Those in the placebo arm of PRECISE 1 or 2 were given the option for open-label CZP at the end of the study and then followed for an additional 54 weeks. Similarly to other anti-TNFs, those on continuous CZP had a response rate of 40% versus 27% for those who received interrupted CZP. Twenty percent of those who started the open-label extension completed the 7-year follow-up. At 7 years, a higher proportion of those who started the extension study in remission remained in remission versus those not in remission at the start of the extension, indicating that those who achieved remission on CZP could maintain a long-term remission [52].

Mucosal Healing

PRECISE 1 and 2 did not have mucosal healing end points. The Endoscopic *Muc*os*a*l *I*mprovement in Patients with Active *C*rohn's Disease Treated with CZP (MUSIC) trial was an open-label single-arm study to assess the efficacy of CZP for mucosal healing [53]. Subjects were given CZP 400 mg at weeks 0, 2, 4, and 8 then every 4 weeks, and the primary outcome was endoscopic improvement assessed via CEDIS at week 10 compared to baseline; the main secondary outcome was endoscopic improvement at week 54. Of the 89 subjects enrolled, 88% had a week 10 colonoscopy revealing a significant decrease in mucosal lesions (mean CDEIS decrease of 5.7 from baseline, 95% CI 5.3, 7.6, $p < 0.001$) with 4% (95% CI 1, 11) being in mucosal healing [53]. At week 54, the mucosal healing rates increased to 13% (95% CI 6, 25). Although this study lacked a control group, a significant decrease in mucosal lesions was noted on CZP that persisted through 1 year.

Fistula Healing

In PRECISE 1, the rate of fistula healing was similar in the CZP and placebo arms (30% and 31%, respectively) [48]. In PRECISE 2, only 14% of patients had draining fistulas on inclusion, and thus no conclusions could be drawn for fistula closure [49]. A small Swiss multicenter cohort questionnaire-based study, reflecting the real-world experience with CZP, noted that 73% (8/11 subjects) had a 50% decrease in the number of draining perianal fistulas at 6 weeks [54].

Pediatric Efficacy

Similar to the adult population, anti-TNFs have been effective in inducing and maintaining remission in pediatric IBD. The REACH (*R*andomized, Multicenter, Open-Label Study to *E*valuate the Safety and Efficacy of *A*nti-TNF alpha *Ch*imeric Monoclonal Antibody in Pediatric Subjects with Moderate to Severe CD) study assessed the efficacy of a three-dose induction on reducing the signs and symptoms of CD in children. 84% of subjects had a clinical response at week 10 with 58.9% in clinical remission. Improvements were seen in quality of life, steroid use, and height among those with evidence of growth delay. Other studies have validated the effect of IFX on children with CD in respect to mucosal healing and promoting growth [55, 56]. Within the REACH cohort, infliximab was able to rapidly reduce symptomatic perianal disease [57]. Similar results for induction and maintenance of remission were noted with adalimumab [58].

Top-Down or Step-Up

Trials for anti-TNFs typically include moderate to severe CD and are often limited to those with medically refractory disease to standard therapy. Anti-TNFs became the "top" of the treatment pyramid following immunomodulators and steroids. However, if anti-TNFs are the most effective therapy (as SONIC data suggests) [14], then perhaps they should be used earlier in the course of the disease prior to a moderate to severe flare. The difficulty of this strategy is that not all patients will progress to moderate to severe disease. A population-based study from Denmark determined that 50% of patients will be in remission 1 year from CD diagnosis with only one third having active disease [59]. Aggressive early therapy may over-immunosuppress a portion of the population who would otherwise not need immunosuppression. However, a large European randomized controlled trial (top-down) assessed early combination IFX with azathioprine versus steroids and sequential azathioprine followed by IFX [60]. All patients were diagnosed within 4 years and were naïve to steroid, immunomodulators, or anti-TNFs. Early combined therapy resulted in a greater proportion of remission at weeks 26 (60% vs. 36%, $p < 0.006$) and 52 (62% v. 42%, $p < 0.03$).

While both the top-down trial and SONIC suggested that early combined immunosuppression for CD was superior to sequential therapy, concerns about side effects, infections, and cost appear to limit this strategy [61, 62]. The REACT trial attempted to measure the benefits of early combined therapy (i.e., a top-down approach) through a large open-label cluster randomized trial [63]. Of the 41 practices randomized, the primary outcome of steroid-free remission was similar between the two strategies; however, the 2-year composite outcome of surgery, hospitalization, or serious disease-related complication was lower in the early combined immunosuppression group. An individual patient's needs/risk factors may therefore dictate the decision for initial therapy; however, the available data favors a top-down (or early aggressive) approach on the whole.

Why Aren't All TNFs the Same?

While anti-TNF medications represent an effective class of therapy for CD, not all anti-TNFs are equal. There is currently no prospective head-to-head trial or two anti-TNFs; however, some anti-TNFs have their key benefit only in certain subgroups (e.g., CZP only met induction end points for the high CRP subgroup), while others do not appear to work in CD. Etanercept is an anti-TNF commonly used in RA that failed to demonstrate clinical efficacy for CD in a phase II trial [64]. Other anti-TNFs also failed to produce a benefit in phase II and III trials for CD [65–68]. Differing clinical activity between drugs is likely influenced by different in vitro mechanisms. For example, while IFX can bind both the monomeric (inactive) and trimeric (active) form of soluble TNF and results in a stable complex [69], etanercept predominately binds the active form of soluble TNF and does not form as stable a complex as other anti-TNFs, which can lead to dissociation of the drug and target [70]. Etanercept does have the benefit of binding lymphotoxin (TNF-beta), but that does not appear clinically relevant in CD [71]. The drug makeup itself may also play a role in efficacy. Notably, only IgG1 monoclonal antibodies have thus far demonstrated achievement in all relevant outcomes including clinical remission, reduction of CRP, and mucosal healing [72].

There are key administration and dosing differences between the three anti-TNFs that also likely contribute to varying efficacy and may influence decision-making in certain clinical scenarios. IFX is the only FDA-approved anti-TNF that is an infusion (IV). The benefits of an infusion are quick time to peak serum drug concentration and easy ability to vary the dose. ADA and CZP are subcutaneous (SC) injections that are typically fixed-dose prefilled pens, although syringes are available. The benefits of an injection are ease of patient use (typically at home) and lower healthcare utilization cost when compared to an infusion center [73].

Beyond these clinical differences, there are pharmacokinetic differences between IV and SC routes that are important. IV administration allows for reproducible bioavailability with each infusion, while the SC route likely involves uptake through the lymphatic system followed by a slowed release into the vascular system [74]. This process can result in variable bioavailability and longer time to peak drug concentration. Additionally, due to dendritic cells in the skin, the SC route may increase the probability of developing antidrug antibodies [75]. Without direct comparison trials, it is impossible to ubiquitously recommend a single anti-TNF over another. Rather, the decision to start a specific anti-TNF should incorporate patient factors (preference, prior therapy, insurance coverage), pharmacokinetic factors (need for rapid, high drug concentrations, antibody development), and cost.

Conclusion

In summary, the class of anti-TNFs have clearly changed the landscape for treating CD. They are effective at inducing and maintaining remission, mucosal healing, and fistula healing. Overall, they appear to be cost-effective due to short-term

decreases in hospitalizations and surgeries as well as improving quality of life. It is not known at this time if the anti-TNFs alter the natural history of CD. While anti-TNFs have been approved for CD since 1998, longer follow-up data is needed to determine if the natural history of CD can be altered. Improvements in therapeutic strategies including combination therapy and therapeutic drug monitoring will likely continue to improve outcomes and reduce side effects of anti-TNF usage.

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Chapter 4
Anti-TNF Therapy for Treatment of Extraintestinal Manifestations of Inflammatory Bowel Disease

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Extraintestinal manifestations (EIM) of inflammatory bowel disease (IBD) are common, affecting up to one half of IBD patients [1–7], and are of major clinical importance because of their impact on the health and quality of life of those affected. EIM of IBD can affect nearly any organ system with a range of severity from mild to debilitating. Patients may experience one or multiple EIM simultaneously, and the presence of one EIM increases the likelihood of developing other EIM [3, 6]. In some cases, the EIM may be more severe than the intestinal disease itself. While some EIM such as erythema nodosum and pauciarticular arthritis typically parallel luminal disease activity, others such as uveitis and ankylosing spondylitis may be active without concomitant intestinal disease [8, 9]. This pattern and the approach to treatment is further complicated by the fact that EIM of IBD may develop even before the onset of gastrointestinal symptoms [8].

Although EIM of IBD can affect nearly every organ system, the use of anti-TNF therapy has been examined in only a subset of manifestations and is of varying efficacy depending on the condition being studied. Most data regarding the use of anti-TNFs for EIM of IBD are retrospective and have focused on patients with Crohn's disease (CD) rather than ulcerative colitis (UC). Nonetheless, for some extraintestinal conditions, the data for the use of anti-TNF therapy are robust.

Both infliximab and adalimumab can be effective in controlling certain EIM of IBD as will be reviewed below. Data for the use of certolizumab pegol and golimumab for EIM are lacking and, as has been the case for luminal disease,

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etanercept is probably less effective than infliximab and adalimumab, although data regarding this comparison are limited. A study outlining the Danish experience with infliximab from 1999 to 2005 noted that 80% of patients with CD and skin or joint symptoms had improvement or remission in symptoms [10], and similar overall response rates have been reported for adalimumab [11]. More recently, a systematic review of 9 interventional and 13 non-interventional studies also concluded that infliximab and adalimumab are effective for some classes of EIM including certain musculoskeletal, dermatologic, and ocular manifestations [12]. Consistent with this report, the 2016 ECCO consensus document on the use of anti-TNF drugs for the management of EIMs in IBD patients also noted anti-TNFs to be effective for certain EIMs and recommended considering their use in patients with spondyloarthropathy, arthritis, dermatologic manifestations such as pyoderma gangrenosum or erythema nodosum and uveitis [13].

Peripheral Arthritis

IBD-associated peripheral arthritis is categorized into 2 distinct subtypes, termed type 1 and type 2. Type 1 peripheral arthritis often occurs acutely, affects the large joints (knees most commonly), and typically tracks with luminal disease activity. On the other hand, type 2 usually occurs independently of intestinal disease, affects multiple small joints (especially the metacarpophalangeal joints), and is more commonly chronic [8, 14].

In line with existing data that anti-TNF therapy is effective in the treatment of rheumatoid and psoriatic arthritis [15], available evidence suggests that anti-TNFs are effective in the treatment of IBD-associated peripheral arthritis. A prospective, open-label study of Crohn's patients who had failed prior therapy (steroids, azathioprine, 6-mercaptopurine, or methotrexate) looked at patients with arthritis or arthralgia treated with infliximab (dosed either 5 mg/kg at 0 weeks for luminal disease or at 0, 2, and 6 weeks for fistulizing disease). The study showed that 61% (36/59) had improvement in their joint symptoms and 46% (27/59) of patients had symptom resolution [16]. In another study, 7 of 11 patients with Crohn's disease and inflammatory arthralgia reported improvement after treatment with a single 5 mg/kg infusion of infliximab [17].

Although data for adalimumab are more limited, the CARE trial provides evidence for its use for IBD-associated arthritis. Of over 900 patients with CD studied, 20 of 82 patients who had baseline arthritis had resolution of their arthritis at the conclusion of 20 weeks of treatment with adalimumab [18].

Generally, anti-TNF therapy should be a leading consideration for treatment of peripheral arthritis in patients with indications for systemic therapy of luminal disease. In the absence of a need for luminal-directed systemic therapy, a decision to undertake anti-TNF therapy for IBD-associated peripheral arthritis should be made in consultation with a rheumatologist.

Axial Arthritis

Anklylosing spondylitis (AS) and sacroiliitis are associated with IBD, although they occur less frequently than peripheral arthritis and typically manifest independently of intestinal activity [8, 14].

The efficacy of anti-TNF therapy for AS in the absence of IBD is well established [19–22]. In a multicenter randomized placebo-controlled trial, 53% (18/34) of patients with AS treated with infliximab (5 mg/kg at 0, 2, and 6 weeks) had symptomatic improvement at 12 weeks, compared to 9% (3/35) in the placebo group ($p < 0.0001$) [20]. An open-label follow-up study of the same cohort after 3 years of infliximab maintenance suggested that infliximab was effective in maintaining remission of AS [21].

The use of anti-TNF therapy for axial arthritis in patients with concomitant IBD is less well studied. The largest study of patients with both IBD and spondyloarthropathy compared 24 patients with Crohn's (16 of whom had active disease) given infliximab (5 m/kg at 0, 2, and 6 weeks then 3–5 mg/kg every 5–8 weeks) to 12 patients with active Crohn's on other treatments. Although there was a similar improvement in CDAI scores between the groups, the infliximab group had significantly better arthritis disease scores [23]. In a smaller cohort of 11 patients with Crohn's-associated inflammatory lower back pain treated with infliximab, 7 saw benefit [17].

Adalimumab also appears to be effective in treating IBD-related axial arthritis [11, 18]. In the open-label CARE trial, for example, 15 of 16 patients with AS treated with adalimumab had resolution of their joint symptoms after 20 weeks of therapy [18].

Based on the available data, anti-TNF therapy should be considered for treatment of axial arthritis in patients in whom systemic therapy for luminal disease is warranted, and in conjunction with a rheumatologist for patients with IBD-associated axial arthritis who lack an indication for luminal-directed systemic therapy.

Uveitis

Although there are several ocular manifestations of IBD, only for uveitis does there exist a body of literature supporting treatment with anti-TNF therapy. This typical chronic condition that presents with eye pain, blurry vision, photophobia, and headaches can develop before or after the onset of bowel symptoms and frequently occurs concurrently with arthritis [8, 9, 24].

Although not considered first-line therapy, anti-TNF agents have an important role in treating uveitis. They counter the role of TNF in fueling ocular inflammation, as demonstrated in animal models and analyses of human ocular fluids [25]. Adalimumab, infliximab, and etanercept have been studied in uveitis; however, these studies include patients with refractory uveitis and are not limited to patients

with underlying IBD [26–31]. Infliximab seems to be more effective than etanercept, and adalimumab may be more effective than etanercept as well.

In a 2005 study, data from 4 placebo-controlled trials and 3 open-label studies of patients with AS being treated with infliximab or etanercept were analyzed to assess outcomes of patients with concomitant anterior uveitis. Follow-up data on 397 patients demonstrated that patients treated with ant-TNF agents had 6.8 uveitis flares per 100 patient-years vs 15.6 in the placebo group. Flares were less frequent in those treated with infliximab than etanercept, although this finding was not statistically significant [27].

Similarly, a retrospective study of 17 children with chronic uveitis treated with high dose infliximab (10–20 mg/kg at varying intervals) showed a favorable response to the anti-TNF: 13 children had complete resolution of intra-ocular inflammation within 1–2 weeks of their first for second infusion, and the other 4 had resolution of symptoms after up to 7 infusions [28]. Another retrospective study of childhood uveitis (from conditions other than known IBD) in 21 patients with active recalcitrant uveitis also showed favorable though more limited responses to both etanercept and infliximab. Thirty-eight percent of those treated with infliximab had a "good" response, defined by a 50% or greater reduction in corticosteroid and immunosuppressive use, while 54% had a moderate response in which either the corticosteroid or immunosuppressive was reduced by $\geq$50 [29]. Those treated with infliximab had a trend towards fewer complications and a higher rate of improvement of glaucoma and visual acuity than those treated with etanercept [29].

The data for adalimumab are more limited than for infliximab. A retrospective study of 18 children with chronic uveitis treated with adalimumab after failing other immunosuppressive therapies showed an 88% percent response rate as measured by the frequency of relapse. As in the other studies, most of these children had juvenile idiopathic arthritis, and none had IBD [26].

Although most of the available evidence for anti-TNF treatment of uveitis is from studies of uveitis unrelated to IBD, the data can certainly be extrapolated to uveitis associated with IBD and some smaller studies do show a benefit in this population. The decision to use an anti-TNF for refractory uveitis, however, should always be made in conjunction with an ophthalmologist.

Pyoderma Gangrenosum

Pyoderma gangrenosum (PG) is a rare chronic cutaneous ulcerating skin condition that is sometimes associated with pathergy [32]. The use of anti-TNFs for this EIM of IBD has not been widely studied; however, the quality of the data is among the most robust for EIM and clearly demonstrates a benefit.

In one of the few placebo-controlled randomized trials examining the use of anti-TNF therapy for the treatment of EIMs, infliximab was given to 13 patients with PG at 5 mg/kg as a single dose. Effectiveness compared to 17 placebo controls was

evaluated at 2 and 6 weeks based on patient questionnaires and physician assessment. At week two, there was improvement in 46% of the infliximab group versus 6% of the placebo group. At that point, all non-responders were offered and accepted open-label infliximab. Sixty-nine percent (20/29) showed improvement at 6 weeks, with 21% (6/29) deemed in complete remission [33].

Retrospective studies show a more robust response, attributable in part to less limited dosing strategies. In one early retrospective study of 13 patients with moderate to severe PG treated with infliximab, 3 responded after induction dosing, the remaining 10 had response with ongoing dosing, and all patients were able to stop corticosteroids [34]. In a more recent study of 67 patients in Spain with PG (61.2% with underlying Crohn's and 37.3% with UC), 31 were given infliximab (24) or adalimumab (7), with improvement of PG in 29 (93.5%) [35]. Furthermore, the results show that infliximab and adalimumab were definitive (i.e., no subsequent therapy was needed over the study period) 91.7% and 100% of the time, respectively [35].

It is important to recognize that there are also reports of "paradoxical" PG developing during treatment with infliximab [36–38]. In two cases, therapy was transitioned to cyclosporine or adalimumab with resolution of skin lesions [36, 38]. In another case of a patient with underlying RA, infliximab was transitioned to etanercept but the lesions persisted until their treatment with minocycline [37]. These cases suggest that paradoxical PG is not a class effect, but might instead be a manifestation of immune response to a particular biologic agent.

Erythema Nodosum

Erythema nodosum (EN) is a dermatologic condition consisting of subcutaneous, tender, red nodules that occur most commonly on the shins [32]. EN has been described in association with several systemic inflammatory conditions but, among patients with IBD, EN is most commonly associated with Crohn's [8, 9]. Since the activity of EN typically parallels the activity of intestinal disease, first-line therapy focuses on treatment of the underlying IBD. When the intestinal disease responds, the EN typically remits as well [6]. However, successful treatment of idiopathic (and non-IBD-associated) EN with adalimumab has been reported [39]. In addition, as in PG, "paradoxical" EN has been reported with the use of infliximab [40].

Primary Sclerosing Cholangitis

Despite early reports of infliximab leading to biochemical improvement of comorbid primary sclerosing cholangitis (PSC) in patients with UC, this has not been borne out in subsequent work. A randomized double blind placebo-controlled trial

of infliximab versus placebo in 10 patients with PSC did not show biochemical, symptomatic, or histologic differences between the two groups after 6 months [41]. Indeed, it is generally agreed that there is no role for infliximab in the treatment of PSC, although it may be appropriate for the treatment of UC in patients also affected by PSC.

Bone Metabolism

Although osteopenia or osteoporosis occurs at higher rates in the IBD population, the pathophysiology of this association is not fully understood [42]. The causes are likely multifactorial; major risk factors include corticosteroid use, calcium and vitamin D deficiency, age, immobilization, and the inflammatory milieu of the disease state [42].

Data regarding the effect of anti-TNF therapy on bone density is not definitive, but suggests that there may be benefit, possibly by mitigating the inflammatory state or by a direct effect of TNF antagonism on bone metabolism. Multiple studies have shown an improvement in biomarkers of bone metabolism in patients with Crohn's disease treated with infliximab [43–45]. Others have investigated more clinically relevant endpoints, particularly bone mineral density (BMD). One study of 46 patients with CD treated with infliximab 5 mg/kg every 6–8 weeks for 1 year had an increase of BMD of 2–3% at the left femur and lumbar spine. There was no correlation between the change in BMD and baseline osteopenia, steroid use, calcium use, or changes in CRP [46]. In a similar trial, 15 CD patients treated with infliximab were compared retrospectively to 30 CD patients not treated with infliximab. Patients on infliximab were dosed with 5 mg/kg every 4–8 weeks for a mean period of 18 months. Lumbar BMD increased in the infliximab group (8.13% ± 7.7%) despite the control group having more weight gain over the same time span (22.6 ± 11 months) [47].

A retrospective trial of 61 patients with CD and low BMD treated with infliximab (23) and/or bisphosphonate (36) also examined changes in BMD. Controlling for steroid use, patients on both infliximab and a bisphosphonate had a greater increase in lumbar BMD T-score than those on just a bisphosphonate (6.7%/year vs. 4.5%/year), but infliximab alone had no effect on BMD. Patients on a bisphosphonate alone had an increase in lumbar BMD of 4.0% versus a decrease of 3.7% in those not on a bisphosphonate. The authors speculate that concurrent infliximab may confer added benefit to therapy with a bisphosphonate alone and that a larger sample size may have been able to detect a benefit of infliximab alone [48].

Although the data regarding infliximab and BMD is encouraging, given that it's largely retrospective and uncontrolled with small numbers and effect sizes and that there are available alternative treatments with more substantial supporting evidence, we would not recommend anti-TNF therapy in IBD patients for the purpose of improving bone density alone.

Conclusion

Anti-TNFs provide a valuable tool for the treatment of multiple EIM of IBD, although the data supporting their use are mostly retrospective and lack significant numbers of UC patients. With these limitations in mind, this class of biologics appears to be effective for the treatment of IBD-associated peripheral and axial arthritis as well as pyoderma gangrenosum. Outside of IBD, anti-TNF agents appear effective for uveitis, and, although there is limited data regarding uveitis specifically in IBD patients, its use is reasonable in refractory cases. Bone density may improve with anti-TNF therapy as well, but the data is still insufficient to recommend it for this indication alone. Some conditions, such as PSC, do not benefit from the use of anti-TNFs. Finally, it is important to recognize that anti-TNF drugs can cause "paradoxical" manifestations, such as PG or EN, that remit with withdrawal of the medication; this, however, does not seem to be a class effect. Future studies—ideally with a randomized control design and sufficient UC patients—are needed to enrich the current evidence and enhance our ability to manage these difficult patients.

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Chapter 5
Use of Biologics in the Postoperative Management of Crohn's Disease

Benjamin H. Click and Miguel Regueiro

Burden of Postoperative Recurrence

Prior to the routine use of immune-modifying therapies for Crohn's disease (CD), the majority of patients required surgery with clinical postoperative recurrence (POR) rates as high as 30–60% [1]. Subsequent endoscopic evaluations demonstrated that as many as 70–90% CD patients who underwent surgical resection developed endoscopic disease within 1 year. Symptoms will recur in this 30–60% of patients within 3–5 years [2–4]. With the advent and routine use of biologic agents such as the antitumor necrosis factor (aTNF) agents, the need for surgical intervention has been reduced, but not eliminated. Biologic era studies have shown the cumulative risk of surgery at 1, 5, and 10 years from diagnosis is 16.3%, 33.3%, and 46.6% [5]. Furthermore, 50% of patients will require repeat surgery within 5 years of first surgery. Thus, POR poses a significant threat to patient health and well-being.

Clinically, POR is often silent. In one study of postoperative CD patients, Rutgeerts et al. observed that 72% (21/29) had endoscopic recurrence within 1 year; however, the majority of these patients had no clinical symptoms [6]. Additionally, following 89 patients after resection, only 20% were symptomatic at 1 year and 34% at 3 years despite endoscopic disease in 73% and 85%, respectively [3]. In the initial study of infliximab for prevention of POR, Regueiro et al. observed a low kappa coefficient (0.12) between patient's endoscopic score and their clinical

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Table 5.1 Types of recurrence rates from time of resection in Crohn's disease

Time post-resection		
1 year	Clinical	0–44%
	Endoscopic	0–84%
	Surgical	4–25%
5 years	Clinical	32%
	Endoscopic	55–77%
	Surgical	4–25%
10 years	Clinical	52%
	Endoscopic	74%
	Surgical	12–57%

Adapted from Connelly et al. [60]

Crohn's Disease Activity Index (CDAI) score suggesting a significant discordance between clinical symptoms and endoscopic findings in POR (Table 5.1) [7]. As such, relying on patient-reported symptoms to detect POR can miss a significant portion of affected patients. Ultimately, postoperative CD recurrence can be thought of on a continuum of endoscopic, clinical, and surgical recurrence.

Detecting Postoperative Recurrence

Endoscopy

Given the lack of overt clinical symptoms in many patients with POR, multiple methods of POR detection have been investigated. Endoscopy is perhaps the most well studied. The importance in detecting endoscopic recurrence of CD lies in the downstream effects. Rutgeerts et al. demonstrated that endoscopic disease severity at 1 year directly correlated with progression to symptomatic recurrence and most strongly predicted clinical outcomes [3]. The authors then suggested an endoscopic grading system, the Rutgeerts score, identifying key endoscopic findings (Table 5.2) that correlated with outcomes. The Rutgeerts scoring system defines disease severity based on the extent of aphthous ulceration in the neoterminal ileum. Absence of lesions is classified as Rutgeerts i0, five or fewer aphthous ulcers; i1, more than five aphthous lesions with normal intervening mucosa or larger skip lesions; or i2, lesions confined to the ileocolonic anastomosis. Diffuse neoterminal ileitis defines i3, and the addition of large ulcers (≥5 mm), nodules, and/or luminal narrowing delineates the most severe classification, i4.

For patients with Rutgeerts score i0 or i1 at 1 year, only 8.6% had clinical symptoms at 8 years [3]. Conversely, patients with Rutgeerts score i4 had a 100% symptomatic recurrence rate at only 4 years. Those with severe endoscopic recurrence (i3–i4) were the most likely to progress to another Crohn's disease-related surgery [3, 8, 9]. Consequently, postoperative clinical studies have designated endoscopic recurrence using the Rutgeerts scoring system as i2–i4, whereas endoscopic remission includes i0–i1. This designation of endoscopic recurrence or remission

Table 5.2 Rutgeerts scoring system for postoperative endoscopic recurrence in the neoterminal ileum following resection in Crohn's disease

Rutgeerts score	Endoscopic findings
i0	No aphthous ulcer
i1	≤5 aphthous ulcers
i2	>5 aphthous lesions with normal intervening mucosa or larger skip lesions or lesions confined to the ileocolonic anastomosis
i3	Diffuse aphthous ulcers throughout neoterminal ileum with inflamed intervening mucosa
i4	Large ulcers (≥5 mm) with diffuse inflammation, nodules, and/or luminal narrowing

using the Rutgeerts score has not been validated as a measure of treatment response. Intra-observer reliability using the Rutgeerts scoring system has been shown to be fair to good with kappa between 0.43 and 0.67 [10, 11]. The point of most discrepancy likely results from the difference between i1 and i2 endoscopic appearance as the addition of a single aphthous ulcer can upgrade an i1 lesion to i2. Despite the limitations, due to the correlation with clinical outcomes, the Rutgeerts scoring system has stood as the gold standard as detection of POR.

Fecal Calprotectin

While sensitive for detecting recurrence, ileocolonoscopy is an invasive and somewhat costly procedure with associated risks. As such, there have been efforts to identify noninvasive detection methods of POR. One such method is fecal calprotectin. Fecal calprotectin (fCal) is a molecule produced by mucosal leukocytes and epithelial cells as sites of mucosal injury.

Initial studies evaluating the utility of fCal as a marker of POR were conflicting. Lasson et al. reported there was no difference in fCal levels in postoperative CD patients with endoscopic recurrence compared to patients with endoscopic remission at 1 year [12]. However, this study was limited by small size ($n = 30$). A subsequent, larger study of 86 asymptomatic postoperative CD patients demonstrated significantly higher levels of fCal in patient with endoscopic recurrence (i2–i4) than those in endoscopic remission (i0–i1) (mean ± s.e.m.: 473 ± 78 μg/g vs. 115 ± 18 μg/g; $p < 0.0001$) [13]. The same study suggested a cutoff value of 100 μg/g to detect endoscopic recurrence with a 95% sensitivity, 54% specificity, 69% positive predictive value (PPV), 93% negative predictive value (NPV), and 73% overall accuracy. In a meta-analysis of ten prospective studies totaling 613 postoperative CD patients, Qiu et al. estimated a pooled sensitivity of 82% (95% CI 73–89%) and pooled specificity of 61% (95% CI 51–71%) for detecting endoscopic recurrence with an overall PPV of 2.11 (95% CI 1.68–2.66) and NPV 0.29 (95% CI 0.197–0.44) [14]. Furthermore, these authors also analyzed fCal for detection of clinical recurrence and found a pooled sensitivity of 59% (95% CI 47–71%) and pooled specificity of 88% (95% CI 80–93%) with PPV of 5.10 and NPV 0.47. This study suggests that

fecal calprotectin can be a useful, noninvasive screening tool for detecting of POR. In an analysis of a randomized controlled control of postoperative CD patients undergoing colonoscopy at 6 and 18 months with fCal measurements, Wright et al. found similar predictive capability of fCal and suggested a potential avoidance of colonoscopy in 47% postoperative patients using the testing characteristics of fCal [15].

Furthermore, Wright et al. also investigated fCal levels as a marker of response to treatment. In their study, patients randomized to receive step-up postoperative medical therapy or not (see POCER trial discussion under "Postoperative Prophylaxis" section). The authors found fCal concentrations significantly decrease in response to intensification of drug therapy in patients with evidence of endoscopic recurrence (from 324 to 180 μg/g at 12 months ($p = 0.005$) and to 109 μg/g at 18 months ($p = 0.004$)), whereas patients in endoscopic remission who did not step up medical therapy had increasing fCal concentrations (from 129 to 153 μg/g at 12 months ($p = 0.194$) and to 178 μg/g at 18 months ($p = 0.245$)) [15]. This suggests that fCal may also serve as a noninvasive, indirect measure of treatment response in treatment of POR.

C-Reactive Protein

The utility of serum inflammatory marker C-reactive protein (CRP) in predicting POR has been analyzed in several studies with discordant results. Boschetti et al. collected CRP data in their 86 asymptomatic postoperative CD patients and found a weak but significant difference in CRP concentrations between patients with endoscopic remission and endoscopic recurrence (3.0 ± 0.7 and 8.5 ± 1.4 mg/L, respectively; $p = 0.001$) [13]. Furthermore, a significant increase of CRP levels according to Rutgeerts score was also observed ($p_{trend} = 0.02$), but without significant differences between individual subscores. When compared to fCal, CRP was less accurate (53% vs. 77% for fCal) in predicting endoscopic recurrence, and the area under the curve for fCal was 0.86 compared to <0.70 with CRP suggesting fCal as the superior testing modality. Conversely, in the same randomized control trial for step-up medical therapy following surgical resection in CD patients, Wright et al. also collected CRP data and found that CRP was not significantly correlated with endoscopic recurrence (Rutgeerts i2–i4) or scored endoscopic severity (i0–i4) [15]. Given the conflicting results, further studies are needed on the utility of CRP in predicting endoscopic and clinical recurrence postoperatively.

Ultrasound

Noninvasive radiographic studies including abdominal ultrasound have also been investigated in detecting POR. A study of traditional transabdominal ultrasound (TUS) in 32 CD patients who had undergone one or more intestinal resections

revealed an accuracy of 93.7% in detecting POR confirmed by radiography and endoscopy and biopsy, 82% sensitive and 100% specificity when using a bowel wall thickness >5 mm as a positive detection [16]. This study was limited by small number of POR occurrences ($n = 9$). These findings were corroborated by Andreoli et al. in 41 postoperative CD patients with TUS and concurrent ileocolonoscopy using the same bowel wall thickness cutoff with 81% sensitivity, 86% specificity, 83% accuracy, 96% PPV, and 57% [17].

The addition of contrast improves the capability of US in a technique termed small intestine contrast ultrasonography (SICUS). Using SICUS and an oral contrast solution with a decreased bowel wall thickness cutoff of 3 mm for at least 4 cm at the perianastomotic area, bowel dilation (>25 mm), or stricture (<10 mm), Calabrese et al. analyzed 72 postoperative CD undergoing ileocolonoscopy and SICUS within 6 months and found an increased sensitivity of 93% [18]. Bowel wall thickness also strongly correlated with Rutgeerts score ($p = 0.0001$, $r = 0.67$). These findings were supported when using intravenous contrast-enhanced US as well. Paredes et al. using cutoffs of >5 mm bowel wall thickness or >46% contrast enhancement determined a 98% sensitivity, 100% sensitivity, 100% PPV, and 92% NPV for detecting endoscopic recurrence (i1–i4) [19]. While suggesting the utility of abdominal ultrasound in detecting POR, the clinical usefulness of these techniques in the United States remains limited due to the requirement of experienced radiologist with advanced training.

Predictors of Postoperative Recurrence

Patient Factors

Many studies have evaluated factors influencing the development of POR. These are outlined in Table 5.3. These factors can be divided into patient-oriented, disease-related, and surgery-specific characteristics. The strongest and most consistent patient-specific factor is cigarette smoking after surgery. Sutherland et al. demonstrated both 5- and 10-year recurrence rates were significantly increased in smokers (36% and 70%, respectively) than in nonsmokers (20% and 41%, respectively) with an odds ratio (OR) of 2.1 ($p = 0.007$) [20]. Women smokers were also found to be at higher risk than men who smoked (OR 4.2; 95% CI 2.0–4.2 women; OR 1.5; 95% CI 0.8–6.0 men). The risk of recurrence with smoking is also dose dependent with patients smoking ≥15 cigarettes daily having higher rates or POR and other studies reporting a clear dose response [21, 22]. Patients who quit smoking postoperatively have a POR risk similar to nonsmokers. In a questionnaire study of 267 CD patients following ileocecal resection, Ryan et al. found that patients who quit smoking following surgical resection had significantly lower relative incidence rates (RIR) for one, two, and three reoperations for POR at any site (RIR 0.25, 95% CI 0.15–0.41; RIR 0.30, 95% CI 0.16–0.57; and RIR 0.25, 95% CI 0.10–0.71, respectively) as well as recurrent ileocecal CD (RIR 0.27, 95% CI 0.15–0.47) [23]. Thus postoperative smoking represents a significant modifiable risk factor for POR.

Table 5.3 Factors associated with development of postoperative Crohn's disease recurrence

	Strength of risk
Patient	
Smoking	++
Age at onset	~
Disease duration prior to surgery	~
Family history	+/~
Disease	
Penetrating/perforating	++
Prior CD surgery	+++
Anti-TNF prior to surgery	+
Surgery/pathology	
Anastomosis type	~
Myenteric plexitis	+
Active inflammation	+
Granulomas present	~

+ Weak
++ Moderate
+++ Strong
~ Equivocal or unknown

There are several patient-related factors that have had discordant associations resulting in inconclusive interpretation. Patient age at onset of disease has been evaluated in several studies with conflicting results. It is possible that positive association with disease recurrence could be related to increased duration of follow-up and thus likelihood of recurrence over time rather than a true causative relationship [24].

Similar to patient age at disease onset, shorter duration of disease prior to surgical resection may be a factor influencing POR, though this is still in question due to conflicting results. Varying definitions of "short duration" in individual studies have hampered pooling and comparative studies. One could imagine that a shorter duration of disease prior to requiring surgical resection may reflect a more aggressive disease phenotype, thus placing the patient at higher risk of POR.

A family history of inflammatory bowel disease was demonstrated by Unkart et al. to convey a 2.2-fold increased risk of repeat surgery in 176 postoperative CD patients though this finding has not been replicated [25].

There have also been studies evaluating genetic risk factors for POR. Fowler et al. examined 194 CD patients who underwent bowel resection with 69 patients requiring repeat resection. Patients who were homozygous for SMAD3 risk allele were independently associated with increased risk of repeat surgery (hazard ratio [HR] 4.04, $p = 0.001$) [26]. Similarly, Germain et al. in a study of 200 genetic variants demonstrated that patients with CARD8 risk allele homozygosity carried a sevenfold increased risk of surgical recurrence compared to non-risk allele carriers (OR 7.56, 95% CI 1.13–50.37) [27]. Several studies have examined the role of NOD2 (also known as CARD15), which has been previously associated with ileal and stricturing disease. These studies revealed conflicting results. A meta-analysis of six cohort studies comprising 1003 CD patients examining the risk of NOD2 polymorphisms suggested an increased risk of further surgical resection but failed

to reach significance (OR 1.58, 95% CI 0.97–2.57, $p = 0.06$) which the authors felt was likely due to study heterogeneity (Cochran Q: 12.36, $p = 0.03$, I: 59.6%). Lastly, interleukin-10 has been studied by Meresse et al. in a group of 36 postoperative CD patients and did not detect any association with endoscopic recurrence [28]. Consequently, there likely exists various genetic signatures which may predispose patients to POR; however, the current strength of data is suboptimal, and larger cohort studies with defined and consistent protocols are needed.

Disease Factors

Disease behavior is a frequently cited risk factor for surgical resection with stricturing and penetrating phenotypes at increased risk of surgery. However, relating disease behavior to postoperative recurrence is difficult given the fluctuating nature of CD and changes in the behavior pattern over time and in response to medical therapy. In a meta-analysis of 12 studies examining postoperative recurrence, Pascua et al. found that penetrating/fistulizing phenotype was a risk factor for endoscopic recurrence (OR 1.59, 95% CI 1.37–1.84 for every 10% placebo-treated patients with fistulizing disease) [29]. In the same study, patients who had prior surgery for CD indications were at significantly increased risk of POR (OR 1.14, 95% CI 1.04–1.26 for every 10% increase). This risk association has been replicated in other studies as well. Simillis et al. demonstrated that patients who have surgery with a particular disease behavior often have recurrence of that same behavior requiring reoperation [30]. It follows that any history of CD-related surgeries, regardless of disease behavior, is a strong predictor of postoperative recurrence. However, it should be noted that most studies did not differentiate between penetrating complications related to stricturing disease and de novo perforating disease without stricture.

The requirement of certain medications prior to surgery has also been shown to predict the risk of postoperative recurrence. The use of anti-TNF therapy presurgery has been associated in several studies to predict higher rates of POR [31, 32]. The medication themselves are not likely responsible for the disease recurrence, but they are more likely a reflection of disease activity, severity, or complication(s) prior to resection.

Surgical Technique/Findings

Anastomotic technique has been suggested as influencing POR. A difference in outcomes has been postulated from the wider luminal capacity of a stapled anastomosis preventing fecal stasis and bacterial overgrowth compared to a hand-sewn end-to-end anastomosis. Yamamoto et al. followed 45 patients who underwent stapled side-to-side anastomosis ("functional end to end"), and 78 underwent conventional sutured end-to-end anastomosis and found that cumulative 1-, 2-, and 5-year ileocolonic recurrence rates requiring reoperation were significantly lower in the

stapled anastomosis (0%, 0%, and 3%, respectively) compared to sutured end to end (5%, 11%, and 24%, respectively, $p_{\text{log-rank}} = 0.007$) [33]. These findings have been corroborated in several other, mostly retrospective, studies [24]. However, in two prospective randomized controlled trials of anastomosis type in 98 and 139 CD patients, both studies failed to show a significant difference in either clinical or endoscopic recurrence by anastomotic type.

Three studies have independently found myenteric plexitis to be a significant predictor of POR, both endoscopic and clinical [34, 35]. Furthermore, the severity of plexitis appears to correlate with severity of endoscopic recurrence at both early (3 months) and later (12 months) time points.

Characteristic findings in the surgical specimen have also been investigated as potentially related to POR. The degree of histologic inflammatory activity has been shown in several studies to correlate with increased rates of anastomotic recurrence in ileocolonic CD [24]. The presence of granulomas in surgical pathology has contradictory data with several large studies favoring a predisposition to POR if the surgical specimen contained granulomas [36–38]. However, the significance of this histologic finding in relation to POR remains uncertain.

Several early reports suggested an association between wide macroscopic margins and lower recurrence risk. Fazio et al. conducted a randomized controlled trial of 152 CD patients who underwent ileocolonic resection to limited (2 cm) or extended (12 cm) margin from macroscopic disease [39]. There were no significant differences in recurrence rates between the groups (25% limited, 18% extended). Of the group with microscopic activity at the margin, 31.7% had recurrence, whereas 17.8% of activity-free margin patients had POR though this difference failed to reach significance ($p = 0.07$). Thus, margin size or histologic activity does not seem to influence POR.

Prevention of Postoperative Recurrence

Given the frequency and impact of CD recurrence postoperatively, many studies have aimed to determine potential ways to prevent or reduce POR. Historically, treatment paradigms for POR followed a "bottom-up" approach with the use of steroids, antibiotics, and/or 5-aminosalicylates (5-ASA). As disease flared or progressed, immunomodulators or biologics (if available at the time) were then added. Thus there exists a time effect in studies of medical therapy for POR.

Nonbiologic Treatment Options

Traditional therapies including 5-ASAs, antibiotics, and immunomodulators have been shown to moderately reduce the risk of clinical and endoscopic recurrence. Mesalamine, a 5-ASA agent, is a safe but minimally effective option to reduce

POR. A Cochrane analysis by Doherty et al. demonstrated a significant reduction in both clinical recurrence (RR 0.75, 95% CI 0.62–0.94) and severe (Rutgeerts ≥ i3) endoscopic recurrence (RR 0.50, 95% CI 0.29–0.84) compared to placebo but with a number needed to treat (NNT) of 12 and 8, respectively [40]. A subsequent meta-analysis by Ford et al. demonstrated that this effect was exclusive to mesalamine as sulfasalazine was of no benefit to prevent POR compared to placebo in 448 patients (RR = 0.97, 95% CI 0.72–1.31) [41]. The authors conclude that mesalamine is of modest benefit in preventing POR but should only be used when immunosuppressive therapy is either not warranted or contraindicated.

In the previously mentioned Cochrane meta-analysis, Doherty et al. also examined the impact of nitroimidazole (including metronidazole) antibiotics and found that these agents significantly reduced the risk of clinical (RR 0.23, 95% CI 0.09–0.57, NNT = 4) and 3-month endoscopic (Rutgeerts ≥ i2) (RR 0.44, 95% CI 0.26–0.74, NNT = 4) recurrence compared to placebo [40]. However, these agents were associated with significantly higher risk of serious adverse events (RR 2.39, 95% CI 1.5–3.7), and the clinical recurrence effect lost statistical significance after exclusion of ornidazole. Thus the role of antibiotics in prevention of POR seems to be of limited benefit and short-term due to adverse events.

Immunomodulators have also been studied in the prevention of POR. In the aforementioned Cochrane meta-analysis, Doherty et al. examined two trials comparing thiopurines to placebo for prevention of POR and found that the use of azathioprine (AZA)/6-mercaptopurine (6-MP) significantly reduced the risk of clinical (RR 0.59, 95% CI 0.38–0.92, NNT = 7) and severe (Rutgeerts ≥ i3) endoscopic recurrence (RR 0.64, 95% CI 0.44–0.92, NNT = 4) at 12 months [40]. Comparing mesalamine to thiopurines, mesalamine carried a significantly higher risk of endoscopic recurrence at 12 months (RR 1.45, 95% CI 1.03–2.06) but had significantly fewer serious adverse events (RR 0.51, 95% CI 0.30–0.89). Similar findings were observed in a concurrent meta-analysis of the same studies by Peyrin-Biroulet et al. but found the superiority of immunomodulators to placebo extended to 2 years in prevention of clinical recurrence (mean difference 13%, 95% CI 2–24%, $p = 0.0016$, NNT = 8) [42]. However, immunomodulators were not effective in prevention of very severe (Rutgeerts i3–i4) recurrence. In a recent randomized, double-blind, placebo-controlled, parallel-group trial of 6-MP in POR, Arnott et al. studied 240 CD patients undergoing intestinal resection and found that patients receiving placebo were more likely to have clinical recurrence (CDAI >150 plus 100-point rise) (23.2% vs. 12.5%), but adjusted analysis was not statistically significant ($p = 0.07$) [43]. Stratifying by smoking status showed a significant difference between placebo and 6-MP in smokers in clinical recurrence (HR 0.127, 95% CI 0.04–0.46, NNT = 3) but not in nonsmokers (HR 0.898, 95% CI 0.42–1.94, NNT = 31). Significantly more patients receiving 6-MP maintained complete endoscopic remission (Rutgeerts i0) at 1 year (29.7% vs. 14.4%, $p = 0.006$) and 3 years (22.5% vs. 12.5%, $p = 0.041$). The authors concluded that thiopurines modestly reduce POR in CD with a significant effect in smokers, but not in nonsmokers.

The combination of short-term metronidazole with AZA may improve outcomes further. Postoperative CD patients treated with metronidazole for 3 months and

AZA (100–150 mg daily depending on body mass) for 12 months had significantly less endoscopic recurrence (Rutgeerts i2–i4) at 1 year than metronidazole alone (43.7% vs. 69.0%, $p = 0.048$) [44].

Budesonide has been studied in two controlled trials in prevention of POR. Meta-analysis of these two studies did not reveal any difference between those treated with budesonide compared to placebo (mean difference 7.9%, 95% CI 6.0–21.9%, $p = 0.263$) [45].

Biologics for Prevention of POR

There is increasing evidence that biologic agents are the most effective therapy to prevent POR. The most well-studied agents in this class are the antitumor necrosis factor alpha (anti-TNFα) agents. The first report of successful use of prophylactic infliximab (IFX) in a CD colitis patient after a partial colonic resection occurred in 2006 by Sorrentino et al. [46]. Since this initial description, multiple studies have focused on the role of anti-TNFs in preventing POR. Regueiro et al. performed the first randomized, placebo-controlled trial examining the ability of IFX (initiated within 4 weeks of surgery) to prevent endoscopic recurrence 1 year after ileocolonic resection [47]. In this study of 24 CD patients at moderate to high risk for POR, patients randomized to IFX had significantly lower rates of endoscopic recurrence compared to placebo (1/11, 9.2% vs. 11/13, 84.6%, $p = 0.0006$). Following these patients out to 5 years postoperatively, patients assigned to IFX continued to have significantly lower rates of endoscopic recurrence (22.2% vs. 93.9%, $p < 0.0001$) and longer mean time to first endoscopic recurrence (1231 ± 747 days vs. 460 ± 121 days, $p = 0.003$) [48]. Patients who were initially assigned to IFX had significantly longer time to repeat surgery (1798 ± 359 days vs. 1058 ± 529 days, $p = 0.04$). Those who stayed on IFX for a longer period also had significantly lower rates of surgical recurrence (20.0% vs. 64.3%, $p = 0.047$) suggestive of a maintenance effect of prophylactic IFX. This effect was further shown by Sorrentino et al. when patients maintained on IFX (5 mg/kg) for 3 years postoperatively had IFX stopped [49]. Of 12 patients who had no evidence of endoscopic or clinical recurrence prior to cessation of IFX, 10/12 (83%) developed endoscopic recurrence after 4 months without IFX. Mucosal integrity was restored with retreatment with lower-dose IFX (3 mg/kg every 8 weeks). Yoshida and colleagues similarly demonstrated a durable effect of IFX when following 31 postoperative CD patients who were maintained on 5 mg/kg every 8 weeks IFX ($n = 15$) or placebo ($n = 16$). Both arms received oral mesalamine 1.5 g/day for trial duration. They found significantly higher rates of maintained clinical, serologic (CRP), and endoscopic remission in patients treated with IFX than placebo [50].

In a subsequent follow-up landmark study, Regueiro et al. performed a prospective, multicenter, randomized, double-blind, placebo-controlled trial comparing IFX (5 mg/kg every 8 weeks, no induction dosing) to placebo for individuals at increased risk of POR (PREVENT study) [32]. In this study, patients were included

as increased risk if they had at least one (or more) prior resection within 10 years, or resection for a penetrating complication (abscess, fistula), or perianal fistulizing disease, or active smoking. Patients were randomized by number of risk factors (1 or ≥1). Patients were allowed to continue oral mesalamine or immunosuppressives at stable doses. Antibiotics and steroids were prohibited. Primary endpoint in this study was a composite endpoint of both clinical recurrence defined by ≥70-point CDAI increase and total CDAI ≥ 200 and evidence of endoscopic recurrence (Rutgeerts ≥i2) or new penetrating complication at week 76 postoperative. If clinical recurrence occurred, patients could have infliximab increased to 10 mg/kg every 8 weeks. A total of 297 patients were randomized. The study was terminated at week 104 because the primary endpoint was not met. Prophylactic IFX was associated with a numerical, but not statistically significant, reduction in clinical recurrence rates (12.9% IFX vs. 20.0% placebo, $p = 0.097$). Similarly, composite clinical recurrence and endoscopic recurrence rates were lower in the IFX compared to placebo groups (4.1% vs. 9.3%) but failed to reach statistical significance ($p = 0.056$). In a secondary endpoint analysis, rates of endoscopic recurrence alone (22.4% IFX vs. 51.3% placebo) or endoscopic recurrence or new penetrating complication were significantly reduced in the IFX group (30.6% IFX vs. 60.0% placebo, $p < 0.001$). Several reasons were postulated by the authors to explain the primary endpoint failure in this study. First, the placebo clinical recurrence rate in this study was smaller than previously reported (20.0% vs. 38.5%, respectively). The majority of the study population (69.6%) only had one risk factor, and 57.4% were undergoing their first CD intestinal resection perhaps diluting the effect of a "high-risk" population. Furthermore, the additive effect of risk factors hypothesized in the study has not been formally replicated. These may have led to an overestimation of IFX effect. Additionally, there was a low median CDAI score in the study population (105.5), which required many patients to double their CDAI to meet the clinical recurrence cutoff of CDAI ≥200. This likely limited the rates of composite recurrence. Lastly, there was a lower rate of immunosuppressive use in the PREVENT trial compared to the prior 2009 Regueiro et al. study (17.5% vs. 45.8%, respectively). Immunomodulators increase IFX levels, reduce immunogenicity, and increase efficacy of IFX. Lastly, the composite endpoint utilized in this study had not been previously investigated or validated. Thus, within the limitations of the study design, prophylactic IFX did not significantly reduce clinical recurrence but did reduce endoscopic recurrence.

Localized injection of infliximab has also been investigated in a pilot open-label study of eight CD patients with localized (<5 cm length) endoscopic recurrence without clinical recurrence (CDAI < 150) [51]. This study found no significant reduction in median endoscopic or histologic score after 14–21 months of follow-up.

Comparing IFX to thiopurines, in an open-label pilot study of 22 high-risk postoperative CD patients to compare AZA (2.5 mg/kg/day vs. IFX (standard induction followed by 5 mg/kg maintenance)) for the prevention of POR, Armuzzi et al. found a numerical but nonsignificant reduction in endoscopic recurrence rates with IFX (40% AZA vs. 9% IFX, $p = 0.14$) [52]. There was significantly less histologic

activity in the IFX-treated group (80% AZA vs. 18% IFX). There were no significant differences in clinical recurrence after 12 months.

Adalimumab (ADA) has similarly been studied for prevention of POR. First reported by Savarino et al. in 2012 when treating six CD patients post-ileocecectomy, ADA induction and maintenance (160/80/40 mg every 2 weeks) resulted in complete clinical, radiographic, and endoscopic remission for 3 years [53]. Similarly, in a prospective, 2-year, pilot study, Papamichael et al. followed 23 high-risk CD patients after resection. Out of eight patients started on prophylaxis ADA (induction followed by maintenance dosing) at day 14 post-resection, only 1/8 (12.5%) patient had endoscopic recurrence at 6 months and 2/8 (25%) at 24 months [54]. The remaining 15 patients demonstrated endoscopic POR at 6 months postoperative but were intolerant to IFX and AZA. After 24 months of treatment with ADA, 9/15 (60%) achieved complete mucosal healing. These studies were limited by lack of placebo arm. In a randomized controlled trial of ADA (160/80/40 mg every 2 weeks) compared to AZA (2 mg/kg/day) or mesalamine (3 g/day) in prevention of POR, Savarino et al. demonstrated significantly lower endoscopic recurrence rates in patients treated with ADA compared to AZA (6.3% ADA vs. 64.7% AZA, OR 0.036, 95% CI 0.004–0.347) or mesalamine (83.3%, OR 0.013, 95% CI 0.001–0.14) [55]. Similarly, ADA-treated patients had significantly lower rates of clinical recurrence (12.5% ADA vs. 64.7%, OR 0.078, 95% CI 0.013–0.464) and mesalamine (50%, OR 0.143, 95% CI 0.025–0.819). Thus, similar to infliximab, adalimumab appears to be superior to both thiopurines and 5-ASA agents in prevention of POR. Recurrence rates utilizing various medications using data from randomized, controlled trials are demonstrated in Table 5.4.

Using a Bayesian network meta-analysis strategy of direct and indirect comparisons, Singh et al. were able to compare treatment effects of multiple pharmacologic interventions in preventing POR by combining data from 21 trials comprising 2006 postoperative CD patients with seven different treatment strategies [45]. Compared to placebo for prevention of clinical recurrence (CDAI > 150 or clinical relapse as defined by individual study investigators), mesalamine (RR 0.60, 95% CI 0.37–0.88), antibiotics (RR 0.26, 95% CI 0.08–0.61), immunomodulator monotherapy (RR 0.36, 95% CI 0.17–0.63), immunomodulator with antibiotics (RR 0.11, 95% CI 0.02–0.51), and anti-TNF monotherapy (RR 0.04, 95% CI 0.00–0.14) were all

Table 5.4 One year clinical and endoscopic Crohn's disease recurrence rates reported in randomized controlled trials (Adapted from Regueiro [61])

	Clinical recurrence (%)	Endoscopic recurrence (%)
Placebo	25–77	53–79
5-Aminosalicylates	24–58	63–66
Budesonide	19–32	52–57
Nitroimidazole	7–8	52–54
Azathioprine/6-mercaptopurine	34–50	42–44
Antitumor necrosis factor[a]	0–13	6–22

[a]Includes infliximab and adalimumab

significantly superior. Of the examined treatment modalities, only budesonide (RR 0.93, 95% CI 0.40–1.84) was not significantly better than placebo in preventing clinical recurrence. Similarly, when evaluating prevention of endoscopic recurrence (Rutgeerts ≥ i2), antibiotics (RR 0.16, 95% CI 0.15–0.92), immunomodulator monotherapy (RR 0.33, 95% CI 0.13–0.68), immunomodulator with antibiotics (RR 0.16, 95% CI 0.04–0.48), and anti-TNF monotherapy (RR 0.01, 95% CI 0.00–0.05) were significantly better than placebo. For prevention of endoscopic recurrence, neither mesalamine (RR 0.67, 95% CI 0.39–1.08) nor budesonide (RR 0.86, 95% CI 0.61–1.22) was significantly different than placebo. The authors concluded that anti-TNF monotherapy was the most effective pharmacologic intervention for prophylaxis of POR with large effect sizes relative to all other strategies (clinical recurrence, RR 0.02–0.20; endoscopic recurrence, RR 0.005–0.04).

The safety of anti-TNF therapy has been demonstrated in several studies. Regueiro et al. found no increased risk of adverse events in IFX-treated patients compared to placebo including postoperative complications up to 1 year after surgery [56]. Similarly, Savarino et al. reported ADA-treated postoperative CD patients had fewer adverse events than AZA- and mesalamine-treated patients over a 2-year follow-up period [55].

To date, no studies evaluating POR using certolizumab pegol, ustekinumab, or vedolizumab have been reported. The positioning of the anti-interleukin-12/anti-interleukin-23 (ustekinumab) and anti-integrin (vedolizumab) in the prevention of postoperative CD recurrence remains to be determined.

Methods to Treat Postoperative CD Recurrence

Waiting for Recurrence

While postoperative CD recurrence occurs in the majority of patients, it is not ubiquitous. Thus universal postoperative prophylaxis would likely be overtreating a subset of patients, exposing them to unnecessary medications, risks, and expense. Several studies have shown that anti-TNF agents are capable of inducing remission in patients who have developed POR. Yamamoto and colleagues studied 26 postoperative CD patients who were in clinical remission (CDAI < 150), but at 6 months post-resection had endoscopic recurrence despite mesalamine (3 g/day) prophylaxis [57]. Eight patients were started on IFX (5 mg/kg every 8 weeks), eight patients received AZA (50 mg/day), and ten were continued on mesalamine (3 g/day). After 6 months, significantly more patients developed clinical recurrence in the mesalamine (70%) and AZA (38%) groups than the IFX-treated cohort (0%). Furthermore, endoscopic improvement was induced in 75% IFX (38% with complete mucosal healing) compared to 38% AZA (13% complete healing) and 0% mesalamine group ($p = 0.006$ improvement, $p = 0.10$ for complete healing). Similar results were observed by Sorrentino et al. following 43 postoperative CD patients [49]. At 6 months post-resection, 24 patients developed endoscopic recurrence (≥i2) and 13

were initiated on IFX and 11 on mesalamine for 1 year duration. The majority (54%) of patients treated with IFX had endoscopic remission (<i2), while no mesalamine-treated patients had endoscopic improvement. ADA appears equally efficacious in treating early recurrence as shown in the aforementioned study by Papamichael et al. [54]. ADA promoted mucosal healing in 60% of treated patients (n = 15) who had endoscopic disease at 6 months post-resection. Together, these studies suggest that anti-TNF therapy appears effective in achieving mucosal healing in patients who develop early postoperative recurrence. Thus, watching and treating if or when disease recurs are reasonable options in select patients.

Postoperative Prophylaxis

As discussed previously, the immediate postoperative use of multiple medications can significantly decrease the rates of endoscopic and clinical occurrence with the largest effect observed in anti-TNF agents.

In a landmark study, the timing of first ileocolonoscopy after surgery to detect endoscopic recurrence and optimal medical therapy to treat endoscopic recurrence was evaluated in the POCER [58]. The primary outcome of this multicenter, randomized trial was endoscopic recurrence at 18 months post-resection. Postoperative CD patients were randomized in a 2:1 fashion to receive colonoscopy at 6 months (active care) or no 6-month colonoscopy (standard care). All patients underwent colonoscopy at 18 months postoperatively. Patients were maintained on postoperative prophylaxis based on risk of recurrence. Patients were considered high risk if they were active smokers (any number of cigarettes) and had perforating disease or prior resection. Low-risk patients lacked these factors. All patients received metronidazole 400 mg twice daily for 3 months postoperatively. If not tolerated, dose was decreased to 200 mg twice daily or stopped. Patients at high risk for recurrence also received AZA 2 mg/kg/day or 6-MP 1.5 mg/kg/day within 1 month of surgery for 18 months. Patients intolerant to thiopurine were started on ADA (160/80/40 mg induction then 40 mg every 2 weeks) for 18 months. Medical therapy was “stepped up” if there was evidence of endoscopic recurrence (≥i2) at 6-month colonoscopy. Low-risk patients with 6-month endoscopic recurrence were started on thiopurine therapy. High-risk patients receiving thiopurine-added ADA induction and maintenance and those already receiving ADA maintenance were escalated to 40 mg weekly dosing. The authors found that the 18-month primary endpoint of endoscopic recurrence was significantly less in the active care arm than the standard care arm (49% vs. 67%, p = 0.03). Analyzing the immediate use of ADA compared to later ADA addition to thiopurine therapy at 6 months (in the high-risk cohort) demonstrated no significant difference in endoscopic recurrence at 18 months (immediate post-op commencement, 12/28, 48%; 6-month step-up, 20/33, 61%, p = 0.17). Thus, early endoscopy with escalation of medical therapy significantly alters the future rates of endoscopic disease. Furthermore, early endoscopic-guided anti-TNF initiation

appears as efficacious as immediate initiation postoperatively and may reduce costs and side effects. However, nearly half of patients within the active care arm still had endoscopic recurrence at 18 months post-resection, suggestive of a continued unmet need in the treatment of POR.

Practical Strategies for Treating Postoperative Recurrence

There are two emerging strategies to postoperative CD management. One strategy, in alignment with the POCER study methods, would be to stratify postoperative treatment based on risk of recurrence and treat high-risk patients (smokers, perforating disease, or prior CD resection) with thiopurine or anti-TNF if intolerant of thiopurines (Fig. 5.1). Patients should then undergo early (at 6–12 months) ileocolonoscopy with escalation of medical care for endoscopic (≥i2) recurrence. Untreated patients would be started on thiopurine therapy, and patients receiving thiopurines would be advanced to anti-TNF therapy or increased dosing of anti-TNF therapy.

The second strategy (and the authors' practice) is to start prophylactic treatment for high- and moderate-risk patients (Fig. 5.2). Those at low risk for recurrence would not be started on postoperative medical POR prophylaxis. Low-risk patients are those undergoing first CD-related surgery for short (<10 cm) stricture with long-standing CD (>10 years). Patients at moderate risk include those undergoing first CD-related surgery but with shorter disease duration (<10 years) with a longer affected bowel segment (>10 cm). Moderate-risk patients would receive thiopurine

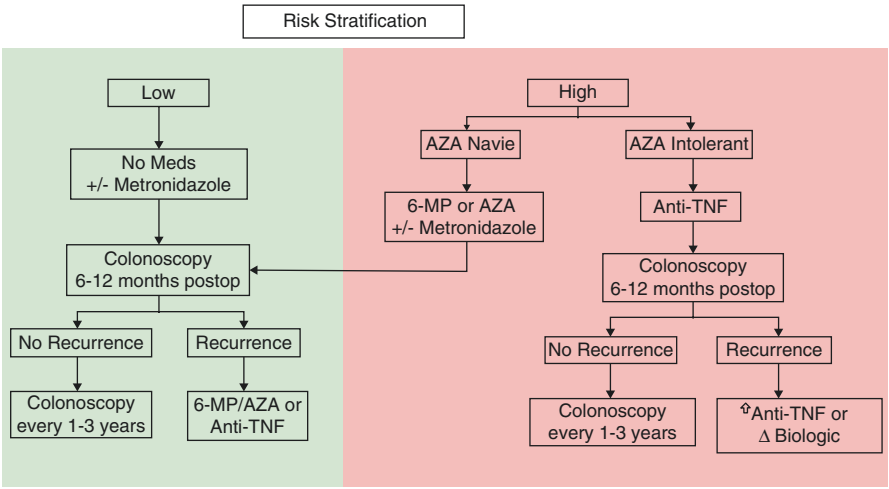

Fig. 5.1 "Watchful waiting" algorithm for management of postoperative Crohn's disease recurrence. High-risk patients include active smokers, those with perforating disease, or prior CD resection. Low risk includes all other patients

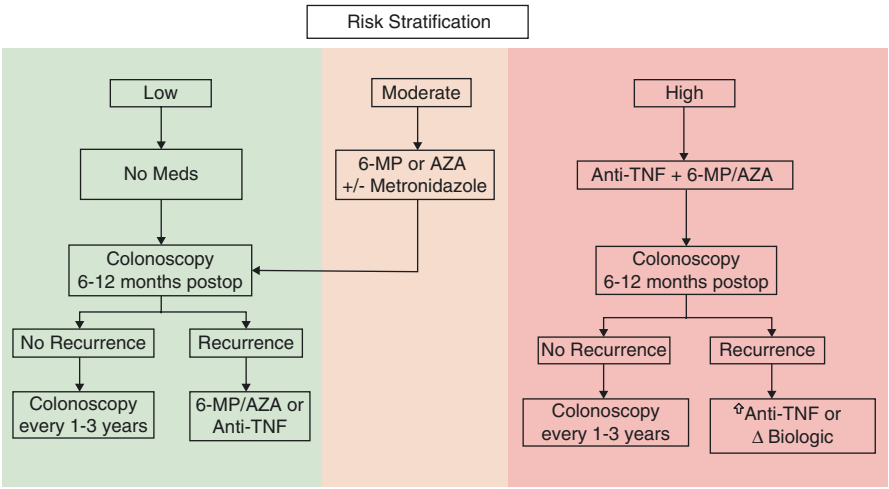

Fig. 5.2 Postoperative prophylaxis for all patients but low-risk paradigm for prevention of postoperative Crohn's disease recurrence. Low-risk patients are those undergoing first CD-related surgery for short (<10 cm) stricture with long-standing CD (>10 years). Patients at moderate risk include those undergoing first CD-related surgery but with shorter disease duration (<10 years) with a longer affected bowel segment (>10 cm). High-risk patients include perforating or penetrating disease, active smokers, and/or patients with prior intestinal resection

therapy immediately after surgery. If a patient can tolerate metronidazole, this is reasonable to combine with immunomodulator therapy given the increased benefit. High-risk patients include perforating or penetrating disease, active smokers, and/or patients with prior intestinal resection. Those at high risk would receive postoperative combination therapy with thiopurines and an anti-TNF agent.

All patients regardless of risk would undergo colonoscopy at 6–12 months with treatment escalation based on endoscopic findings of recurrence. Low-risk patients would be initiated on therapy, likely with an immunomodulator. Moderate-risk patients would be initiated on an anti-TNF agent with induction followed by maintenance dosing for anti-TNF-naïve patients. High-risk patients on postoperative combination therapy with evidence of recurrent disease should have medications optimized including drug and antibody levels with adjustments based on findings and/or consider switching to alternative anti-TNF agent. It should be noted that while commonly practiced, postoperative combination therapy with an anti-TNF agent and a thiopurine has not been formally studied in prevention of postoperative recurrence.

The timing of medication initiation in most clinical studies has generally been within 2–4 weeks of surgery. This time period allows for adequate identification and treatment of most postoperative infectious complications.

Comparing these two strategies—early postoperative medical prophylaxis and endoscopy-guided therapy—was studied by Ferrante and colleagues. The authors performed a randomized controlled trial of 63 CD patients randomized to either routine early postoperative weight-based AZA within 2 weeks of surgery ($n = 32$) or

endoscopic evaluation within 6–12 months of surgery and subsequent initiation of weight-based AZA in presence of endoscopic recurrence [59]. There was a nonsignificant, marginal benefit of routine postoperative medical prophylaxis in preventing both endoscopic (17/32 vs. 18/31; RR 0.91; 95% CI 0.59–1.42) and clinical (12/32 vs. 14/31; RR 0.83; 95% CI 0.46–1.50) recurrence compared to endoscopy-guided therapy, respectively. The American Gastroenterological Association clinical guidelines estimated that routine postoperative prophylaxis in a low-risk population (0–1 risk factor for recurrence) estimated that per 1000 patients treated with this strategy, there would be 34 fewer patients with clinical recurrence and 27 fewer patients with endoscopic recurrence [62]. In a high-risk patient population (>1 recurrence risk factor), routine medical prophylaxis may result in 85 fewer patients with clinical recurrence and 72 fewer episodes of endoscopic recurrence per 1000 patients treated. It should be noted the AGA guidelines judged this trial to be of low overall quality due to high risk of bias, significant difference in baseline prognostic factors such as smoking rates, high attrition rate (33%), and early trial termination due to slow recruitment (63/200 proposed patients). Consequently, there is currently little high-quality evidence to suggest routine postoperative medical prophylaxis compared to a watch-and-wait strategy.

The choice between the two approaches should be one based on practitioner comfort as well as shared decision-making with the patient with a balance of the risk of disease recurrence on an individual level, risk of medication side effects, as well as cost and convenience of medical and/or endoscopic therapy.

Future Research

Given the residual rates of recurrence even with aggressive postoperative medical management, clearly there still exists an opportunity for improvement in prevention and treatment of postoperative CD recurrence. Newer biologic agents such as the anti-interleukin-12/anti-interleukin-23 agent ustekinumab and anti-integrin agent vedolizumab may also prevent POR, but there are no data at the time of this publication, and future study is required. With an increasing understanding of the complex mechanistic pathways underlying Crohn's disease, potential mechanistic signatures may be on the horizon to inform clinicians of the optimal medical regimen for prevention of POR. Similarly, distinct molecular markers of disease recurrence with increased sensitivity and specificity may help in detection of POR. A validated risk score to predict risk of disease recurrence for an individual patient based on presurgical factors would help patients and providers choose the appropriate therapeutic approach postoperatively. New endoscopic scoring mechanisms are being explored to determine key endoscopic findings predictive of response and clinical outcomes. With the influx of biosimilar medications, data thus far in the routine treatment of CD points toward nearly equivalent efficacy with biosimilars; however, their efficacy in POR needs to be established. Similarly, the routine use of combination of anti-TNF agents with thiopurines in prevention of POR has not

been definitively established as superior to either agent alone. Thus, while significant inroads have been made in the understanding and treatment of postoperative CD recurrence, there are many avenues for further exploration to help address this frequent entity.

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Chapter 6
Biologics in Pregnancy and Breastfeeding

Jill K.J. Gaidos and Sunanda V. Kane

Introduction

Inflammatory bowel diseases, including ulcerative colitis and Crohn's disease, are commonly first diagnosed in the second and third decades of life [1]. As these are chronic inflammatory diseases, they typically require lifelong treatment, which means continuing medications throughout the childbearing years. The potential effect that medications will have on the developing fetus and the impact on pregnancy of the mother's underlying inflammatory bowel disease (IBD) are among some of the common concerns that female IBD patients have prior to conception. As pregnancy is exclusion criteria for most clinical trials of new therapeutic agents, determining the safety of a drug in pregnancy and with breastfeeding becomes based on clinical experience, typically with unintentional use at first and then with intentional use due to a lack of other effective therapies. In addition, this slow process gets restarted with each new therapy that becomes available.

Having IBD, even quiescent disease, is a risk factor for pregnancy complications, such as preterm premature rupture of membranes, preeclampsia, and venous thromboembolism [2–4], as well as for adverse pregnancy outcomes, such as preterm birth, small for gestational age infants, and stillbirth [5]. Active disease at the time of conception further increases the risk for preterm birth and spontaneous abortion (SA) [6, 7], while worsening disease activity during pregnancy leads to a higher risk

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Table 6.1 Outcomes definitions

Term	Definition
Adverse pregnancy outcomes	Spontaneous abortion/miscarriage
	Induced abortion
	Preterm birth (delivery <37 weeks of gestation)
	Small for gestational age (birth weight <10th percentile for gestational age)
	Stillbirth
	Ectopic pregnancy
Adverse fetal/neonatal outcomes	Congenital anomalies
	Low birth weight (<2500 g)
	Intrauterine growth restriction
	Newborn seizure
	Neonatal intensive care unit admission
	Infant mortality

for low birth weight, preterm birth, and stillbirth [8–13]. Preconception counseling about the importance of obtaining disease remission at least 3 months prior to conception as well as the importance of adherence to the appropriate medical treatment in order to maintain remission during pregnancy is paramount to optimizing pregnancy and neonatal outcomes (Table 6.1). This chapter will provide the most recent evidence regarding the safety of the currently available biologic medications, including anti-TNFα inhibitors, anti-integrin medications, and anti-IL-12/IL-23 agents, during pregnancy and with breastfeeding. The US Food and Drug Administration has implemented a revision to the medication labeling used to indicate safety in pregnancy and breastfeeding and is no longer using letters to indicate the pregnancy category (i.e., A, B, C, D, X) [14]. As such, we will not be referencing these previously used categories in this chapter.

Antitumor Necrosis Factor Agents

Tumor necrosis factor plays a major role in the development and continuation of inflammation in IBD. The antitumor necrosis factor α (anti-TNFα) agents are a group of monoclonal antibodies that inhibit the activity of TNFα, thus blocking the signaling that leads to inflammation. This group of medications includes infliximab (Remicade®, Janssen, Malvern PA), which is a chimeric mouse/human immunoglobulin (Ig) G1 monoclonal antibody approved for use in Crohn's disease and ulcerative colitis; adalimumab (Humira®, Abbott, Abbott Park, IL), which is also a fully human IgG1 monoclonal antibody approved for use in Crohn's disease and ulcerative colitis; certolizumab pegol (Cimzia®, UCB, Brussels, Belgium), which is a polyethylene glycol (PEG)ylated Fab' fragment of a humanized anti-TNFα monoclonal antibody approved in the United States for the treatment of Crohn's disease; and golimumab (Simponi®, Janssen, Malvern PA), which is also a fully human

IgG1 monoclonal antibody to TNFα approved for use in ulcerative colitis. As more recent studies have shown that earlier treatment with these agents leads to improved patient outcomes and prevents complications from their disease [15], the use of these agents is becoming more common in younger patients, including women of childbearing age.

Placental Transfer of Biologic Agents

Fetal immunity is achieved through the passive and active transfer of IgG from the maternal circulation to the fetal circulation [16]. Active transfer occurs at the surface of the syncytiotrophoblast placental layer through the selective binding of the Fc gamma portion of the maternal IgG antibody to the Fc receptor neonatal molecule which then transports the IgG antibody to the fetal circulation [17]. There is a continuous, linear increase in the active transport of IgG starting at approximately 13 weeks of gestation and continually progressing until delivery [18–20]. There is a preferential transport of IgG1 followed by IgG4, IgG3, and then IgG2, which is important as many of the new medications used to treat inflammatory bowel disease are IgG antibodies [21] (Table 6.2).

Anti-TNF agents with complete antibodies, including infliximab (IFX), adalimumab (ADA), and golimumab (GOL), are actively transported to the fetal circulation through the mechanism described above. As certolizumab pegol (CZP) is a fragmented Fc portion, it is only passively transferred from the maternal to fetal circulation.

Several studies have confirmed the placental transfer of IFX and ADA as evidenced by detectable drug levels in cord blood [22–28]. In a prospective study looking specifically at placental transfer of anti-TNF medications, Mahadevan et al. included 31 pregnant women with IBD (11 IFX, 10 ADA, and 10 CZP) and measured drug concentrations in the maternal serum, infant serum, and cord blood at the time of birth then monthly in the infant serum until the drug concentrations were no

Table 6.2 Current biologic agents, molecular structure, and safety

Medication	Molecular structure	Safety in pregnancy	Safety with breastfeeding
Infliximab	Anti-TNF, IgG1	Low risk	Compatible
Adalimumab	Anti-TNF, IgG1	Low risk	Compatible
Certolizumab pegol	Anti-TNF, Fab' fragment	Low risk, only passively transferred to the fetus	Compatible
Golimumab	Anti-TNF, IgG1	Low risk	Compatible
Natalizumab	Antihuman α4 integrin, IgG4	Discontinue 3 months prior to conception	Likely compatible, limited studies in humans
Vedolizumab	Antihuman α4β7 integrin, IgG4	Low risk	Likely compatible, limited studies in humans
Ustekinumab	Anti-IL-12/IL-23, IgG1	Limited studies in humans	Likely compatible, limited studies in humans

longer detectable [23]. At the time of birth, the median ratio of cord blood to maternal drug concentration for IFX was 160% (range 87–400%); for ADA, it was 179% (range 98–293%); and for CZP, it was 3.9% (range 1.5–24%). In this study, the ADA levels remained detectable in the infant serum for up to 11 weeks from birth, while the IFX was detectable for up to 7 months. More recently, a prospective multicenter study of 80 pregnant women with IBD exposed to anti-TNF medications, including 44 on IFX and 36 on ADA with 39 on concomitant thiopurines, measured maternal blood and cord blood drug levels at the time of birth as well as infant blood levels every 3 months until the drug concentrations were no longer detectable [26]. Similar to previous studies, the median cord blood drug concentration was more than the median maternal drug concentration at the time of birth for both medications (for IFX: 5.9 μg/mL (range 0.12–28.7) vs. 2.0 μg/mL (range 0–22.2); for ADA: 2.0 μg/mL (range 0–12.1) vs. 1.5 μg/mL (range 0–10.0)). At birth, the mean ratio of infant to mother drug concentration was 1.97 for IFX (95% CI 1.50–2.43) and 1.21 for ADA (95% CI 0.94–1.49). Notably, this study found a much longer time for drug clearance in the infants with the mean time for drug clearance of ADA of 4 months (95% CI 2.9–5.0) and 7.3 months for IFX (95% CI 6.2–8.3; $P < 0.0001$); however, the drugs remained detectable in some infants until 12 months of age. In all of the studies, the presence of detectable anti-TNF drug concentrations did not result in an increase in adverse pregnancy or fetal outcomes. However, while these drug concentrations are detectable, the infants are essentially immunosuppressed and should not be administered live vaccines until serum concentrations are no longer detectable. The previous recommendation was to avoid the rotavirus, oral polio virus, and bacille Calmette-Guerin (BCG) vaccines for the first 6 months [29, 30]; however, this time frame may need to be extended to the first 12 months of life, or the use of anti-TNF drug concentration testing may need to be implemented prior to administration of a live vaccine to an infant with intrauterine anti-TNF exposure.

Anti-TNFα Medications in Pregnancy

Infliximab

Few studies looking at pregnancy outcomes in women with IBD have limited their study cohorts to those only exposed to IFX. A study using data from an infliximab safety database included 96 pregnant women with autoimmune diseases (82 Crohn's disease, 1 UC, 8 rheumatoid arthritis (RA), 2 juvenile rheumatoid arthritis, 3 unknown) who were exposed to IFX (ranging from within 3 months prior to conception to exposure during the first trimester) [31]. The 96 pregnancies resulted in 64 (67%) live births, 14 (15%) SAs, and 18 (19%) elective abortions, which were reported to be similar to the expected rates for the general US population. Review of the FDA-mandated infliximab safety registry (TREAT) revealed 142 pregnancies in women exposed to IFX with 83.1% (118/142) live births, 92.4% (109/118) of

which were healthy without any congenital defects or adverse events compared to 90.7% (68/75) live births and 85.3% (58/68) of which were healthy with no congenital defects or adverse events in the IBD patients on other therapies [32]. An early retrospective chart review including ten women exposed to IFX during pregnancy reported live births of normal infants in all cases, three were born premature (<37 weeks gestation) and one had a low birth weight (<2500 g) [33]. In another case series of four women who continued IFX treatment during pregnancy, all delivered full-term, healthy infants, with detectable cord blood drug levels in 75% (3/4) and undetectable drug levels in one infant with the longest duration between last infusion, at gestational week (GW) 21, and delivery [28]. None of the children were noted to have an increased rate of infections, and all developed protective antibody levels at 6 months of age to the *Haemophilus influenzae* type B and pneumococcal vaccines.

Adalimumab

With respect to studies that only included ADA, there are several case reports of ADA use during preconception, and into the first trimester [34], several reports of ADA continued throughout pregnancy due to ongoing active IBD [35, 36] and a report of the use of ADA during pregnancy for worsening, steroid-refractory disease [37]. In each of these case reports, regardless of when treatment with ADA was initiated or how long into the pregnancy it was continued, all pregnancies resulted in the birth of a healthy infant without any developmental abnormalities at 6 months [35, 36], at 1 year [37], and at up to 2 years of observation [34]. In a prospective cohort study by the Organization of Teratology Information Specialists (OTIS), data presented in abstract form showed no increase in adverse fetal outcomes among women with RA treated with ADA compared to a cohort of women with RA not treated with ADA and compared to a cohort of healthy controls [38]. A recent analysis of adverse events data from the Adalimumab Pregnancy Exposure Registry (APER), which is a prospective observational cohort study conducted by OTIS, includes 15,132 patients with RA exposed to ADA and found no increase in the risk of SA or major birth defects in the ADA-exposed RA cohort compared to the unexposed RA cohort and the healthy controls [39].

Certolizumab Pegol

An initial case report of the use of CZP during pregnancy included a 22-year-old woman who received 11 injections preconception, 1 injection during the first trimester, and 1 injection in the third trimester due to active Crohn's disease [40]. The patient delivered a normal healthy infant with normal development as of 1 month of age. More recently, outcomes from 339 pregnancies (192 in women

with Crohn's disease, 118 in women with rheumatic disease) exposed to CZP were obtained through review of a large pharmaceutical safety database [41]. Of the 339 pregnancies (113 reported retrospectively and 226 reported prospectively), 254 (74.9%) resulted in live births, 52 (15.3%) miscarriages, 32 (9.4%) induced abortions, and 1 stillbirth. Of the 226 prospectively reported pregnancies, there were 182 (80.5%) live births, 21 (9.3%) miscarriages, 22 (9.7%) induced abortions, and 1 stillbirth. Overall, the authors found that there were some differences in outcomes by report source (i.e., prospective vs. retrospective reporting) with improved outcomes in the prospectively reported cohort, but overall there was no increase in the risk of adverse pregnancy or fetal outcomes with the use of CZP in pregnancy.

Golimumab

Using individual patient cases reported to the manufacturer, one study presented in abstract form has looked at the outcomes of 47 pregnancies among women with autoimmune diseases (30 RA, 1 psoriatic arthritis [PsA], 5 ankylosing spondylitis, 11 UC) treated with golimumab [42]. There were 26 (55.3%) live births, 13 (27.7%) SAs, 7 (14.9%) induced abortions, and 1 (2.1%) ectopic pregnancy. Methotrexate was taken concurrently in 12 pregnancies and was used in 4 of the 13 (30.8%) of the reported SAs and in the 1 case of reported congenital anomaly. Overall, however, the rate of SA was noted to be similar to the background rate.

Studies Including More Than One Anti-TNFα Agent

Most studies looking at pregnancy and neonatal outcomes following exposure to anti-TNF agents during pregnancy have not found any difference in the rates of adverse outcomes between those exposed to these medications compared to the women who are treated with alternative therapies [43–46]. In fact, one study reported improved pregnancy and neonatal outcomes with anti-TNF monotherapy (OR 0.57, 95% CI 0.41–0.79) and particularly with CZP use (OR 0.12, 95% CI 0.07–0.20, $P < 0.001$) [47]. To address the specific questions raised about the risks of adverse pregnancy and fetal outcomes with intrauterine anti-TNF exposure, the Multicenter National Prospective Study of Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) registry was created [48]. The study cohorts are divided into groups based on drug exposures and, at the time of initial data presentation, included 1052 women (337 unexposed; 265 in AZA/6MP; 102 in IFX, ADA, or CZP; 59 on combination) and found no increased risk for adverse pregnancy or fetal outcomes associated with use of thiopurines or anti-TNF agents; however, there was an increased rate of infections noted at 12 months in the infants who had been exposed to combination therapy in utero.

Several studies have found an increased risk for SA following anti-TNF exposure during pregnancy. Using the British Society for Rheumatology Biologics Register (BSRBR) to determine outcomes of 130 pregnancies in RA patients exposed to anti-TNF medications (including exposure to IFX, ADA, and etanercept) prior to or during pregnancy, the authors found a slightly, but not significantly, increased rate of SA in those exposed to anti-TNF medications at the time of conception; however, this rate was most pronounced in the cohort on concomitant methotrexate (MTX) or leflunomide (LEF) (33%) compared to the group exposed to anti-TNF without MTX or LEF (24%), to those exposed to anti-TNF medications prior to conception (17%), and to those in the TNF-naïve group (10%) [49]. Another retrospective database study including 86 pregnancies in women with autoimmune diseases who were counseled by the Israeli Teratology Information Service regarding exposure to anti-TNF medications (35 IFX, 25 etanercept, 23 ADA), 97.6% exposed only in the first trimester, found an increased rate of SA in the TNF-exposed group (10.8%) compared to the rate in a group of women who were not exposed to potentially teratogenic agents (2.9%), but not significantly increased compared to pregnancies in a disease-matched cohort (5.8%) [50]. Similarly, a recent study of pregnancy outcomes of women with IBD in Japan included 24 pregnancies with exposure to anti-TNF agents (23 IFX, 1 ADA), 7 pregnancies in women with thiopurine monotherapy, 10 pregnancies in women treated with combined IFX and thiopurines, and 31 pregnancies in nonexposed women and also found an increased rate of SA in the TNF-exposed groups (monotherapy and combination therapy groups) compared to the other non-TNF-exposed groups (17.7% vs. 0%, $P = 0.009$) [51]. In all three of these studies, there were no differences between the groups in fetal outcomes.

A prospective observational cohort study comparing adverse events reported to the European Network of Teratology Information Services (ENTIS) in 495 pregnancies in women with autoimmune diseases exposed to anti-TNF medications (including IFX, ADA, CZP, GOL, and ETA) in the first trimester to outcomes of 1532 pregnancies in women not exposed to anti-TNF agents but who had contacted ENTIS for other non-medication-related concerns found no increased risk of SA or stillbirth with TNF exposure but, however, did find a higher incidence of preterm birth (ORadj 1.69, 95% CI 1.1–2.5) [52]. In addition, the study found an increased risk of major birth defects in the TNF-exposed cohort compared to the nonexposed cohort (5.0 % vs. 1.5%, adjusted odds ratio [ORadj] 2.20, 95% CI 1.01–4.8); however, there was no distinct pattern of birth defects to suggest a drug-related effect.

With respect to risk factors associated with adverse pregnancy and neonatal outcomes, a retrospective study including 124 IBD patients with 133 pregnancies followed in Groupe d'Etude Thérapeutique des Affections due Tube Digestif (GETAID) centers with exposure to anti-TNF medications during pregnancy or less than 3 months prior to pregnancy showed no difference in the pregnancy or neonatal outcomes compared to a control group [46]. However, on multivariate analysis, the risk factors associated with adverse pregnancy outcomes included current smoking ($P = 0.004$), occurrence of a flare during pregnancy ($P = 0.006$), a stenotic Crohn's

phenotype ($P = 0.004$), and prior pregnancy complications ($P = 0.007$), while the only risk factor associated with newborn complications was having a disease duration of >10 years ($P = 0.007$). Prior exposure to anti-TNF therapy during pregnancy was not found to be a risk factor. Because of the lack of consistent evidence showing a risk for adverse pregnancy or neonatal outcomes, the use of anti-TNF medications during pregnancy has been deemed to be low risk in rheumatologic and gastroenterological expert recommendations [29, 30, 53, 54].

Anti-TNF Medications in Combination with Immunomodulators

Following the Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease (SONIC) trial, which showed improved remission rates with combination anti-TNF and thiopurine medications compared to treatment with either agent alone [55], as well as the recommendations for treating to target therapeutic endpoints in IBD, including treating with immunosuppressive therapy for patients with characteristics of more aggressive disease [15], more IBD patients are frequently on combination therapy. Several studies have included a cohort of women receiving anti-TNF medications in combination with thiopurines to compare the pregnancy and fetal outcomes with women on other treatment regimens. A subanalysis of a retrospective, multicenter trial found improved outcomes with combination therapy as evidence by a higher rate of adverse pregnancy and fetal outcomes, due to a higher rate of preterm delivery, in the anti-TNF monotherapy cohort compared to the combined anti-TNF and thiopurine cohort (60.9% vs. 39.1%, $P = 0.04$ and 16% vs. 0%, $P = 0.02$) [45]. In the previously mentioned PIANO registry, data from 2012 presented in abstract form included 1052 women enrolled with 337 unexposed, 265 on thiopurine monotherapy, 102 on anti-TNF therapy, and 59 on combination therapy and reported no increase in any complication associated with the use of anti-TNF medications; however, there was a significant increase in fetal infections at 12 months of age in the infants exposed to combination therapy compared to the infants in the unexposed group (RR 1.50, 1.08–2.09) [48]. Similarly, a recent prospective study including 80 pregnancies in women with IBD including 39 women on combination therapy found a greater than twofold increased risk for any infection in the first year of life for the infants with in utero exposure to combination therapy compared to those exposed to anti-TNF monotherapy (RR 2.7, 95% CI 1.09–6.78, $P = 0.02$) [26]. All of the noted infections had a benign course without adverse sequelae.

This possible increased risk of infection in the newborn needs to be weighed carefully against the need to continue combination therapy in the mother in order to maintain disease remission. As such, two studies have shown no increase in short-term relapse rates after transitioning from combination therapy to anti-TNF monotherapy [56, 57]; however, this needs to be completed early in the preconception stage in order to ensure continued disease remission at the time of conception [30].

Effect of Anti-TNFα Medications on Newborn Outcomes

Intrauterine anti-TNF exposure, particularly later in pregnancy, has raised concerns about an increased risk for infections in the infant as well as concerns about altering neonatal immune development. One case series of four newborns with intrauterine exposure to IFX, including in the third trimester (T3), reported severe neutropenia at birth in all of the infants, which returned to normal by 14 weeks of age [58]. This finding has not been replicated in other studies. Using the PIANO registry, Mahadevan et al. assessed outcomes related to anti-TNF exposure during T3, including 422 pregnant women exposed to biologics in the third trimester of pregnancy compared with 597 pregnant women unexposed to biologics in the third trimester (70 with exposure to an anti-TNF in the first and/or second trimester but discontinued prior to T3), and found no difference in the risk of preterm birth, risk of worsening disease activity in T3 or in the first 4 months postpartum, or an increased risk of infant infections in up to 12 months of follow-up [59]. Specifically looking at immune response following vaccination in infants with gestational exposure to anti-TNF agents, a recent prospective study of a subset of subjects from the PIANO registry, including ten infants exposed to IFX and two exposed to ADA, measured immunoglobulin levels and antibodies to tetanus and *Haemophilus influenzae* after vaccination and found five infants with low IgM levels, with unclear clinical significance, but an adequate vaccine response in 92% of the infants [60]. Other similar studies have confirmed an adequate immune response to vaccinations in infants with intrauterine anti-TNF exposure [22, 28].

Following a case report [61] and systematic review [62] that suggested intrauterine anti-TNF exposure leads to a VACTERL (includes vertebral defects, anal atresia or imperforate anus, cardiac abnormalities, tracheoesophageal fistula or tracheal atresia/stenosis, esophageal atresia, renal and/or radial abnormalities, preaxial limb abnormalities) congenital anomaly, a subsequent population database study evaluated this association and could not confirm an increased risk for congenital anomalies within the VACTERL spectrum [63]. Despite these few studies and the previously mentioned studies which found an increased risk of infection within the first year of life following intrauterine exposure to combined anti-TNF and immunomodulatory medications [26, 48], most studies of neonatal outcomes in pregnancy following intrauterine anti-TNF medication exposure have not found an increased risk of adverse fetal outcomes, particularly congenital malformations, compared to disease-matched cohorts or cohorts on immunomodulators [43–47, 50, 51, 64].

Several studies have investigated long-term outcomes following intrauterine anti-TNF exposure. A study of 25 children ages ≥12 months who were exposed to anti-TNF agents during gestation were all found to have normal growth and development except 1 child (a dizygotic twin, diagnosed with a mild delay at 6 months of age) [65]. Twenty (80%) of the children had at least one infection with 60% receiving antibiotics. Vaccinations were given according to the recommended protocol, including BCG within 1 week of birth in 15 of the children with intrauterine exposure to IFX, which resulted in large skin reactions in three of the children, but

no other complications. Cellular immunity was noted to be normal in all infants, and response to vaccination, which was evaluated in 15 of the children, was adequate. One of the most recent updates from the PIANO registry includes an assessment of developmental milestones using the Denver Developmental Score completed by the mother at 4, 9, and 12 months as well as by using the Ages and Stages Questionnaire at 1, 2, 3, and 4 years of age which showed that, in all areas of development, the infants exposed to thiopurines, anti-TNF agents, or combination therapy had similar or better achievement of milestones compared to the unexposed infants [66].

Duration of Anti-TNFα Medication Use in Pregnancy

Disease remission in the pregnant IBD patient is the driving factor regarding when to discontinue anti-TNF therapy during pregnancy. The current recommendations are to give the last IFX infusion at around 20 weeks of gestation or the last ADA injection around 24 weeks of gestation in those in disease remission; CZP may be safely continued throughout pregnancy [30]. The purpose of tailoring the dosing schedule is to maintain remission in the mother while minimizing exposure to the fetus. In one case-control study, 51 women in remission discontinued anti-TNF therapy before GW 25 which did not result in an increased rate of disease flare (5/51, 9.8%) compared to the rate of flare in the cohort who continued anti-TNF therapy beyond week 30 (5/32, 15.6%; $P = 0.14$) [25]. In another study of 31 pregnancies in 28 women, all with quiescent disease, 12/18 (71%) discontinued IFX before GW 30, and all women remained in remission, while all of the women on ADA discontinued treatment before GW 30 which resulted in a disease flare in 2/13 (15.3%) [24]. Both of these studies concluded that anti-TNF medications can be safely discontinued in the second trimester in women with quiescent disease.

The goal of discontinuing anti-TNF therapy in the second trimester is to limit drug exposure during the time of highest transmission of immunoglobulins from the mother to the fetus. Several studies have shown that timing of the last anti-TNF administration correlates with maternal serum and cord blood levels, however, not in a linear fashion. In a study looking at cord blood levels of IFX, ADA, and CZP, Mahadevan et al. noted that a longer duration of time from the last dose to delivery did not always correlate with lower cord blood drug concentrations [23]. For example, there were two infants with intrauterine ADA exposure, one last exposed 7 days prior to birth and the other 56 days prior to birth, yet they had similar cord blood drug concentrations at birth (6.17 and 6.01 μg/mL). Similarly, in two infants with intrauterine IFX exposure, cord blood drug levels at birth were 23.6 and 28.2 μg/mL despite the last dose in the first at 14 days prior to delivery and at 55 days prior to birth in the second. This variability is likely due to differences in maternal dose and interval, individual pharmacokinetics, as well as immaturity of the newborn reticuloendothelial systems. A similar variability in cord blood drug concentrations was also noted by Julsgaard et al. to which they concluded that it is “not possible to identify a gestational week to stop maternal anti-TNF treatment that would reliably

predict undetectable drug concentrations at birth." [26] However, despite the variability in cord blood drug concentrations, no studies have shown an increase in adverse neonatal outcomes that correlate with infant drug levels. Because of the persistence of these drug levels, it is imperative that all live vaccines be held for at least 6 months and possibly up to 1 year, in infants with a history of intrauterine anti-TNF exposure.

Anti-integrin Agents

Currently, there are two anti-integrin medications available for treatment of inflammatory bowel disease. Natalizumab (Tysabri®, Biogen Idec) is a humanized monoclonal IgG4 antibody against the α4 subunit of the α4β1 and α4β7 integrin molecules and is approved for the treatment of multiple sclerosis (MS) and Crohn's disease. Vedolizumab (Entyvio®, Takeda) is also a monoclonal IgG4 antibody that targets only the α4β7 integrin molecule, making the mechanism of action more specific to the gastrointestinal mucosa, approved for the treatment of ulcerative colitis and Crohn's disease.

Natalizumab

Studies of supratherapeutic doses of natalizumab (NAT) in animals have shown mixed outcomes, including no fetotoxic or teratogenic effects [67] to increased spontaneous abortion rate and hematologic effects including mild anemia and thrombocytopenia [68]. The current recommendations are for anyone considering conception to discontinue NAT 3 months prior to conception due to the role α4-integrins and their ligands play in mammalian development and due to the absence of data on pregnancy and fetal outcomes following intrauterine exposure to NAT. Several case reports of NAT exposure during pregnancy, including three women with MS, have all resulted in healthy, full-term infants, one of which was small for gestational age [69–71]. Several prospective studies of NAT exposure during pregnancy in 137 women with MS have not showed an increase in adverse pregnancy or fetal outcomes that could be attributed to NAT exposure [72, 73]. A study from the Tysabri (natalizumab) Pregnancy Exposure Registry (TPER), presented in abstract form, included 375 women with autoimmune diseases (368 with MS, 7 with Crohn's disease) who were exposed to NAT within 90 days of conception [74]. Of these pregnancies, there were 314 live births, 13 elective abortions, 34 spontaneous abortions, 1 stillbirth, and 11 ongoing pregnancies, and 10 women were lost to follow-up. The authors reported that in 28 pregnancies in 26 women, major and/or minor defects were observed, but no further details are provided. Overall, however, the study did not show any effect of NAT exposure on pregnancy outcomes.

Looking specifically at NAT exposure during the third trimester, a recent case series of 13 pregnancies in 12 women with severe MS who continued treatment with NAT throughout the pregnancies due to severe relapsing disease refractory to other therapies reported thrombocytopenia ($n = 6$) and anemia ($n = 8$) in 10 of the 13 infants, which resolved by approximately 4 months of age [75]. One infant was born small for gestational age with subsequent developmental delay at 1 year of age after the mother developed a catastrophic relapse which required intense treatment. At the time of delivery, another infant was noted to have ultrasound findings of a cystic formation in the brain, possibly due to an intracranial hemorrhage; however, as previously reported [76], this was no longer detectable at 12 weeks of age, and the child had no developmental delay as of 2 years of age. In a recent study from the PIANO registry, pregnancy outcomes following exposure to biologics in T3 included nine subjects who were exposed to NAT and found no differences in the outcomes between study groups [59]. A recent, large prospective observational study included 101 women with MS exposed to NAT during T1 and compared pregnancy and fetal outcomes to a disease-matched (DM) cohort not exposed to NAT and to a healthy control (HC) group [77]. There were higher rates of miscarriage (17.3% NAT exposed, 21.1% DM vs. 4.1% HC, $P = 0.0004$) and lower birth weights (3159 ± 478.9 grams NAT exposed, 3198.3 ± 515.3 g DM vs. 3436.7 ± 549.5 g in HC, P=0.001) in the NAT exposed and DM cohorts compared to HC, but there were no significant differences in the outcomes of the NAT exposed compared to the DM cohort. In addition, there were no differences in the rates of major malformations or premature births between all cohorts. These recent studies have not shown a correlation between NAT exposure in pregnancy and adverse pregnancy or fetal outcomes.

Vedolizumab

Due to its recent FDA approval, the data on the safety of vedolizumab (VDZ) use in pregnancy is limited to data from the VDZ clinical development program, which included 24 pregnancies in women exposed to VDZ, resulting in 11 (45.8%) live births, 2 premature, and 1 (4.16%) congenital anomaly 79 days after a single dose of VDZ in a healthy volunteer with prior pregnancies complications [78]. This descriptive abstract provides some insight into the pregnancy outcomes following exposure to VDZ; however, further studies are clearly needed.

Anti-IL-12/IL-23 Agents

Ustekinumab (UST) is a human monoclonal antibody that decreases cytokine activity by binding to the p40 subunit on both IL-12 and IL-23. It has completed clinical trials for the treatment of Crohn's disease and is projected to be FDA approved for this treatment indication later in 2016; however, it has been available for treatment

of psoriasis and psoriatic arthritis (PsA) for several years. As such, there is still little evidence on the safety of the use of UST in pregnancy; however, what little data that is available comes from animal studies and case reports in the dermatology literature.

Pregnancy outcomes in animal studies have been mixed. One study of another IL-12/IL-23 antibody used in pregnant monkeys resulted in masculinization of the female infants [79], while use of UST during pregnancy and nursing in macaques showed no adverse pregnancy or fetal outcomes [80]. Importantly, in this last study, the rates of spontaneous abortions were similar in the UST-exposed and UST-unexposed cohorts.

In humans, data on the safety of use in pregnancy is limited to unpublished data from clinical trials and from several case reports of UST use during pregnancy. As of June 2010, the unpublished data from the clinical trials for the use of UST for treatment of psoriasis included 42 exposures in pregnancy which resulted in 10 live births of normal infants, 2 live births with adverse events (no further details provided), 6 SAs, 8 elective abortions, and 16 unknown outcomes [81]. There has been only one case report of an adverse pregnancy outcome which occurred in a 35-year-old smoker with a 10-year history of psoriasis and two prior healthy pregnancies who was diagnosed with an unintentional pregnancy following her fifth UST injection [82]. Despite smoking cessation, she experienced a SA at GW 12. All other case reports of UST exposure prior to conception [83] and during pregnancy [84–86] have resulted in full-term, healthy infants with normal development at up to 16 months of follow-up [85].

The most current consensus statement regarding the use of UST in pregnancy acknowledges that the current evidence does not show an increased rate of adverse fetal outcomes with intrauterine exposure; however, given the limited amount of evidence available, UST should only be used during pregnancy when other treatment options which are compatible for use during pregnancy are not effective to control maternal disease [87]. Discussion regarding the possible risks and benefits of continuing therapy needs to occur on a case-by-case basis.

Breastfeeding While on Biologics

Anti-TNF Agents

Two early case reports of IFX use during breastfeeding reported undetectable drug levels in breast milk (samples obtained on three occasions in one study [22] and obtained daily for 30 days in the other [88]). Another study looking at the excretion of IFX into breast milk in three patients with Crohn's disease (one obtained 7 days after IFX infusion, one at 5 days after IFX infusion, and one at 43 days after IFX infusion) also reported undetectable levels in the breast milk of all three women [89]. More recent studies, however, have shown that anti-TNF drug levels are detectable in breast milk. In a similar study of three patients with Crohn's disease

who resumed treatment with IFX following delivery, breast milk samples were obtained daily for up to 8 days post-IFX infusion which showed detectable drug levels as early as 12 h post-infusion with a peak of 90–105 ng/mL on day 2–3 with serum levels during that same time were 18–64 μg/mL, which correlates to a level in breast milk of approximately 1/200th of the level in serum [90]. In a third case report of three women (two with Crohn's disease, one with UC) who continued on IFX postpartum, breast milk samples were obtained at the time of an infusion and daily for the next 5 days which showed a range in breast milk drug concentrations from only minimal amounts becoming detectable at day 2 post-infusion to a maximum drug concentration of 300 ng/mL at day 6 post-infusion [91]. All of the children were healthy with no adverse effects from IFX exposure in the breast milk. This study did not include the maternal serum drug concentrations for comparison; however, they did calculate that breastfed infants of mothers being treated with IFX are estimated to receive an IFX dose of approximately 0.045 mg/kg bodyweight/day, which is significantly less than the maternal dose.

Looking at ADA in breast milk, a case report of a 26-year-old woman with Crohn's disease who resumed ADA postpartum had serum and breast milk samples collected every 2 days for 8 days which showed a peak in the serum drug concentration of 4300 ng/mL at day 3 postinjection and a peak in the breast milk level at 31 ng/mL on day 6 postinjection, which corresponded to a level of less than 1/100 the serum level [92]. In a study case series of four patients, two receiving IFX and two receiving ADA, the IFX levels in breast milk were found to be 1/20th of the maternal serum level while the breast milk ADA levels were <1/1000th of the maternal serum levels [93]. In all cases, there were no adverse effects from the medications and no increase in infections or allergic reactions, and all were noted to have normal weight gain and normal development.

Only one study has measured levels of CZP in breast milk, obtained 4 hours postinjection, 3 days postinjection, and 6 days postinjection, and all breast milk samples had undetectable levels of CZP [23]. There is evidence of excretion of golimumab in the breast milk of cynomolgus macaques, but no human studies have yet been reported [94].

Multiple studies have shown that serum drug levels in the infants continue to trend down despite breastfeeding from mothers who continue to receive treatment with anti-TNF agents [22, 26]. This provides evidence that the orally absorbed drug does not result in therapeutic drug levels.

Anti-integrins

The natalizumab prescribing information indicates prior detection of NAT in human breast milk [95]. The vedolizumab prescribing information indicates prior detection of VDZ in the milk of lactating monkey, but no testing in human breast milk has been performed [96].

Ustekinumab

Animal studies have confirmed the presence of UST in the milk of lactating monkeys [80], which has been generalized to humans with the assumption that it is also excreted in human breast milk. Similar to anti-TNF agents, the absorption of UST through the GI tract is assumed to be minimal, with little to no therapeutic effect; however, that is not definitively known.

Summary and Patient Counseling

Women with IBD have an underlying increased risk for adverse pregnancy outcomes, which are further increased in the setting of active disease. Disease remission prior to conception as well as throughout pregnancy is the most important factor associated with good outcomes. Current available evidence suggests that the use of anti-TNF medications during pregnancy and with breastfeeding is likely safe; however, the use of combination anti-TNF and immunomodulatory therapy has been shown to increase the risk of newborn infections in the first year of life. Currently, there are limited data on the safety of anti-integrin medications and anti-IL-12/IL-23 therapies; however, given the molecular structure, they are likely actively transported to the fetal circulation during pregnancy. With the active transfer of these biologic medications to the fetus comes the risk of immunosuppression and the importance of avoiding live vaccines for the first 6 months of life and possibly up to 1 year or until the serum drug concentrations are no longer detectable in the child.

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Chapter 7
Concomitant Use of Immunosuppressive Therapy with Tumor Necrosis Factor (TNF) Antagonists in Inflammatory Bowel Disease

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Efficacy

TNF-Antagonists

The rationale for using concomitant immunosuppressive therapy with TNF-antagonists comes from the impact these agents have on antidrug antibody formation and drug concentrations, which in turn may influence treatment efficacy and outcomes [1–5]. Randomized controlled trials (RCTs) and observational data have supported this hypothesis [6], but the association between concomitant immunosuppressive use and treatment outcomes is less well established.

Comparative effectiveness RCTs have demonstrated that the combination of infliximab and azathioprine is more efficacious than infliximab monotherapy for both CD and UC [7, 8]. The combination of infliximab and methotrexate however has not been demonstrated to be more efficacious than infliximab monotherapy in CD [9] (Table 7.1).

At face value, these data would suggest that when using concomitant immunosuppressive therapy, providers should only use azathioprine, but several considerations need to be made when interpreting these results. First, COMMIT had no minimum disease activity requirement for entry which resulted in the recruitment of patients with a much milder disease course. Second, COMMIT used a high-dose steroid induction regimen in both treatment arms. Given the known treatment benefits of concomitant steroid use and impact of triple induction (steroids + azathioprine + infliximab)

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Table 7.1 Comparative effectiveness randomized controlled trials of infliximab monotherapy versus combination therapy with an immunosuppressive agent

	Crohn's disease				Ulcerative colitis	
	SONIC [7]		COMMIT [9]		UC-SUCCESS [8]	
	IFX	IFX + AZA	IFX	IFX + MTX	IFX	IFX + AZA
Clinical remission (%)	44	57	78	76	22	40
Mucosal healing (%)	30	44	–	–	55	63
Antidrug antibody (%)	14.6	0.9	20.4	4.0	19.0	3.0
IFX concentration	1.6 μg/mL	3.5 μg/mL	3.8 μg/mL	6.4 μg/mL	–	–

IFX infliximab, *AZA* azathioprine, *MTX* methotrexate

Table 7.2 Stratified analysis of randomized controlled trials for TNF-antagonists according to baseline immunosuppressive use

		Antidrug antibody		Clinical remission	
	Agent	TNF-antagonist monotherapy	Combination therapy	TNF-antagonist monotherapy	Combination therapy
PRECISE 2	CTZ	12%	2%	64%	61%
CLASSIC II	ADA	3.8%	0	45%	48%
PURSUIT	GOL	3.8%	1.1%	50%	44%

IFX infliximab, *CTZ* certolizumab, *ADA* adalimumab, *GOL* golimumab

on treatment success [10], the use of high-dose steroids and recruitment of a population with a milder disease course and increased propensity to respond to therapy may have obscured the clinical benefit of concomitant methotrexate therapy [11, 12]. The measurable impact of methotrexate on antidrug antibodies and infliximab drug concentrations would suggest that a therapeutic benefit does exist when using this immunosuppressive agent.

No comparative effectiveness studies are currently available comparing TNF-antagonist monotherapy versus TNF-antagonist combination therapy for other TNF-antagonists such as adalimumab, certolizumab, and golimumab. In post hoc analyses, when stratifying RCTs by baseline immunosuppressive use, the concomitant use of an immunosuppressive appears to impact the pharmacokinetics of these TNF-antagonists, but this did not directly translate to improved treatment outcomes within these trials [6, 13–18] (Table 7.2).

Pooled analyses of RCTs and observational data for adalimumab have suggested that the use of concomitant immunosuppressive therapy results in improved rates of remission at 12 weeks compared to adalimumab monotherapy (OR 0.78, 95% 0.64–0.95). Although this would suggest that a clinical benefit may exist, this improved efficacy at 12 weeks did not translate to improved rates of remission at 52 weeks within this meta-analysis (OR 1.08, 95% CI 0.87–1.33) [19]. A second meta-analysis that pooled patient level data from three TNF-antagonist RCTs in CD (infliximab, adalimumab, certolizumab) similarly observed that no clinical benefit was present

when adding an immunosuppressive agent to adalimumab [20]. Within this second meta-analysis, an interesting observation was that the use of concomitant immunosuppressive therapy was associated with a trend toward improved rates of remission at 6 months for infliximab (OR 1.73, 95% CI 0.97–3.07), but not adalimumab (OR 0.88, 95% CI 0.58–1.35) or certolizumab (OR 0.93, 95% CI 0.65–1.34) [20]. When interpreting these data, we must remember that a significant proportion of the adalimumab and certolizumab patients enrolled had failed infliximab therapy, and thus the use of concomitant immunosuppressive agents represents the continuation of an immunosuppressive agent when switching TNF-antagonists as opposed to starting an immunosuppressive agent de novo in these patients. Furthermore, this meta-analysis excluded patients naïve to immunosuppressive therapy and thus represents a step-up approach to combination therapy as opposed to the more efficacious top-down approach. These variations in observations help to highlight the fact that the timing of adding an immunosuppressive agent to TNF-antagonist is as important as the potential impact it has on TNF-antagonist pharmacokinetics. This concept is further supported by two RCTs showing that early combined immunosuppression is superior to traditional step-up algorithms.

The "top-down" trial is a randomized trial where 133 patients were randomized to either early combined immunosuppression with infliximab (ECI; $n = 67$) or conventional management (CM; $n = 66$) where patients received steroids followed in sequence by azathioprine and infliximab [21]. At 26 weeks, a higher proportion of patients in the ECI group were in steroid-free clinical remission without surgical resection as compared to the CM group (60% vs. 35.9%, $p = 0.006$), and this difference continued through week 52 (61.5% vs. 42.2%, $p = 0.0278$). At week 104, the rates of mucosal healing (absence of ulcers) were significantly higher in the ECI group as compared to the CM group (73% vs. 30.4%, $p = 0.0028$). Notably, the rates of serious adverse events were similar between both groups (30.8% vs. 25.3%, $p = 1.0$). This study was the first to demonstrate that the early use of combined immunosuppressive therapy impacted treatment outcomes. Although they were able to demonstrate statistically significant differences in outcomes that correlate with long-term disease-related complications (i.e., mucosal healing), the small size of the study precludes its ability to directly quantify the impact on outcomes of interest such as hospitalization, surgery, and overall complications.

The REACT trial is a cluster randomization trial in which community practices in Canada ($n = 34$) and Belgium ($n = 5$) were randomly assigned in a 1:1 ratio to either ECI with a TNF-antagonist (ECI; $n = 21$ centers, $n = 1084$ patients) or CM where immunosuppression and TNF-antagonist use were determined by the primary provider (CM; $n = 18$ centers, $n = 898$ patients) [22]. The primary outcome (remission as defined by a Harvey-Bradshaw score (HBS) ≤ 4 in the absence of steroids) was achieved in a similar proportion of the ECI and CM groups at 12 (66% vs. 62%, $p = 0.65$) and 24 months (73% vs. 65%, $p = 0.35$). Within this study, however, a significantly higher proportion of patients in the ECI group received combination immunosuppressive/TNF-antagonist combination therapy at 12 months (15.1% vs. 6.5%, $p < 0.001$) and 24 months (19.7% vs. 9.6%, $p < 0.001$), and the ECI group had highly significant and clinically important reductions in the rates of

complications (HR 0.74, 95% CI 0.62–0.89) and surgeries (HR 0.68, 95% CI 0.49–0.95) and the combined outcome of hospitalizations, complications, and surgeries (HR 0.74, 95% CI 0.62–0.87). Within this trial, an important point to be noted is that they followed a treat-to-target algorithm where adjustments in therapy were made if patients had not achieved clinical remission at 3–6-month intervals. This approach may have factored into the overall impact of ECI and suggests that the timing of concomitant immunosuppressive therapy and the manner in which we monitor and adjust dosing are equally important.

In aggregate, direct comparative effectiveness studies demonstrate that the concomitant use of an immunosuppressive agent improves treatment outcomes and reduces disease-related complications in IBD. The optimal approach to using concomitant immunosuppressive therapy with TNF-antagonists is early in the disease course with frequent monitoring and adjustments in dosing or therapies when clinical remission has not been achieved. The ideal choice of which immunosuppressive agent to use appears to be azathioprine (6-mercaptupurine can likely be used as well) based on efficacy, but providers will need to take into consideration differences in trial characteristics and variations in outcomes across trials. Consideration for immunosuppressive safety will therefore likely drive the decision as to which immunosuppressive agent is chosen on an individualized basis.

Safety

When taking into consideration the optimal use of a therapeutic agent or the combination of therapies, we must take into consideration the impact safety will have on patient outcomes and adherence. Specifically, we must understand the safety profile when immunosuppressive agents are added or continued alongside biologic agents and the populations at greater risk for adverse events when using concomitant immunosuppressive therapy. Two of the most notable safety concerns with concomitant immunosuppressive therapy are serious infections and malignancy.

Serious Infections

Treatment-related serious infections can be broadly categorized as those resulting in the interruption or discontinuation of therapy, hospitalization, or death. Although randomized controlled trials have not demonstrated an increased risk for serious infections with the addition of immunosuppressive agents to biologics, population-based studies have observed an increased incremental risk, with the majority of this risk being attributed to the concomitant use of steroids [23–27]. Any prednisone use can increase the risk of serious infections, but doses higher than 20 mg of prednisone for 2 or more weeks are associated with the most significant risk for serious infections, and this risk persists for up to 90 days after exposure [28, 29]. This risk can be further augmented in certain patients who are already at an increased baseline risk for treatment-related serious infections. Two subgroups of particular importance are

the elderly (≥65 years) and those on chronic narcotics [6, 28, 30, 31]. The exact mechanism through which narcotics increase the risk for serious infections and mortality is unclear, and this may simply serve as a proxy for more complicated disease, disease-related complications, or disease severity, the latter also being independently associated with an increased risk for infectious complications [28, 32–35].

Two important opportunistic infections that should be specifically considered when starting a concomitant immunosuppressive agent are hepatitis B and *Clostridium difficile* (*C. diff*). The use of immunosuppressive medications increases the risk for hepatitis B reactivation, with the greatest risk being seen in patients who are hepatitis B DNA and/or surface antigen positive being treated with long-term combination therapy with TNF-antagonists [36–38]. The occurrence of *C. diff* in IBD is associated with higher morbidity and mortality as compared to the general population [39, 40], and the use of immunosuppressive therapy, but not biologics (TNF-antagonists), has been associated with an increased risk of developing *C. diff* [36].

Malignancy

One of the most important considerations to be made when using concomitant immunosuppressive therapy in IBD is the potential increased risk for developing malignancy [41]. IBD patients are at an increased risk for malignancy at baseline [42–45], and the use of TNF-antagonists does not appear to increase this risk overall [46]. The concomitant use of immunosuppressive therapy, however, is clearly linked to an increased risk for malignancy and, in particular, an increased risk for lymphoma [47–49]. This increased risk for lymphoma is seen with concomitant thiopurine use, and the two populations at greatest risk for lymphoma development are the elderly (≥65 years) and young (≤35 years) males who are at a particular increased risk for the development of a fatal lymphoma subtype, hepatosplenic T-cell lymphoma (HSTCL). In both subgroups, the risk of lymphoma is duration dependent, with the greatest risk being seen after 2 years of use [49–54]. Another important malignancy linked to thiopurine use is skin cancer. Several studies have now demonstrated that thiopurines increase the risk for nonmelanoma skin cancer (NMSC) development, and this increased risk is nearly doubled when used in combination with a TNF-antagonist [48, 55, 56]. The risk of melanoma, however, appears to be increased by the use of TNF-antagonists but not immunosuppressive agents, and this risk is potentially higher among patients receiving long-term TNF-antagonist therapy [56].

Opportunities to Optimize the Use of Concomitant Immunosuppressive Therapy

When combining safety and efficacy data for the use of concomitant immunosuppressive therapy, several opportunities arise to optimize the personalization of these treatment decisions. (Fig. 7.1) Based on prior RAND appropriateness panels, systematic reviews, and our review of the literature, the use of concomitant immunosuppressive

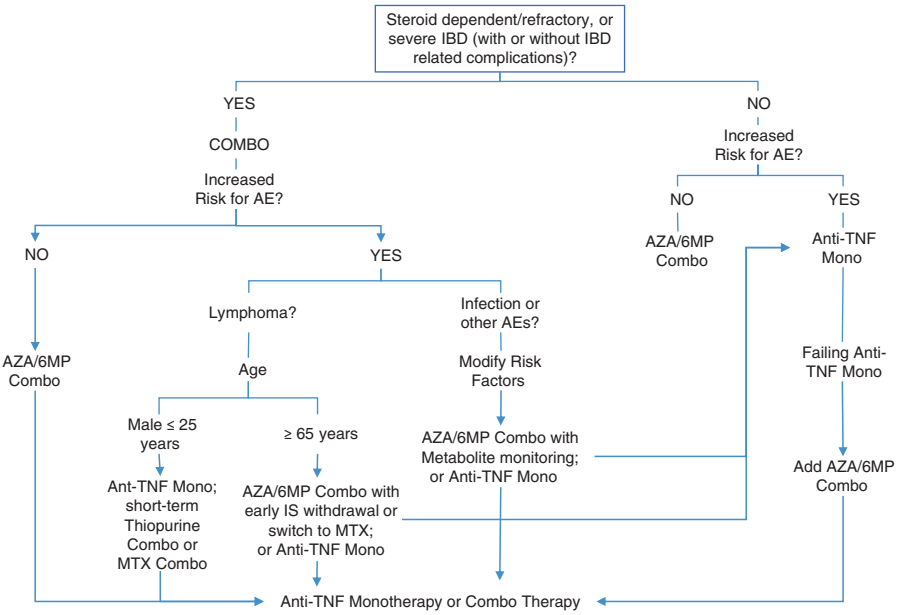

Fig. 7.1 Considerations when determining whether to use a concomitant immunosuppressive agent with TNF-antagonists. *IBD* inflammatory bowel disease, *AE* adverse event, *AZA* azathioprine, *6MP* 6-mercaptopurine, *anti-TNF* tumor necrosis factor antagonist, *MTX* methotrexate, *IS* immunosuppressive

therapy as a general rule of thumb appears to be most appropriate for IBD patients with extensive disease or those at risk for disease-related complications (i.e., steroid dependent or refractory) [6, 18, 57]. Among these individuals, the decision to personalize the use of concomitant immunosuppressive therapy can be made through an assessment of safety and long-term risks. In young males at risk for HSTCL, short-term use of concomitant thiopurines, TNF-antagonist monotherapy, or the use of methotrexate as the concomitant immunosuppressive agent may be most appropriate given the fatal nature of this lymphoma. In the elderly or individuals at risk for lymphoma with extended use of thiopurines, TNF-antagonist monotherapy, discontinuation of the thiopurine after 1–2 years of use, or switching to methotrexate may be reasonable options. The risk of malignancy in patients using thiopurines rises exponentially after 2 years of use [50, 58], and the risk of malignancy in patients discontinuing thiopurines appears to return to the baseline risk seen in patients without prior exposure [58]. Thus, withdrawing the thiopurine after 2 years of use can be considered, particularly in patients at low risk for relapse upon immunosuppressive withdrawal [18] (Table 7.3). This approach is however associated with reductions in TNF-antagonist drug concentrations and the development of antidrug antibodies, so patients should be followed up closely to optimize TNF-antagonist dosing as needed [59–62].

In individuals at an increased risk for serious infections or other thiopurine-related adverse events, opportunities to optimize the use of concomitant immunosuppressive

Table 7.3 Factors associated with disease relapse after stopping an immunosuppressive agent

Extensive disease or elevated inflammatory markers (CRP, platelet count, white blood count)
Evidence of mucosal activity on endoscopy
Short duration in remission prior to stopping
Short duration of steroid-free remission

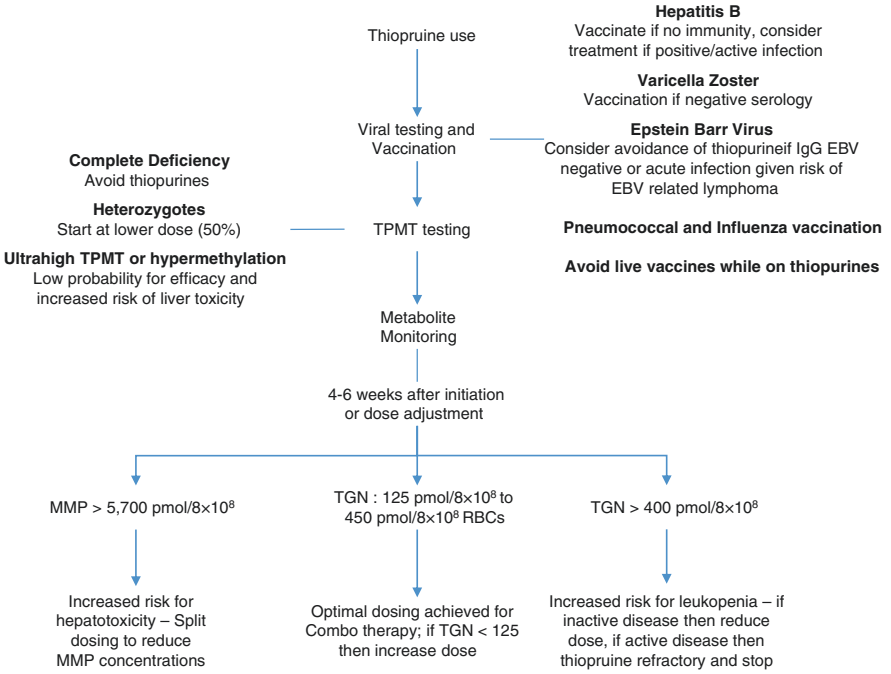

Fig. 7.2 Clinical algorithm to monitor concomitant immunosuppressive use and optimize effectiveness

therapy can be taken through modifying risk factors and thiopurine metabolite assessments [63–67] (Fig. 7.2). The traditional therapeutic efficacy window for thiopurine monotherapy is a thioguanine (TGN) level of between 235 pmol/8 × 10^8 and 450 pmol/8 × 10^8 RBCs. When using thiopurines as concomitant immunosuppressive agents, however, the therapeutic efficacy window for reducing antidrug antibodies may be lower (125 pmol/8 × 10^8 RBCs) [68–70]. A crude measure of TGN levels is peripheral RBC mean corpuscular volume (MCV) [71]. In a post hoc analysis of SONIC, patients who had achieved a mean increase in MCV of 7 were more likely to be in steroid-free remission, achieve mucosal healing, and obtain an infliximab concentration of >3, as compared to those who hadn't achieved a delta change in MCV of 7 or more. As patients will need regular blood test monitoring while on thiopurines, following peripheral MCV measurements could serve as a reliable interim surrogate for achieving optimal thiopurine concentrations.

Future Considerations

We have summarized the current evidence available to guide concomitant immunosuppressive use with TNF-antagonists, but several questions remain. With the advent of immune pathway-specific biologics, consideration can be given to using a second biologic in place of the immunosuppressive agent to achieve optimal clinical outcomes [72]. Another important concept under evaluation is the personalization of treatment decisions when using concomitant immunosuppressive agents based on an individual patient's risk profile for developing complications. As not all IBD patients will progress on to disease-related complications or adverse events, the blanket use of concomitant immunosuppressive therapy may be unnecessary in certain subgroups. A web-based program linking a video decision aid about the benefits and risks of Crohn's therapy to a personalized decision-making tool which presents a prediction of disease severity based on patient demographics, disease characteristics, genetic variables, and serological markers has now been developed. Providers are able to input these data in the program which then graphically depict a patient's individual risk for disease-related complications. This web-based patient communication tool has now been validated in both adult and pediatric Crohn's disease patients, and the impact of this tool on provider and patient decisions is currently under investigation [73, 74].

Summary

In summary, the combination of TNF-antagonists with immunosuppressive agents is clearly superior to TNF-antagonist monotherapy for improving treatment response and long-term outcomes. The optimal timing of using combined immunosuppressive therapy is early in the disease course prior to the development of disease-related complications. When using concomitant immunosuppressive therapy, opportunities exist to personalize treatment decisions and mitigate treatment-related risks through appropriate disease and drug monitoring. In a subset of patients, TNF-antagonist monotherapy may be appropriate, but providers will need to approach this decision with caution to ensure loss of response and immunogenicity do not occur. As new biologics and small molecules are developed, comparative effectiveness studies will be needed to understand if these new agents should be used as monotherapy or in combination with currently available biologics or immunosuppressives. When guiding patients through this decision-making process, a combined approach of optimizing efficacy and minimizing safety concerns should be taken through a personalized approach. We have provided a summary outline for consideration, but the decision will ultimately need to be personalized based on patient and provider preferences.

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Chapter 8
Therapeutic Drug Monitoring of Biologic Agents

Frank I. Scott and Mark T. Osterman

Crohn's disease (CD) and ulcerative colitis (UC) represent the two primary forms of inflammatory bowel disease (IBD). CD is a transmural inflammatory process that can involve any component of the alimentary tract, whereas UC is confined to the mucosal lining of the colon in the vast majority of individuals. Historically, therapies for moderate-to-severe CD and UC have included immunosuppressive therapies such as glucocorticoids or thiopurines [1, 2].

With the approval by the US Federal Drug Administration (FDA) of the first monoclonal antibody directed against tumor necrosis factor-α (anti-TNF), infliximab, for the treatment of CD in August, 1998, the treatment landscape of moderate-to-severe IBD was permanently altered. In initial clinical trials, infliximab induced clinical remission in 33% of patients, and 41% demonstrated a clinical response by 12 weeks [3]. Subsequent studies demonstrated clear efficacy in maintenance of remission in CD, which was followed by similar estimates of induction and maintenance of response and remission in UC [4, 5]. Further research has demonstrated that the clinical impact of these medications is even greater when combined with thiopurines, such as azathioprine or 6-mercaptopurine (6MP) [6, 7].

Several subsequent anti-TNF therapies have been approved for IBD. Modifying the chimeric IgG structure of infliximab, adalimumab and golimumab are fully human IgG molecules in an injectable format [8, 9]. Adalimumab is FDA approved for both CD and UC, while golimumab has been FDA approved for UC. Certolizumab

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pegol, a humanized injectable anti-TNF, is a pegylated Fab' fragment and has demonstrated efficacy in inducing and maintaining remission in CD [10, 11].

In addition to the anti-TNFs, a new class of biologics inhibiting leukocyte trafficking has also been approved for the management of IBD. Natalizumab, a monoclonal antibody directed against the alpha-4 integrin, was the first of these agents and is FDA approved for both CD and multiple sclerosis [12]. Widespread utilization of natalizumab in CD has been limited largely due to its known association with progressive multifocal leukoencephalopathy (PML) [13]. Vedolizumab, a biologic therapy targeting the alpha-4 beta-7 heterodimer, lending this compound gut-specific inhibition of leukocyte trafficking, is approved for both CD and UC and has not been associated with an increased risk of PML [14].

The Clinical Impact of Immunogenicity and Pharmacokinetics of Biologic Therapies in IBD

While both anti-TNFs and anti-integrins have demonstrated clear benefit in inducing and maintaining remission in CD and UC, it was recognized early on that these compounds were potentially immunogenic, likely secondary to their large amino acid-based structure [15]. In the ACCENT I trial, one of the first clinical trials of maintenance infliximab in CD, 28% of individuals had detectable antibodies to the drug if they had received only one dose of the drug; only 9% of those maintained on 5 mg/kg of the drug had developed antibodies at week 54 [4]. While the fully human structure of adalimumab was designed in part to reduce such immunogenicity, phase 3 trials of this agent also demonstrated immunogenicity, with 2.6% of individuals in the CLASSIC II maintenance trial in CD and 2.9% in the ULTRA maintenance trials in UC developing antibodies to the drug [16, 17]. Antibodies against certolizumab pegol were appreciated in up to 17.7% of individuals in clinical trials as well [11, 18]. The binding sites, or epitopes, of these anti-drug antibodies can be highly variable, either interfering directly with TNF-α binding or, alternatively, binding to other epitopes on the drug, thereby hastening their metabolism [19]. Interestingly, in a study assessing antibodies to infliximab (ATIs) and their binding sites by Ben-Horin and colleagues, antibodies directed against the Fab' fragment of the drug were more common, while global antibody concentrations were more closely correlated with an impact on clinical loss of response to the drug [19]. Similar antibody formation rates have been appreciated with newer anti-integrin monoclonal antibodies, e.g., 3.7% of individuals receiving vedolizumab in clinical trials in UC had detectable antibodies to the drug at some point during the 1-year follow-up period [20].

With the growing recognition of biologic immunogenicity, researchers also began to assess the clinical impact of anti-drug antibodies. It has long been recognized that a large percentage of individuals who initially respond to biologic therapies eventually lose this response, with antibody formation being one of the hypothesized mechanisms. In two early clinical trials of infliximab given episodically, or on a nonscheduled basis only as needed, the duration of response was

significantly shorter in those who had detectable ATIs compared to those that did not [21, 22]. The impact of anti-drug antibodies has not been as profound in early clinical trials of scheduled dosing, however. In the original ACCENT I trial of infliximab in CD, an association between maintenance of clinical response and the presence of antibodies was not appreciated [4]. Similarly, in a retrospective cohort of 105 CD patients receiving infliximab, the presence of antibodies was not associated with decreased duration of remission, C-reactive protein (CRP) levels, or endoscopic improvement [23]. In a study of scheduled dosing in UC by Seow and colleagues, ATI status was not associated with clinical response, although inconclusive levels (meaning that drug was present which prevented antibodies to be measured with conventional enzyme-linked immunosorbent assays [ELISAs]) were associated with improved mucosal healing, clinical responses, and reduced rates of colonic resection in those with an ATI-inconclusive result [24].

The clinical impact of antibodies to adalimumab and certolizumab pegol had also been assessed retrospectively, with conflicting results. In an observational study by Karmiris and colleagues, there was no association between the presence of anti-adalimumab antibodies and short-term response rates, although positive antibodies were associated with lower adalimumab serum levels at 24 weeks [25]. In both the PRECISE-2 and WELCOME trials, the presence of antibodies directed against certolizumab pegol was also not associated with worse clinical outcomes [18, 26]. However, another smaller cohort study using a novel homogenous mobility shift assay did appreciate an association between detectable antibodies and elevated serum inflammatory markers and Crohn's Disease Activity Index (CDAI) [27]. Interestingly, antibodies were present in 35% of patients of this cohort, demonstrating the potential influence that measurement techniques may have on the interpretation and assessment of the impact of antibodies directed against biologic therapies.

Anti-drug antibodies are also associated with an increased risk of adverse events related to biologic therapy. Specifically, several studies have appreciated an increased risk of infusion reactions with infliximab in the presence of antibodies to the drug [5, 21, 23, 24]. These reactions can range from headache or nausea and vomiting to fever, rigors, or even shortness of breath or anaphylactoid reactions. This increased risk has been appreciated in both CD and UC.

Pharmacokinetics and the Clinical Impact of Drug Levels

Serum concentrations of biologic therapies correlate strongly with the time from the last dose, with peaks shortly after a dose is administered, followed by subsequent declines in levels. These drug concentrations are associated with the dose administered, although there do appear to be differences between agents. For example, infliximab, which is administered intravenously, leads to much higher peaks in drug levels than the subcutaneously administered anti-TNF agents. Also, the median half-life of subcutaneous agents may be longer than that of infliximab [28]. Breakdown and clearance of these agents likely involve several mechanisms,

including internalization and phagocytosis with lysosomal degradation or endocytosis and catabolism by the reticuloendothelial system [29]. The rate of degradation is thought to be hastened by binding of anti-drug antibodies.

The importance of maintaining adequate drug levels was assessed in several clinical trials for anti-TNF therapies, though interpretation of these results is often challenging [30]. One primary concern is the early use of clinically oriented, and also potentially subjective, outcome measures such as the CDAI. Another potential pitfall is the type of assay employed to measure drug levels; for instance, conventional ELISAs attempting to measure anti-drug antibodies are unable to do so in the presence of drug. Interpretation of studies that incorporated nonscheduled dosing or alternative dosing regimens from those that are the standard of care now, or did not carefully quantify the impact of dose-modification that may have been allowed in the study, also makes drug level interpretation challenging. Non-standardized timing of drug level measurement has been problematic as well.

Taking these caveats into consideration, several earlier clinical trials did attempt to correlate the impact of infliximab drug levels with clinical response. In early trials of episodic dosing, infliximab serum concentrations >12 μg/mL at 4 weeks after an infusion were associated with a longer duration of response when compared to levels <12 μg/mL (median 81.5 days vs. 68.5 days, respectively) [21], while another study of episodic dosing appreciated higher rates of endoscopic healing and lower inflammatory markers such as CRP with increasing infliximab levels [23]. Similar results have been appreciated in studies involving scheduled dosing as well. In a study examining discontinuation of thiopurine therapy in those also receiving scheduled infliximab and in clinical remission for 6 months or longer, higher infliximab levels were correlated with lower CDAI, lower CRP, and, when comparing levels ≤2.23 μg/mL to >2.23 μg/mL, a higher odds of requiring dose escalation (odds ratio (OR), 3.99 [95% CI, 1.53–10.11) [31]. In patients with UC, subgroup analyses of ACT 1 and 2 demonstrated that higher infliximab levels were associated with increased rates of mucosal healing and clinical response to infliximab [32]. Seow and colleagues noted that in a retrospective cohort of 115 patients receiving infliximab, rates of endoscopic improvement and clinical symptom reduction were greater in individuals with detectable levels of infliximab compared to those with undetectable levels [24]. Undetectable infliximab levels were also associated with a ninefold increased probability of subsequent colectomy in this study. Several large clinical trials in CD support the role of infliximab level monitoring as well. In a post hoc analysis of data from the ACCENT 1 trial, median drug concentration was associated with clinical response as follows: in patients with clinical response, median drug concentration was 12.9 compared to 8.8 during induction at week 6 and 4.6 compared to 1.9 at week 14 [33]. In fact, a serum infliximab concentration >3.5 μg/mL at week 14 was associated with a 3.5-fold increased odds of clinical response (95% CI 1.1–11.4). In the SONIC trials, serum infliximab levels >3 μg/mL at week 30 were associated with increased rates of mucosal healing at week 26 (OR 3.34, 95% CI 1.53–7.28) as well as corticosteroid-free clinical remission at week 50 (OR 3.20, 95% CI 1.38–7.42) [34].

Recent observational data support the association between drug levels of infliximab or adalimumab and rates of mucosal healing. In a cross-sectional study of 145

patients assessing the association between drug levels of infliximab and adalimumab and mucosal healing conducted by Ungar and colleagues, rates of mucosal healing were twofold higher in those with detectable drug levels compared to those without [35]. There also appeared to be a dose-response in this study, with adalimumab serum concentrations >7.1 μg/mL and infliximab serum concentrations >5 μg/mL being strongly predictive of mucosal healing. Interestingly, this effect appeared to be less dramatic at adalimumab levels >12 μg/mL or infliximab levels >8 μg/mL, suggesting that specific pharmacokinetic windows may exist for anti-TNFs.

Other studies have demonstrated a possible association between clinical outcomes and serum concentrations of adalimumab. While a retrospective analysis of the initial data from CLASSIC I and II did not clearly demonstrate a durable association between adalimumab levels and clinical response, more recent data have supported this association [36]. Karmiris and colleagues assessed the association between adalimumab levels and clinical response in 130 patients [25]. Those who received higher loading doses (160 mg followed by 80 mg compared to 80 mg followed by 40 mg) had higher adalimumab trough levels at week 4, which was associated with a significantly higher probability of CRP normalization, longer sustained clinical benefit, and lower rates of primary non-response. Additionally, higher median adalimumab levels were associated with higher early and later response rates, while lower median drug levels were associated with therapy discontinuation. As previously noted, Ungar and colleagues have also demonstrated an association between serum adalimumab concentrations and mucosal healing [35].

Given the lack of commercially available assays to assess drug levels for other anti-TNFs, the impact of drug levels of certolizumab pegol or golimumab is less clear. In an open-label extension of the PRECISE-2 trial (PRECISE-4), higher drug levels of certolizumab pegol were not associated with an increased probability of clinical response after receiving an extra dose of the medication [37]. However, in a subgroup analysis of individuals initiating the drug after failing infliximab, there was an association between subsequent remission and having drug levels in the upper two quintiles [38]. With regard to golimumab, a recent analysis of data from the phase 2 and 3 PURSUIT trials demonstrated that serum golimumab levels during induction at week 6 and during maintenance therapy (weeks 30 and 54) were associated with increased rates of clinical response, mucosal healing, and clinical remission [39]. Further research is required for both of these agents to better assess the association between drug levels and clinical response.

The role of drug levels with newer anti-integrins such as vedolizumab is less clear as that appreciated with anti-TNFs [40]. In the GEMINI 1 and 2 clinical trials, increased dosing frequency from every 8 weeks to every 4 weeks did appear to increase the serum concentrations of the vedolizumab (38.3 ± 24.4 μg/mL vs. 11.2 ± 7.2 μg/mL, respectively) but was not associated with significantly increased rates of clinical response. Interestingly, regardless of dosing, ~95% of α4β7 heterodimers (the target of the drug) were bound to vedolizumab when assessed; this saturation may in part explain the disconnect between serum concentrations and clinical response. Further research is required regarding the impact of drug levels and this specific class of medications.

Measuring Drug Concentrations and Anti-drug Antibodies

Several assays have been developed to measure anti-TNF drug levels and anti-drug antibodies (Table 8.1). Importantly, earlier assays have had some shortcomings with regard to measuring both drug levels and antibodies when each is present, often making interpretation of the results of assays in initial clinical trials challenging [30]. Given these differences, each assay will be reviewed, with particular focus on each assay's limitations.

Many initial studies employed a sandwich ELISA [15]. ELISAs involve adding a patient's serum to an infliximab-coated plate. After washing the plate, labeled infliximab is then added, which cross-links to another binding site on the anti-drug antibody. Importantly, the presence of serum anti-TNF levels can induce a false-negative result for anti-drug antibodies with this assay, as the drug can inhibit binding of the labeled drug after washing [21, 41, 42]. As such,

Table 8.1 Assays used to detect antibodies to infliximab

Assay type	Advantages	Disadvantages	Commercial example in United States
ELISA	• Ease of administration • Generally low cost	• False positives • Interference in measuring antibodies in the presence of drug	• Early Prometheus and Esoterix assays
RIA	• Can detect ATIs in the presence of infliximab • More resistant to cross-reactivity with other antibodies	• Requires the use of radioactive isotopes • Prolonged incubation time for equilibration of binding	• None
HMSA	• Not sensitive to interference by other antibodies • Increased sensitivity compared to ELISA • Able to measure all subtypes of immunoglobulins to anti-TNFs • No radioactive component as in RIA	• Requires further validation, relatively new assay	• Prometheus (HMSA), Mayo (LC-MS/MS)
Electrochemiluminescence	• Can measure ATIs in the presence of drug • Standardized lab equipment • No radioactive components	• ATIs interfere with drug level assessment • Not yet validated, relatively new assay	• LabCorp

Adapted from Scott FI et al. [30, 40]

ELISA-based assays are not currently employed in most commercial tests for anti-TNF levels and antibodies.

An alternative to the sandwich-based ELISA is the fluid-phase-based radioactive immunoassay (RIA). This assay is not typically employed in the United States [42] but has been employed in some parts of Europe. In the RIA, serum is incubated with radiolabeled soluble antigen, followed by the addition of an anti-Fc fragment. These complexes then precipitate out of solution and are collected via centrifugation. The RIA can measure anti-drug antibodies in the presence of the drug and can also measure the drug in the presence of the antibody. The use of radioactive compounds has limited the utilization of this assay, however.

Another liquid-phase assay that has been developed to measure anti-TNF drug levels and antibodies is the high-pressure liquid chromatography mobility shift assay (HMSA). With an initial acid dissociation phase that allows for separation of drug and anti-drug antibody complexes, this assay is capable of measuring both drug levels and anti-drug antibody levels when each is present. After dissolution, fluorescent-labeled drug or anti-drug antibody is used to measure anti-drug antibodies and drug levels, respectively. Liquid chromatography can also be combined with mass spectrometry (LC-MS/MS). These unique approaches allow for increased sensitivity compared to ELISA, without requiring the radiolabeled markers needed for RIA.

One of the most recently developed assays is the electrochemiluminescence immunoassay (ECLIA), a solid-phase test that can measure both anti-TNF levels and antibodies directed against anti-TNFs. Although anti-drug antibodies can be measured in the presence of drug, their presence may increase the inaccuracy of determining the levels of the drug itself. This assay still requires clinical validation [42].

Several of these assays are available commercially. Prometheus has developed two HMSAs: the ANSER IFX assay for the measurement of infliximab and ATI levels and the ANSER ADA assays for the measurement of adalimumab and anti-adalimumab antibodies. As noted, HMSAs are capable of measuring both drug and anti-drug antibodies independently of each other. The ANSER assays have also been evaluated in several clinical studies and have been validated. One significant limitation of preventing widespread utilization of these assays is their cost [42]. LabCorp has also developed a commercially available assay for the measurement of both infliximab and adalimumab drug levels and anti-drug antibodies, specifically ECLIAs. As mentioned, these assays are also capable of measuring anti-drug antibodies in the presence of the drug and are generally less expensive. However, there remains a paucity of data regarding the clinical validity and application of this commercial assay. Lastly, the Mayo Clinic has also developed a new assay combining both mass spectrometry and liquid chromatography. Unlike other assays that determine both antibody levels and drug levels automatically, this two-step assay first measures serum drug concentrations and then reflexively measures antibodies only when the anti-TNF level is below 5.1 μg/mL. This assay is currently available commercially for infliximab, and validation is still required.

Employing Drug Level and Antibody Data in Clinical Care: Therapeutic Drug Monitoring

With data demonstrating the association between drug levels and antibody concentrations with response to medical therapy, several studies have assessed the impact of therapeutic drug monitoring (TDM) on clinical outcomes in IBD. In general, there are two potential approaches to employing these laboratory tests [42]. "Reactive TDM" refers to the utilization of drug levels and antibodies in response to changes in the clinical status of the patient receiving biologic therapy. When a patient has an increase in symptoms or non-response, these assays are then employed to determine if the patient would potentially benefit from modification of the current biologic dose, changing to another anti-TNF, or switching to an alternative class of medication. "Proactive TDM" refers to the use of these assays at specific time points in therapy to ensure that the dose is optimized, prior to loss of response or non-response, with the goal of achieving "therapeutic" trough drug levels to possibly prevent flares of disease. Several studies have assessed these two approaches and will be reviewed.

A standardized algorithm has been developed to guide clinicians in the interpretation of anti-TNF drug level and antibody results (Fig. 8.1). In this example of reactive monitoring, the initial step is determining that active mucosal inflammation is present, ensuring that the symptoms being treated are not related to other etiologies,

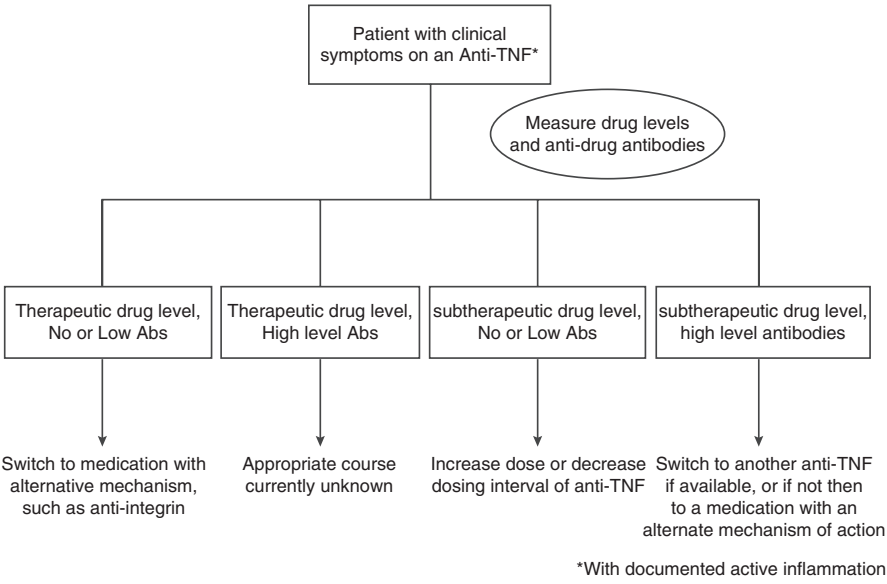

Fig. 8.1 Measurement of anti-TNF drug levels and anti-drug antibodies can yield one of four potential combinations, dependent on the concentration of each. Appropriate interpretation of these results allows clinicians to either optimize the current medication or change to an alternative medication while maximizing the potential clinical benefit

such as overlapping irritable bowel syndrome, infection, bile salt diarrhea, bacterial overgrowth, or other causes. Once inflammation/active disease has been confirmed, a trough sample is collected as data on TDM using trough samples is more robust than at other time points. Trough samples are typically drawn on the day of infusion or injection, before the dose of the anti-TNF is received. If drug levels are low, without detectable antibodies, one could increase the dose of the medication or reduce the dosing frequency. If drug levels are within therapeutic range with undetectable antibodies, one should consider switching to another class of medication with a different mechanism of action, such as vedolizumab. If antibodies are present, the concentration of the antibodies may influence the decision-making process as follows: if antibody concentrations are high, most experts would argue that switching to either another anti-TNF would be appropriate; if the antibody levels are low, there are some data suggesting that antibodies can be suppressed with the addition of immunomodulators and/or increase in anti-TNF dosing, with subsequent improved clinical response and increased drug levels [43]. While promising that this may be a useful approach in patients developing anti-drug antibodies, further research is required to confirm these results in larger cohorts.

Several studies have assessed the clinical utility of reactive TDM, using a similar algorithm as above. An initial retrospective cohort study by Afif and colleagues evaluated the clinical impact of this approach in a cohort comprised of 121 patients with CD, 31 patients with UC, and 3 patients with indeterminate colitis, who were receiving infliximab [44]. Seventy-six patients (49%) underwent TDM evaluation for loss of response, thirty-four (22%) underwent testing for partial response, and eight (5%) underwent testing for primary non-response. The remaining 37 patients were tested for several other indications. Thirty-five of the 155 patients were positive for ATIs. Consistent with the proposed algorithm, 12 patients with ATIs were transitioned to another anti-TNF, with 11 of 12 noting an improved clinical response. Dose optimization of the anti-TNF was performed for 6 of 35 patients with ATIs, of which only 2 had an improved clinical response ($p < 0.016$). Sixty-three patients had subtherapeutic infliximab levels; in this subgroup, 29 underwent dose optimization, with 86% noting a clinical improvement. Six patients changed to another anti-TNF, of which 33% had a clinical response ($p < 0.016$). Collectively, these data support the proposed approach to the interpretation of drug levels and anti-drug antibodies. However, this was a retrospective cohort study and the sample size was small. These results have been supported in several recent additional studies. Vande Casteele and colleagues employed an HMSA-based assay and were able to distinguish between transient antibody formation and persistent antibodies [45]. In those with transient antibodies, the rate of clinical response to dose modification was 69%. However, in those with persistent antibodies measured by HMSA, response to dose modification was only 16% ($p = 0.0028$). Another retrospective study by Pariente and colleagues also suggests that there may be a subset of patients with ATIs who will respond to dose intensification [46]. In a cohort of 76 patients with IBD who had lost response, 16 (22.4%) had ATIs. Ten of these 16 patients underwent dose intensification of IFX, with a 60% response rate, in which there was a 50% response rate among patients with high-titer antibodies.

Another retrospective study examined 199 CD and 42 UC patients, of which 140 were receiving infliximab and 107 were receiving adalimumab, who had lost response underwent drug level and antibody monitoring [47]. In those with loss of response while receiving adalimumab, the presence of trough levels >4.5 μg/mL had a 100% positive predictive value (PPV) of response to switching to an alternative therapy and a 90% PPV for failure to respond to dose intensification. In addition, titers of anti-adalimumab drug antibodies >4 μg/mL had a PPV of 76% for failure to dose intensification. In this retrospective study, the predictive characteristics for infliximab were not as robust as those appreciated by Afif and colleagues, with a PPV of 72% for responding to switching to another class of medication with adequate drug levels and a 56% PPV for failure to respond to dose intensification. Interestingly, the authors did appreciate some evidence of being able to continue anti-TNFs in the setting of low-level antibodies. Specifically, patients with low-level antibodies who had increases in their anti-TNF dose also had significant increases in drug concentration and also had significantly higher clinical response rates when combining both infliximab and adalimumab users. These data suggest that when anti-drug antibodies are present but in low concentration, further anti-TNF titration may be effective, consistent with the findings of Pariente and colleagues [46].

Reactive TDM has also recently been demonstrated to be cost-effective, both in simulation modeling and in clinical practice. Velayos and colleagues constructed a Markov model to simulate those individuals undergoing dose escalation guided by drug level measurement, compared to a strategy of dose escalation based only on symptoms. While clinical outcomes were the same for both cohorts, a significant cost saving was realized, likely secondary to reductions in unnecessary dose escalation [48]. Interestingly, the model was not sensitive to variations in test cost up to $5700 per level measurement [48, 49]. Similar findings were appreciated in a prospective randomized controlled trial of dose escalation versus reactive monitoring in 69 patients with secondary loss of response to infliximab [50]. Comparable clinical response rates were appreciated in each cohort, with significant savings in costs for those undergoing therapeutic drug level monitoring.

Proactive TDM

As opposed to reactive TDM, an alternative approach is to assess drug levels and antibody formation in a proactive manner to ensure that drug levels are within the appropriate proposed therapeutic range during both induction and maintenance therapy. This approach, also known as “proactive TDM,” is designed to maximize the clinical benefit of anti-TNF therapies with the goal of preventing flares of disease by maintaining adequate trough concentrations. In proactive TDM, trough levels and anti-drug antibodies are typically assessed at the end of induction and then at least every 6–12 months, with dose modification or immunomodulator addition when appropriate to optimize levels within a desired therapeutic range.

Several recent studies have attempted to assess the clinical efficacy of proactive TDM, all with infliximab. Cheifetz and colleagues evaluated 48 patients who had undergone proactive TDM [51]. Twelve of these 48 required escalation therapy, whereas 15% required dose reduction. Compared to a control cohort of 78 patients, the monitored group had a significantly lower rate of infliximab discontinuation (HR 0.3, 95% CI 0.1–0.6). The likelihood of remaining on infliximab was highest for those with a trough IFX concentration >5 μg/mL, but similar results were seen with a cutoff level of 3 μg/mL.

Proactive TDM has also been assessed by two randomized controlled trials. In the TAXIT trial, patients with IBD in stable clinical response on infliximab (95% of whom were on infliximab monotherapy) received initial dose optimization to attain infliximab levels of 3–7 μg/mL [52]. After dose modification (if necessary), patients were then randomized to either proactive TDM with target infliximab level 3–7 μg/mL (which also allowed for dose de-escalation) or drug dosing based on increased clinical symptoms or CRP. Although remission rates at 1 year were nearly identical between the two groups, it is important to note that rates of remission were significantly higher in patients with CD after initial dose intensification than prior to dose intensification, thus implying that TDM had a beneficial effect. Also, all patients were initially optimized with TDM and followed subsequently for up to only 1 year, which may not be long enough to appreciate a difference. In addition, the proactive TDM group was significantly less likely to have flared than their counterparts (7% vs. 17%, $p = 0.018$). Costs of therapy were also significantly reduced in the proactive TDM arm.

The other randomized controlled trial, TAILORIX, which is currently published only in abstract form, included 122 patients with active CD who were randomized to one of three strategies after standard IFX induction at 5 mg/kg: (1) a dose increase by 2.5 mg/kg based on drug levels, clinical symptoms, or biomarkers, (2) similar monitoring with a dose increase to 10 mg/kg, or (3) dose intensification to 10 mg/kg [53]. There was no significant difference in individuals without ulceration (47% vs. 38% vs. 40%, respectively) or mucosal healing (51% vs. 65% vs. 40%, respectively) at 54 weeks. However, when examining the percentage of individuals who had sustained IFX levels >3 μg/mL at each time point during the 54 weeks of follow-up, the third group undergoing reactive monitoring had the highest persistently therapeutic drug levels (60%) compared to either the first proactively monitored group (47%) or the second group (46%). As such, these results are somewhat difficult to interpret.

Future Directions: TDM for Biologic Therapies in IBD

With respect to infliximab and adalimumab, for which there are much available data regarding TDM, there are still a number of important data gaps. First, it is unclear what levels should be measured to most accurately assess the drug: trough, peak, area under the curve, time above a minimum threshold, etc. Second, it is likely that different patients will have different thresholds for remission, based on other factors, such

as albumin, weight, disease activity and burden, etc., and therefore TDM will probably be more accurate on an individual rather than population-based level. Third, levels may need to be higher to achieve remission than to maintain remission. Fourth, with respect to antibodies in the era of drug-tolerant assays, the phenomenon of transient antibodies is not well understood. Fifth, assays need to be developed that differentiate neutralizing from non-neutralizing antibodies, which may impart different clinical effects. Sixth, more data are needed to determine whether higher drug levels are needed to achieve remission in UC vs. CD. Seventh, although more difficult and more invasive to obtain, it is possible that tissue drug concentrations may be more accurate predictors of response than serum levels. Eighth, it is unknown what the upper limits of drug levels should be and if high levels are toxic, e.g., it may be possible that high levels could potentially be associated with a higher risk of infection, malignancy, anti-TNF-induced psoriasiform rash, or even immune complex deposition. Finally, more well-designed randomized studies are needed with respect to proactive TDM.

Two other injectable anti-TNFs, certolizumab pegol and golimumab, are marketed for CD and UC, respectively. There are scant data with respect to TDM using these drugs and, thus, more work needs to be done before TDM can be used effectively for these. There is also a paucity of data on TDM with anti-integrin therapy, but it is expected that TDM studies with vedolizumab will be performed in the near future. Similar research will be needed for newer biologic agents, such as ustekinumab, an antibody against a common subunit of both interleukin-12 and interleukin-23, as they become available for the treatment of patients with IBD.

An additional area that will require active research is the role of TDM with further development of biosimilars. Biosimilars are monoclonal antibodies with identical amino acid sequences as the original compound. However, due to different production methods or systems, as these agents are synthesized in living tissue, they may have differences in amino acid glycosylation, phosphorylation, or other posttranscriptional modifications. The immunogenicity profiles of these agents remain uncertain, as assays will need to be developed that measure antibodies specific to the biosimilar but not the reference drug, specific to the reference drug but not the biosimilar, or common to both agents [54]. Randomized controlled studies of infliximab biosimilar CT-P13 from the rheumatologic literature that suggest efficacy and serum concentrations may be similar to that seen with reference infliximab in patients with rheumatoid arthritis or ankylosing spondylitis [55, 56]. However, extrapolating these data to IBD may be problematic due to differences in clearance, dosing, and the inflammatory burden when compared to rheumatologic disorders [54].

Conclusion

Monoclonal antibodies directed against TNF-alpha have revolutionized medical therapy in both CD and UC. There is a growing body of evidence demonstrating associations between clinical outcomes and both anti-TNF serum concentrations

and anti-drug antibodies. Evidence is also mounting for the use of commercial assays to perform TDM when patients have recurrence of symptoms or lack of response to infliximab or adalimumab, and reactive TDM is starting to become the standard of care with respect to anti-TNF therapy in IBD. Further research is required to determine the utility of proactive drug level and antibody monitoring for these two agents. In addition, the role of such methods for and availability of assays to measure newer anti-TNFs, biosimilars, anti-integrin agents, and newer classes of biologic therapy remain to be determined.

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Chapter 9
Use of Biologics in Crohn's Disease and Ulcerative Colitis Prior to Surgery and Perioperative Risks

Afrin Kamal and Bret Lashner

Medical therapy plays a critical role for induction and maintenance of luminal inflammatory bowel disease (IBD) and fistulizing Crohn's disease. The mechanism of disease is thought to be caused by an exaggerated T-cell immune response to enteric bacteria in a genetically vulnerable host. Considering that an exaggerated immune response is responsible for the pathogenesis of IBD, the market developed agents focusing on diminishing this immune activity. Of these therapies, a large bulk falls into the category of "biologic therapy." These agents are monoclonal antibodies targeting tumor necrosis factor, including infliximab (Remicade©), adalimumab (Humira©), certolizumab (Cimzia©), and golimumab (Simponi©), and targeting integrin α4β7 such as vedolizumab (Entyvio©) [1].

Biologic agents attempt to alter the natural history of IBD by aiding in steroid withdrawal while preserving disease remission [2]. These agents have been proven effective. For example, since the commercial availability of infliximab in 1998, the overall rate of IBD surgery has decreased. Unfortunately medical therapy has not been able to erase the need for bowel resection; on average 75% Crohn's disease and 30% ulcerative colitis patients will undergo surgery due to refractory disease or complications. Often, medical therapy proceeds the need for surgery, bringing up concerns regarding perioperative risks with anti-TNF agents [3, 4].

Tumor necrosis factor alpha encompasses several effects on a cellular level. First, as a product of activated macrophages, it regulates cell signal protein of systemic inflammation and thus immune cells [5]. Second, biologic therapies bind to both the soluble and membrane-bound forms of TNF, leading to apoptosis of TNF-expressing inflammatory cells [4]. Inhibition of this key cytokine in the inflammatory process is the primary therapeutic effect for inflammatory bowel disease. Third, TNF-α plays an important role in mediating neutrophil chemotaxis and adhesion during the beginning phases of inflammation, whereas in the proliferative phase of

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healing, TNF-α stimulates fibroblast proliferation and recruitment into the wound. These functions contribute to the role in angiogenesis and collagen synthesis. Inhibition of this function by infliximab and similar agents can play a role in tissue repair and wound healing, possibly impacting postsurgical outcomes [3, 4]. Fourth, TNF-α protects against infections, shown in TNF-deficient mice who were more prone to infections [6]. Inhibiting this function increases risk for opportunistic infections, pneumonia, and sepsis by decreasing both polymorphonuclear cells and T-lymphocytes. As one can imagine, this makes prescribers wary of the safety of biologic therapy in the perioperative setting.

In 1998 the FDA approved infliximab for the treatment of Crohn's disease which has become an important agent for the induction and maintenance of clinical remission. Specifically infliximab has shown value as a steroid-sparing agent and success in closure of enterocutaneous, perianal, and rectovaginal fistulas and maintaining fistula closure [7]. Although infliximab has shown to be effective in controlling Crohn's disease, the reality is 75% eventually undergo surgery for complicating or refractory disease. Considering the bulk of patients that are exposed to biologic therapy prior to surgery, numerous studies have investigated the perioperative risk in both Crohn's disease and ulcerative colitis.

At the Cleveland Clinic, 30-day mortality, wound infection/complications, anastomotic leak, sepsis, intra-abdominal abscess, and readmission rates were measured through contemporary and historical cohorts between 1998 and 2008 on Crohn's disease patients exposed to infliximab within 3 months of an ileocolonic resection [8]. Sixty patients exposed to infliximab were compared to 329 contemporary cohort undergoing ileocolonic resections without prior IFX exposure. The protocol excluded ulcerative colitis and indeterminate colitis and patients with infliximab exposure greater than 3 months before surgery. The type of surgery included an ileocolonic resection; additional procedures such as strictureplasty, small bowel or colonic resections, or prior GI surgeries were excluded.

Results of the study revealed an increased risk with infliximab and 30-day postoperative readmissions (adjusted OR, 2.3 [1.02–5.33], $p = 0.045$), sepsis (adjusted OR, 2.62 [1.12–6.13], $p = 0.027$), and intra-abdominal abscesses (adjusted OR, 5.78 [1.69–19.7], $p = 0.005$). On review it was noted that concomitant use of immunosuppression was higher in the infliximab group (61.7% vs. 16.7%; $p = 0.001$), whereas steroid use was higher in the non-infliximab group (76.9% vs. 65%, $p = 0.05$). Despite the latter having a higher incidence of corticosteroid exposure, the rate of adverse postsurgical outcomes appeared higher in the infliximab-treated arm. In further evaluating timing of infliximab and if 2 vs. 3 months of exposure changed outcomes, the authors took a subset of patients receiving the biologic agent within two months of surgery and studied outcomes after ileocolonic resection. No difference was seen in these subsets. Given TNF-α functions as a potent inflammatory mediator that delays wound healing, the discussion puts no surprise to the increased incidence of sepsis and abscesses with infliximab prior to surgery. The author's consensus was the use of infliximab 3 months prior to ICRA increased risk of 30-day postoperative intra-abdominal abscesses, sepsis, anastomotic leaks, and readmission rates [8].

At the Mayo Clinic in Scottsdale, Arizona, 30-day postoperative complications were measured through historical cohorts between January 1999 and May 2007 on CD patients exposed to immunosuppressive therapy before intestinal resection [2]. Definition of perioperative treatment included exposure of corticosteroids or immunomodulators [azathioprine (Imuran©), 6-mercaptopurine (Purinethol©)] longer than 1 week within 1 month of surgery or if one dose of infliximab was infused within 2 months of surgery. Differing from parallel studies was the allowance of multiple surgery types, with ileocecal resection being the most common but also included total abdominal colectomy, small intestine resection, strictureplasty, and closure of colostomy and ileostomies. Surgical complications were grouped into major and minor, with the former classified as either abdominal intervention (surgical or percutaneous) or requiring monitoring within an intensive care unit.

An aggregate of 112 patients were included in the study—69 of whom received perioperative therapy including anti-TNF agents (24.6%), corticosteroids (68%), and immunomodulators (56.5%). The most common indication for surgery was failure of medical management (28%) closely followed by obstruction (27%). The bulk of patients underwent ileocecal resection (48%), followed by small intestinal resection (21%) and total abdominal colectomy (6%). Of those on immunosuppressive therapy, 22 (32%) experienced postoperative complications (45% major, 64% minor). A small number of patients in the study were on anti-TNF therapy alone ($n = 2$) with only one suffering a complication. As the number of combination drugs was used, the potential likelihood of adverse effects increased—for example, in patients receiving one drug (corticosteroids, immunomodulators, or anti-TNF agents), major complications occurred in five patients (13%, OR—2.0; $p = 0.36$), whereas in patients on three drugs (steroids/immunomodulators/anti-TNF agents), major complications occurred in one patient (33%, OR 6.7; $p = 0.16$). Overall the association between complications and perioperative immunosuppressive therapy was not found to be significant. The authors concluded that complication risks did not increase with number of immunosuppressive therapy and use of anti-TNF for Crohn's disease in the months prior to surgery did not significantly increase short-term postoperative outcomes [2].

In a small retrospective study at Mount Sinai Medical Center in New York, 30-day postoperative complication rates (septic, intra-abdominal, and non-septic), hospital length of stay, and readmission rates were studied between June 1999 and May 2010 on CD patients on immunosuppressive therapy prior to surgery [1]. Definition of perioperative treatment included receiving thiopurines and anti-TNF agents within 3 months of surgery or corticosteroid more than 7 days within 6 weeks of surgery. Types of surgeries were grouped into ileocolic resection, small bowel resection, segmental colectomy, low anterior resection, and diverting stoma. Procedures were grouped into either "elective" or "urgent" with the latter defined as less than 24 h of an unplanned surgery.

A total of 127 procedures had exposure to immunosuppressive medications—anti-TNF agents in 18%, corticosteroids in 37%, and thiopurines in 35%—compared to 69 procedures without treatment exposure. Anti-TNF agents were not broken down by name. Groups were similar in Crohn's disease behavior per Montreal B

classification, type of surgery, and number of intestinal anastomoses. However, patients without perioperative treatment were found to be younger (mean 38.0 vs. 42.9 years, $p = 0.01$) and requiring more urgent procedures (27.6% vs. 13.0%, $p = 0.02$). The study uncovered 45 total complications (23%) at 30 days, further broken down into intra-abdominal septic complications including anastomotic leaks ($n = 8$, 4.1%), intra-abdominal abscesses ($n = 8$, 4.1%), and enterocutaneous fistulas ($n = 4$, 2%). Non-septic complications is comprised of small bowel obstructions ($n = 5$, 2.6%) and postoperative intra-abdominal hemorrhage ($n = 2$, 1%). There were no postoperative deaths. Despite these complications when matched against treatment vs. nontreatment arms, no significant difference in overall morbidity or septic complications was seen. To point out, anti-TNF agents were matched by presence of complications vs. none, revealing a nonsignificant difference ($n = 7$, 15.6% vs. $n = 28$, 18.5%, $p = 1.0$). The study concluded that immunosuppressive therapy, including anti-TNF agents, did not increase postoperative morbidity in patients with Crohn's disease [1].

At the Mayo Clinic in Rochester, Minnesota, a retrospective analysis investigated 30-day infectious and noninfectious complications with anti-TNF therapy before undergoing surgery for CD between January 2005 and February 2009 [9]. Perioperative treatment was defined as anti-TNF within 8 weeks of surgery or up to 30 days postoperative. The authors intended to study anastomotic complications; thus, surgeries included only procedures that left sutures or staple lines at risk for infection. Total proctocolectomy with end ileostomy was excluded given no suture/staple lines would be placed at risk. Emergency procedures and patients with proximal diversions were also excluded. Postoperative complications were grouped into either infectious or noninfectious.

A total of 119 patients treated with anti-TNF was compared to 251 controls observing infectious complications related to the anastomosis and overall complications, including wound infection, pneumonia, and urosepsis. Disease severity was stratified based on ACG categories of disease, identifying the presence of penetrating complications (fistulae or abscess) at time of surgery. Anti-TNF therapy included infliximab at varying doses although majority were at 5 mg/kg every 8 weeks, in addition to adalimumab 40 mg every 2 weeks and certolizumab pegol 400 mg every 4 weeks. Of note prior studies did not utilize other anti-TNF agents beyond infliximab. Between the two groups, overall complication rates were similar—30.3% in the anti-TNF vs. 27.9% in the non-anti-TNF group ($p = 0.63$). A larger fraction of the treated group fell under "severe disease" according to the ACG criteria, whereas the nontreated group was found to have a higher percentage of steroid exposure. Rates of intra-abdominal abscess or anastomotic leak were low (2.4%) with no difference between the groups (1.99% anti-TNF vs. 3.36% non-anti-TNF, $p = 0.44$). Univariate analysis demonstrated age and presence of penetrating disease as the only predictors for intra-abdominal infectious complications. The study did not find a relationship between perioperative anti-TNF therapy and postoperative complications.

From these results, the authors concluded against delaying surgery in patients exposed to anti-TNF 8–12 weeks prior to surgery and discouraged creating a

defunctionalizing proximal stoma to reduce postoperative complications. Considering penetrating disease as a predictor in the study for increased intra-abdominal infectious complications, the authors suggest that the presence of fistula or abscess may be the most important influence for development of complications [9].

From the above studies, consequences of anti-TNF agents on postoperative complications in Crohn's disease remained controversial. Therefore, a meta-analysis was conducted through a literature database between 1966 and September 2011, observing 30-day overall complication rates and infectious and noninfectious complications between patients exposed to anti-TNF agents and those who were not [10]. Infectious complications were broken down into either anastomosis related (abscess, anastomotic leak, or fistula) or other, likewise, noninfectious categorized into intestinal obstruction/prolonged ileus, thromboembolic events, gastrointestinal bleeding, cardiovascular, respiratory, and renal impediments. Heterogeneity was considered significant if a chi-squared test measured a p-value <0.1 or an I^2 >50%.

After applying the exclusion criteria, 8 studies remained with a total of 1641 participants with 423/1641 (25.8%) exposed to anti-TNF agents. All studies utilized infliximab except one that included adalimumab and certolizumab pegol. Investigating infectious complications, six studies were pooled revealing an OR of 1.50 (95% CI, 1.08–2.08, I^2 = 43.0%), supporting clinical significant relationship between preoperative infliximab and postoperative infectious complications (Table 9.1). When results were pooled, overall adverse effects demonstrated a trend for increased risk and however lacked clinical significance (OR 1.72, 95% CI 0.93–3.19, I^2 = 76.1%) with a consistent finding after removing three lower-quality studies although there was significant heterogeneity (Table 9.2). A similar trend was seen in noninfectious complications; however, statistical significance was not reached (OR 2.00, 95% CI 0.89–4.46, I^2 = 52.7%). Given these findings and overall trend in higher risk of postoperative complications, the authors concluded that surgery in patients exposed to anti-TNF agents increased their risk of adverse effects; thus, elective surgery should be scheduled distant from anti-TNF therapy, although the ideal last dose date remained undefined [10].

Table 9.1 Meta-analysis: pooled infectious complications in infliximab preoperatively with Crohn's disease

Study	Infliximab (*n*)	Non-infliximab (*n*)	Total (*n*)	Odds ratio
Appau et al. [8]	60	329	389	2.93 (1.63–5.27)
Canedo et al. [11]	65	160	225	1.19 (0.58–2.42)
Kasparek et al. [12]	48	48	96	1.00 (0.44–2.29)
Marchal et al. [13]	40	39	79	2.27 (0.70–7.38)
Tay et al. [14]	22	78	100	1.38 (0.33–5.72)
Colombel et al. [15]	52	218	270	0.85 (0.39–1.88)
Total	287	872	1159	1.50 (1.08–2.08)

Test for heterogeneity: X^2 = 8.78, df = 5 (p = 0.12), I^2 = 43.0%
Adapted from Kopylov et al. [10]

Table 9.2 Meta-analysis: pooled total complications in infliximab preoperatively with Crohn's disease

Study	Infliximab (*n*)	Non-infliximab (*n*)	Total (*n*)	Odds ratio
Appau et al. [8]	60	329	389	5.63 (3.06–10.34)
Indar et al. [2]	17	95	112	1.37 (0.46–4.09)
Kasparek et al. [12]	48	48	96	2.20 (0.96–5.06)
Marchal et al. [13]	40	39	79	1.24 (0.46–3.33)
Nasir et al. [9]	119	251	370	1.12 (0.69–1.81)
Colombel et al. [15]	52	218	270	0.98 (0.48–2.01)
Total	336	980	1316	1.72 (0.93–3.19)

Test for heterogeneity: $X^2 = 20.94$, df = 5($P = 0.0008$), $I^2 = 76.1\%$
Adapted from Kopylov et al. [10]

The use of anti-TNF agents has proved paramount in the remedy of Crohn's disease, decreasing the overall need for surgery. However, despite this eminent introduction in therapy, the reality is 75% of CD will still undergo surgery as a result of refractory disease or complications. The dilemma for providers has become determining the safety of biologic therapy preceding surgery and whether biologic agents such as Infliximab should be stopped. Numerous studies have been performed to answer this question, the majority utilizing infliximab as their anti-TNF agent. All authors defined preoperative therapy as either two or three months preceding surgery, with 30-day postoperative follow-up. When evaluating Crohn's disease, the consensus has been debated. Several studies such as those performed at Mayo Clinic, Scottsdale; Mount Sinai Medical Center; and Mayo Clinic, Rochester, concluded no significant increase in adverse effects and to not delay surgery. At the Cleveland Clinic however, authors concluded that the use of infliximab 3 months prior to ileocolonic resection with anastomosis (ICRA) resulted in higher postoperative intra-abdominal abscess, sepsis, anastomotic leaks, and readmission rates. Given this disagreement in safety of biologics prior to surgery, a meta-analysis was performed incorporating 8 studies with a total of 1641 patients, demonstrating a trend toward higher total and noninfectious complications, however only significant difference seen among postoperative infections. We would conclude that infectious complications in fact are a postoperative risk with anti-TNF therapy in Crohn's disease and should consider delaying elective surgery. However, if perioperative anti-TNF cannot be avoided, consider a defunctionalizing proximal stoma to reduce adverse effects and to protect the anastomosis.

Chronic ulcerative colitis is an additional debilitating inflammatory bowel disease. After induction of remission, up to 50% will unfortunately experience a relapse in one year, and of this group, half will further require surgical management. Contrasting from Crohn's disease, surgery in UC offers a chance for cure of intestinal symptoms and eradicates the risk of malignancy. Prior to surgery however, the ultimate goal is to sustain mucosal healing through medical management. The 2005 Active Ulcerative Colitis Trials 1 and 2 (ACT 1 and ACT 2, respectively) laid the foundation that has now made infliximab an effective agent in moderate-to-severe UC, with mucosal healing occurring in significantly more patients than placebo

($p \leq 0.009$) [7]. Subsequently infliximab received FDA approval for the treatment of moderate-to-severe UC and endorsement by the American Gastroenterology Association as an agent to treat hospitalized patients with severe UC [4]. When disease surpasses medical salvage, restorative proctocolectomy (RP) and ileal pouch-anal anastomosis (IPAA) become the procedure of choice. Determining one-, two-, or three-stage RP is based on the severity of systemic illness and degree of inflammation. Two-stage procedure is defined as a total proctocolectomy and ileal pouch construction with covering loop ileostomy and then subsequent closure of ileostomy marking the second stage. Three-stage procedure is frequently utilized in acutely ill patients on high-dose steroids, immunomodulators, or severe colon and rectal inflammation [16]. Similar to Crohn's disease, the question regarding safety of preoperative anti-TNF agents and risk of postoperative complications emerged after the introduction of infliximab for moderate-to-severe UC. Thus, multiple studies were designed in the attempt to answer this question.

One of the initial studies to investigate the influence of infliximab on surgical morbidity started at Cedars-Sinai Medical Center in 2007, 2 years after infliximab received FDA approval for moderate-to-severe UC [4]. Between October 2000 and October 2005, 30-day postoperative morbidity and mortality were recorded after two-stage proctocolectomy with ileal pouch-anal anastomosis (IPAA) or if necessary subtotal colectomy (STC). Complications were divided into medical and surgical, with medical complications being divided into major and minor. Major adverse effects included pneumonia, deep vein thrombosis, pancreatitis, acute renal failure, and cerebrovascular accident, whereas minor complications encompassed dehydration, superficial thrombophlebitis, pyoderma gangrenosum, and urinary retention. A preponderance of patients undergoing surgery were preoperatively diagnosed with pancolitis, and all were exposed to IV steroids. The study group is comprised of 17 patients exposed to infliximab preoperatively compared to 134 controls.

Results of the study revealed no statistical significance in medical ($p = 0.99$), surgical ($p = 0.3$), or overall infectious ($p = 0.2$) complications. The bulk underwent IPAA (112 patients, 69%) compared to STC (39 patients, 31%); however, when comparing surgical approaches, no statistical difference in medical, surgical, or infectious complications was seen. In addition, the aim of this study was to investigate the influence of infliximab with other immunosuppressive agents, such as 6-MP or cyclosporine (CsA). Whereas no significant difference in complication rates were observed in 6-MP + infliximab compared to infliximab alone, the groups receiving infliximab plus CsA demonstrated an overall 80% complication rate, specifically infectious, when compared to infliximab monotherapy. The authors concluded that preoperative infliximab use alone may not influence 30-day mortality; however, one should consider infectious complication risks when combining with CsA [4].

At the Mayo Clinic in Rochester, Minnesota, short-term (within 30 days) postoperative complications were measured between 2002 and 2005 on chronic ulcerative colitis patients exposed to infliximab preceding IPAA; the complication rates for anastomotic leak, pelvic abscess, and wound infection were

determined [17]. Definition of perioperative treatment included exposure of therapy with infliximab, corticosteroids, or immunomodulators up to 6 months before surgery. Surgical inclusion was exclusive to IPAA, either two- or three-stage procedures.

A total of 301 patients was included in the study—47 of whom received infliximab. A higher percentage of the infliximab-treated arm suffered with severe colitis ($p = 0.02$) with the main indication for surgery being medical refractory disease. Although two- and three-stage IPAA were included in the study, majority underwent two-stage procedure with closure of the ileostomy at a mean of 3.1 months in both groups. A higher number of patients in the infliximab-treated arm were exposed to corticosteroids (89% vs. 86%, $p < 0.001$), on concurrent azathioprine (AZA) (91% vs. 44%, $p < 0.0001$), and treated with combination of high-dose corticosteroids, ASA, and AZA (70% vs. 19.3%, $p < 0.001$) [17].

Using univariate analysis, infliximab demonstrated an increase in pouch-specific complications (OR = 3.5, 95% CI, 1.6–7.5). However, adjusting for age, severity of colitis, and use of high-dose steroids and AZA/6-MP, there were no further increased odds of pouch-specific complications. Rates of infectious complications (including anastomotic leak, pelvic abscess, and wound infection) in the infliximab-treated arm exceeded the control arm (28% vs. 10%, OR = 3.5; 95% CI, 1.6–7.5), as well as anastomotic leaks and wound infections, without a significant difference in postoperative fistula or anastomotic stricture frequency. The study concluded that preoperative exposure to infliximab significantly increased rate of postoperative infectious complications, with nearly one in five experiencing adverse events. This becomes important since anastomotic leaks and pelvic abscesses play an important role in long-term pouch function [17, 18].

At the Cleveland Clinic, early and late postoperative complications were analyzed between January 2000 and December 2006 on chronic UC patients exposed to infliximab and matched controls undergoing two-stage restorative proctocolectomy [16]. Early complications were defined as within 30 days after ileostomy closure, whereas late complications were those that developed after 30 days of ileostomy closure (e.g., pouchitis, small bowel obstructions, and anastomotic strictures). This study differed in that timing of infliximab did not have to meet inclusion/exclusion criteria; timing ranged between 4 and 37 weeks, a median of 13.5 weeks and three infusions.

An aggregate of 85 patients received infliximab out of 523 total ileal pouches. The extent and severity of colitis, in addition to steroid exposure preceding surgery (11–20 mg) and immunomodulators, were comparable in the infliximab and non-infliximab arms. Results of the study revealed a higher prevalence of pelvic sepsis as an early complication (22% vs. 2%, $p = 0.016$), with parallel rates of postoperative hemorrhage, venous thrombosis, and ileus. Later complications of pouchitis were found at a higher prevalence in the infliximab exposed arm (39% vs. 15%, $p = 0.037$), whereas overall late morbidity, small bowel obstruction, and IPAA strictures were similar between the two groups.

Statistically adjusting for extent and severity of colitis, steroid dose, and use of immunomodulators, use of infliximab leads to greater rates of overall early complications (OR, 3.54; 95% CI 1.51–8.31), specifically rate of pelvic sepsis and pouchitis. Thus, the authors concluded that the use of infliximab therapy in moderate-to-severe UC prior to RP increased rate of early and late postoperative complications [16].

From the above studies, infectious complications were found as the leading adverse effect after preoperative anti-TNF treatment in chronic ulcerative colitis and however were not shared among all studies. Thus, authors at the Xijing Hospital of Digestive Diseases in Xi'an, China, created a meta-analysis to provide further insight into this dilemma [19]. A total of 13 observational studies was included comprising 2933 patients analyzing total, infectious, and noninfectious complications within short time after surgery, generally 30 days. Definition of preoperative infliximab was within 12 weeks preceding surgery in seven studies with postoperative effects determined at 30 days in ten studies and 60 days in one study; the other two omitted this data. Heterogeneity was considered significant when chi-squared-based Q-test had a p-value <0.10 or I^2 >50%.

By delineating complications into infectious, total, and noninfectious, the study provided separate pooled OR comparing infliximab preoperatively vs. controls. Outcomes of the study revealed a pooled OR of 1.10 (95% CI 0.51–2.38; $I^2 = 67\%$) for infectious complications (Table 9.3), pooled OR of 1.09 (95% CI 0.87–1.37; $I^2 = 28\%$) for total complications (Table 9.4), and pooled OR of 1.10 (95% CI 0.76–1.59; $I^2 = 31\%$) for noninfectious complications, all three lacking significant associations with preoperative infliximab and significant heterogeneity among infectious outcomes. Subsequently low-quality studies by the Newcastle-Ottawa Scale (NOS <7) were removed, continuing to demonstrate no clinical difference between infliximab and non-infliximab adverse effects. The authors concluded that preoperative infliximab did not increase risk of postoperative complications in chronic UC prior to surgery [19].

Table 9.3 Meta-analysis: pooled infectious complications in infliximab preoperatively with ulcerative colitis

Study	Infliximab (*n*)	Non-infliximab (*n*)	Total (*n*)	Odds ratio
Selvasekar et al. [17]	47	254	301	3.50 (1.64–7.50)
Schluender et al. [4]	17	134	151	2.40 (0.60–9.63)
Mor et al. [16]	46	46	92	12.50 (1.53–102.26)
Ferrante et al. [20]	22	119	141	0.31 (0.07–1.41)
Coquet-Reinier et al. [21]	13	13	26	0.46 (0.04–5.79)
Gainsbury et al. [22]	29	52	81	0.57 (0.18–1.77)
Schaufler et al. [23]	33	18	51	0.48 (0.10–2.22)
Bregnbak et al. [24]	20	51	71	0.36 (0.10–1.22)
Eshuis et al. [25]	38	34	72	1.57 (0.53–4.66)
Total	265	721	986	1.10 (0.51–2.38)

Heterogeneity: $X^2 = 23.91$; df = 8 ($p = 0.002$); $I^2 = 67\%$
Adapted by Yang et al. [19]

Table 9.4 Meta-analysis: pooled total complications in infliximab preoperatively with ulcerative colitis

Study	Infliximab (*n*)	Non-infliximab (*n*)	Total (*n*)	Odds ratio
Järnerot et al. [26]	7	14	21	1.00 (0.13–7.45)
Selvasekar et al. [17]	47	254	301	1.69 (0.89–3.20)
Schluender et al. [4]	17	134	151	1.43 (0.49–4.15)
Mor et al. [16]	46	46	92	2.97 (1.08–8.14)
Coquet-Reinier et al. [21]	13	13	26	0.48 (0.09–2.65)
Gainsbury et al. [22]	29	52	81	1.02 (0.41–2.55)
de Silva et al. [27]	34	628	662	0.82 (0.36–1.84)
Kennedy et al. [28]	11	27	38	2.51 (0.53–12.04)
Schaufler et al. [23]	33	18	51	0.30 (0.09–1.00)
Bregnbak et al. [24]	20	51	71	1.04 (0.37–2.93)
Nørgård et al. [29]	199	1027	1226	0.89 (0.62–1.28)
Eshuis et al. [25]	38	34	72	1.88 (0.72–4.92)
Total	494	2298	2792	1.09 (0.87–1.37)

Heterogeneity: $X^2 = 15.19$; df = 11 ($p = 0.17$); $I^2 = 28\%$
Adapted by Yang et al. [19]

Bearing in mind the higher risk of infectious complications in Crohn's disease patients after anti-TNF exposure, similar concerns prompted studies in patients with chronic ulcerative colitis. Numerous studies had been performed investigating rates of surgical and infectious complications. Given all studies could not be described in this paper, a few were selected. One study revealed higher overall and infectious complications when patients were exposed to infliximab plus cyclosporine; however, anti-TNF alone did not demonstrate a significant change in medical, surgical, or infectious complications. Other studies exposed higher rates of anastomotic leaks and wound infections after infliximab up to 6 months preceding surgery and greater rates of pelvic sepsis and pouchitis. Given the heterogeneity in results, a meta-analysis was created to achieve a better sense in direction on biologic therapy prior to surgery. A total of 13 studies incorporating 2933 patients was analyzed revealing no significant increase in postoperative infectious, noninfectious, or total complications. Given all these findings, we conclude that in the setting of ulcerative colitis, preoperative biologic therapy may be considered when undergoing two- or three-stage IPAA.

Despite the introduction of anti-TNF agents in the treatment of Crohn's disease and ulcerative colitis, the unfortunate reality is medical therapy may not completely suppress disease activity. If surgery is indicated, the question arises on the safety of preoperative biologic therapy. We conclude that in the setting of Crohn's disease, surgery should be delayed for at least 30 days. If this cannot be achieved, then one can consider an ileostomy to protect the anastomosis. However, in ulcerative colitis, given majority of studies demonstrated lack of adverse effects, we recommend preoperative anti-TNF therapy can be considered prior to a scheduled two- or three-stage IPAA.

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Chapter 10
Cessation of Biologics: Can It Be Done?

Hang Hock Shim and Cynthia H. Seow

Introduction

The inflammatory bowel diseases (IBD) which comprise Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory conditions of the gastrointestinal tract characterized by a relapsing and remitting course which may lead to progressive bowel damage [1, 2]. Historically, treatment of IBD comprised corticosteroids, 5-ASA agents, and immunomodulators including thiopurines and methotrexate. As a result of the limited therapeutic efficacy of these agents, up to 80% of patients with CD and 30% with UC require bowel resection to treat medically refractory disease or to attend to associated complications including strictures, fistulae, and abscesses [3, 4]. The use of biologic therapies, in particular anti-TNF-α agents, has resulted in a significant paradigm shift in the management of IBD with the ability to achieve deep remission [5, 6]. Mucosal healing is associated with lower rates of hospitalization, surgery, postoperative recurrence, colorectal cancer, and improved colectomy-free survival and quality of life [7–11]. Despite the overall favorable safety and efficacy profile, patients on anti-TNF-α therapies may lose response and may have an increased risk of infection and malignancy, and the therapy is expensive. The question therefore arises as to whether withdrawal of biologic therapy

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may be a viable option. The concept of withdrawal of IBD therapies is not new. Prior to the introduction of anti-TNF-α therapies, the withdrawal of azathioprine had been studied and was well demonstrated to be associated with high relapse rate, ranging from 11 to 77% at 1 year [12]. This book chapter will aim to address who, when, and how withdrawal of biologic could be considered. For the purpose of this book chapter, we will focus on anti-TNF-α therapies which are the most widely used biologics as data on withdrawal of other newer biologics (including the anti-integrins, IL-12/23 inhibitors, etc.) are limited at this juncture.

The Case for Continuing Anti-TNF-α Therapy

Anti-TNF-α agents target tumor necrosis factor-α which is a key mediator of inflammation. Targan et al. published the first randomized double-blind placebo-controlled trial comparing a single dose of cA2 (infliximab) to placebo in CD in 1997 with impressive results at week 4 (clinical response 81% versus 17%, clinical remission 33% versus 4%, all comparisons, $p < 0.05$) [13]. This was followed by the ACCENT trial in individuals with CD and the ACT trial in patients with UC which demonstrated the efficacy of induction and maintenance of anti-TNF-α therapy with infliximab [14, 15]. Systematic reviews and network meta-analyses have reported comparable clinical efficacy for all anti-TNF-α agents [16, 17]. Efficacy can be further improved by combining therapy with an immunomodulator and introducing therapy in the early stages of disease [5, 6, 18–20].

Existing data indicates that both gastroenterologists and patients generally prefer to continue anti-TNF-α therapy as long as it is effective and well tolerated, citing concerns of the risk of relapse and lower response with subsequent reintroduction of an anti-TNF-α agent [21, 22]. It has been well documented that episodic anti-TNF-α treatment results in an increased risk of immunogenicity, secondary loss of response, and infusion reactions, and elective switching between anti-TNF-α agents should be avoided due to loss of efficacy [23–25].

The Case for Discontinuing Anti-TNF-α Therapy

The reasons for requesting cessation of therapy should be discussed at length with the patient given that there may be differing concerns by the patient and physician underlying the request. Switching an anti-TNF-α therapy to an alternative biologic therapy may be a reasonable alternative to complete discontinuation of therapy in select circumstances, e.g., intolerance to a class of therapy. Despite the above, there may be specific situations in which the risks of ongoing therapy may outweigh the benefits. The following topics plus the management of IBD during pregnancy are covered in detail in other chapters of the book, but a short summary is provided here.

Infusion Reactions Anti-TNF-α therapies are generally well tolerated with only a small proportion (4%) of patients experiencing infusion or local injection reactions which can be managed by changes to the injection/infusion technique; pretreating with antihistamines, acetaminophen, or corticosteroids; or a switch to an alternate therapy [26, 27]. Acute serum sickness is uncommon (1–3% of patients) but may necessitate cessation of existing therapy [27, 28].

Risk of Infection The TREAT registry followed a large cohort of 6273 individuals with IBD and reported the risk of serious infection for anti-TNF-α therapy being higher (HR 1.43; 95% CI 1.11–1.84) than that seen with immunomodulators (HR 1.23; 95% CI 0.96–1.57) but lower than with corticosteroids (HR 1.57; 95% CI 1.17–2.10) [29]. Mycobacterial, fungal, bacterial, and viral infections have all be reported with anti-TNF-α therapies, but these may be prevented by screening for these infections and providing appropriate prophylaxis or vaccination [30, 31]. In the setting of other recurrent or severe infections, a switch to a gut-specific antibody with lesser systemic adverse effects (such as vedolizumab) could be considered.

Risk of Malignancy No significant increased risk of malignancy was identified in the TREAT registry nor in two separate systemic reviews [32–34]. A number of studies, albeit underpowered, suggest that anti-TNF-α therapies may be safe in the setting of active or recent malignancy [35]. However, an in-depth discussion with the treating oncologist should always be undertaken before deciding to continue or cease anti-TNF-α therapy.

Elderly with IBD The management of the elderly with IBD should take into account altered pharmacokinetics, polypharmacy, age-related changes to the immune system, and comorbid illness, which may increase the risk of infections, malignancy, morbidity, and mortality [36].

Health Economic Concerns While anti-TNF-α therapies have significantly decreased the rates of hospitalization and surgery, the increasing use of these agents has replaced hospitalization and surgery as the main driver of total medical costs [37, 38]. In United States, it was estimated that the annual medication cost per CD patient was $18,637 [39]. The emergence of subsequent entry biologics may result in decreased costs but requires specific study.

The Risk of Discontinuing Anti-TNF-α Therapy

Situations may arise in which patients, physicians, or health jurisdictions request elective cessation of anti-TNF-α therapy based on personal preference or health economic concerns. In these scenarios, it is important to determine how and in whom this is best performed. The overall risk of IBD relapse following withdrawal of anti-TNF-α therapies was reported as 44% (95% CI 37–51, follow-up range 6–125 months) in a meta-analysis of 27 studies by Gisbert et al., with approximately one third of patients in remission relapsing 1 year after discontinuation [40]. Summaries of studies on withdrawal of anti-TNF-α therapies can be found in Table 10.1.

Table 10.1 Studies on the withdrawal of anti-TNF-α therapies

	Authors	Number of participants (*n*)	Study design	Relapse rate	Significant predictors of relapse	Predictors evaluated but not found to be significant	Recapture rate
CD	Brooks et al. [52]	86	Prospective observational	4.7% (3 months)	Ileocolonic disease	Age, gender, disease behavior, previous surgical resection, immunosuppression at start of anti-TNF-α treatment, disease duration, dose escalation of anti-TNF-α agent, concomitant IMM, raised CRP	93%
				18.6% (6 months)	Previous anti-TNF-α treatment		
			(88% concomitant IMM)	36% (1 year)	Raised fecal calprotectin		
	Domenech et al. [42]	23	Prospective observational (69% with concomitant IMM)	31% (1 year)	Perianal disease	Gender, smoking status, previous treatment with IFX, concomitant IMM, location, development of infusion acute reactions	–
				66% (1 year) for perianal disease			
	Louis et al. (STORI) [41]	115	Prospective observational (100% with concomitant IMM)	43.9% (1 year)	Male, absence of surgical resection, elevated leucocyte count >6.0 × 10^9/L, hemoglobin ≤ 145 g/L	Age, smoking status, location, previous resection, disease duration, treatment duration	88%
				15% (1 year) for those with ≤2 predictors of relapse	C-reactive protein ≥5.0 mg/L		
					Fecal calprotectin ≥ 300 μg/g		
	Reenaers et al. (long-term follow-up of STORI trial) [77]	102/115 (long-term outcome)	Prospective observational (100% with concomitant IMM)	85% (median 8 years)	Upper GI involvement	Not reported (only abstract is available)	40%
					Elevated leucocyte count > 6.0 × 10^9/L		

Molnar et al. [43]	121	Prospective observational (85% with concomitant IMM)	45% (1 year)	Previous biologic therapy Dose intensification of biologic therapy	Gender, concurrent steroid use at biologic initiation, high CRP, smoking status	50%
Annunziata et al. [78]	16	Retrospective (% on IMM not available)	62.5% (5 years)	Absence of normalized intestinal wall thickness	–	–
Ampuero et al. [44]	75	Retrospective (100% concomitant IMM)	30.9% (1 year)	CRP > 5 mg/L Younger age at diagnosis	Gender, smoking status, location, duration of treatment	100%
Molnar et al. [53]	50	Retrospective (86% concomitant IMM)	56% (1 year)	Fistula Smoking status	Location of disease	–
Papamichael et al. [66]	100	Retrospective (84% with concomitant IMM)	48% (10 years)	Age at diagnosis <25 (multivariate analysis)	Disease location, behavior (perianal), fistulizing disease, type of infliximab therapy (episodic or scheduled), number of infliximab infusions, CRP, previous ileocolonic resection, smoking at initiation of infliximab, IMM or type of IMM after infliximab cessation, positive ATIs during infliximab therapy or at the time of infliximab cessation	–

(continued)

Table 10.1 (continued)

	Authors	Number of participants (*n*)	Study design	Relapse rate	Significant predictors of relapse	Predictors evaluated but not found to be significant	Recapture rate
	Ramos et al. [79]	25	Retrospective (% of IMM not reported)	16% (1.6 ± 1 year)	Not reported	Not reported	–
	Waugh et al. [54]	48	Retrospective (67% concomitant IMM)	50% (1.3 year) 35% remained well with no relapse at 7 years follow-up	Nil identified	Age, gender, disease location, duration from diagnosis to the start of infliximab therapy, concomitant IMM, number of infliximab doses	–
UC	Farkas et al. [80]	51	Prospective observational (100% concomitant IMM)	35% (0.3 year)	Previous biological therapy	Gender, smoking status, appendicectomy, disease extent, extraintestinal manifestation, concomitant IMM, previous surgery, dose intensification	94%
	Munoz Villafranca et al. [81]	19	Prospective observational (57.8% with concomitant IMM)	25% (1–2 years)	Not reported	Not reported	–
	Fiorino et al. [82]	193	Retrospective (65.3% with concomitant IMM)	47.7% (median follow-up of 2 years)	Infliximab discontinuation Absence of concomitant thiopurines	Age, disease extension, disease severity, previous therapies, smoking status	77%

CD/UC	Bortlik et al. [83]	CD: 61 UC: 17	Prospective observational (77% of CD and 59% of UC with concomitant IMM)	CD: 18% (0.5 year), 41% (1 year), 49% (2 years) UC: 23% (0.6 year), 23% (1 year), 36% (2 years)	Non-colonic location for CD, previous anti-TNF-α treatment, previous surgery	Type of anti-TNF-α agent, smoking status, disease behavior, corticosteroid therapy within 1 year before biologics withdrawal, concomitant IMM, CRP level, fecal calprotectin, anti-TNF-α trough levels at the time of anti-TNF-α withdrawal	82%
	Dai et al. [49]	CD: 109 UC: 107	Prospective observational (31% concomitant IMM)	CD: 21% (1 year) UC: 14% (1 year)	Nil	Clinical remission, mucosal healing, gender, disease duration, smoking status, history of appendicectomy, location, behavior, extraintestinal manifestations, previous surgery, previous biological therapy, CRP level, effect of induction therapy	CD: 78.3% UC: 66.7%
	Hlavaty et al. [84]	CD:17 UC: 5	Prospective observational (36% with concomitant IMM for cohorts in clinical remission) (64% with concomitant IMM for cohorts in deep remission)	Cohorts with deep remission, 18% (0.5 year), 27% (1 year) Cohorts with clinical remission, 18% (0.5 year), 27% (1 year)	Male	Type of IBD, age, disease duration, CD location, behavior, smoking status, previous surgery, type and duration of anti-TNF-α agent, concomitant azathioprine, fecal calprotectin, CRP, hemoglobin	100%

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Table 10.1 (continued)

Authors	Number of participants (*n*)	Study design	Relapse rate	Significant predictors of relapse	Predictors evaluated but not found to be significant	Recapture rate
Molander et al. [67]	CD,17; UC, 30	Prospective observational (83% with concomitant IMM)	CD: 29% (1.1 year)	Nil identified	Age, gender, duration of disease, location, disease activity at discontinuation	100% (CD)
	IBDU: 5		UC: 35% (1.1 year)			90% (UC)
Armuzzi et al. [55]	CD: 65	Retrospective (% of with concomitant IMM not reported)	CD: 49% [median 1.1(0.3–6.2) years]	Absence of mucosal healing	Not reported	–
	UC: 31		UC: 41% [median 1.3(0.3–2.5) years]	High CRP		
Casanova et al. [60]	CD: 717 UC: 338	Retrospective (71% with concomitant IMM)	24% (1 year)	Adalimumab (rather than infliximab)	Not available	75%
			38% (2 years)			
			46% (3 years)	Elective discontinuation of anti-TNF-α therapy		
			56% (5 years)	Discontinuation of anti-TNF-α due to adverse events		
				Younger age at discontinuation		
				No maintenance IMM		

	Caviglia et al. [85]	CD: 29	Retrospective (100% CD and 33% UC with concomitant IMM)	CD: 69% [median 1.3 (0.4–2.5) years]	Not reported	Not reported	–
		UC: 9		UC: 56% [median 0.5 (0.3–1.3) years]			
	Ciria et al. [86]	CD:24	Retrospective (% of concomitant IMM not reported)	35% (median follow-up 1.7 years)	Absence of mucosal healing	Type of IBD	–
		UC: 10					
	Farkas et al. [87]	CD:41	Retrospective (85% CD and 73% UC with concomitant IMM)	CD: 78% (0.4 year)	Nil identified	Clinical remission	81% (CD)
		UC:22		UC: 59% (0.6 years)		Mucosal healing	54% (UC)
	Luppino et al. [88]	CD: 21 UC: 10	Retrospective (100% with concomitant IMM)	42% (median time to relapse 1.5 years)	Longer disease duration	Not available	80%
	Marino et al. [89]	CD: 8 UC: 2	Retrospective (20% with concomitant IMM)	CD: 75% (mean 1.2 (SD ± 0.7) years]	Not available	Not available	100%
				UC: 0% (mean 1.7 years)			

(continued)

Table 10.1 (continued)

Authors	Number of participants (*n*)	Study design	Relapse rate	Significant predictors of relapse	Predictors evaluated but not found to be significant	Recapture rate
Steenholdt et al. [57]	CD: 53 UC: 28	Retrospective 86% concomitant IMM (CD and UC)	CD: 39% (1 year), 88% (10 years)	CD: longer disease duration	Not available	96% (CD)
			UC: 25% (1 year), 60% (4.5 years)			71% (UC)
Gisbert et al. [40]	27 studies	Systematic review, Meta-analysis	CD: 38% (0.5 year), 40% (1 year), 49% (>2.1 years)	Younger age	–	80%
				Smoking status		
				Longer disease duration		
			UC: 28% (1 year)	Fistulizing perianal CD		
				Low hemoglobin		
				High C-reactive protein		
				High fecal calprotectin		
				Absence of mucosal healing		

	Kennedy et al. [45]	146 CD, 20 UC; 11 cohort totaling 746 patients (meta-analysis)	Retrospective observational	*Observational*	CD: younger age at diagnosis (<22 years old) Elevated white cell count > 5.25×10^9/L Elevated fecal calprotectin (> 50μg/g)	Continued immunomodulator	88% (CD)
				CD: 36% (1 year)		Mucosal healing	76% (UC/IBDU)
				56% (2 year)			
				UC/IBDU: 42% (1 year)	UC: no predictive factor identified		
				47% (2 years)			
				Meta-analysis			
				CD: 39% (1 year)			
			Systematic review, Meta-analysis	UC/IBDU: 35% (1 year)			
	Torres et al. [12]	37 studies	Systematic review	50% (CD/UC), 2 years	Markers of active disease	–	54.7–100% (CD)
					Poor prognostic factors including complicated or relapsing disease course		67–100% (UC)

IMM Immunomodulator, *CD* Crohn's disease, *UC* ulcerative colitis

Table 10.2 Predictors of relapse following anti-TNF-α therapy withdrawal

	UC (Ref.)	CD (Ref.)
Patient factors		
Male		[41]
Young age at diagnosis		[66]
Smoking		[43, 64]
Disease factors		
Phenotypic picture		
Behavior		Fistulizing [53]
Location/extent		Perianal [42, 64]
		Ileocolonic [52]
Markers of disease activity		
Low hemoglobin		[41]
High C-reactive protein		[41, 90]
High leucocyte counts	[90]	[90]
High fecal calprotectin	[56]	[41, 52, 56]
Absence of mucosal healing	[40]	[40]
Absence of normalization of mucosal cytokine gene expression		[58]
Absence of normalization of mucosal TNF-α	[59]	
Treatment factors		
Absence of concomitant immunomodulator	[60]	[60]
Previous immunomodulator failure		[64]
Late initiation of biologic therapy		[66]
Previous biological therapy		[43, 52]
Dose intensification of biologic therapy		[43]
Anti-infliximab antibody		[91]
Previous surgical resection		[41]

Predictive Factors for Relapse

Multiple factors, both modifiable and non-modifiable, have been suggested to predict risk of relapse for IBD. These can broadly be classified into patient factors, disease factors (disease activity and disease phenotype), and treatment factors as illustrated in Table 10.2.

Patient Factors

The prospective STORI trial studied infliximab withdrawal in 115 CD patients who had been treated with combination therapy with an immunomodulator for at least 1 year with a minimum of 6 months of steroid-free remission. On multivariate analysis, males were significantly more likely to relapse than females (HR 3.5; 95% CI 1.7–7.0) [41]. This finding was however not replicated by other studies [42–44].

Younger age at diagnosis was reported by two separate meta-analyses to be an adverse prognostic factor following anti-TNF-α therapy withdrawal [40, 45]. Smoking has been reported as a risk factor for relapse in patients with CD, in keeping with existing data that it augments disease progression [46].

Disease Factors

Disease Phenotype

CD patients with a fistulizing phenotype or with perianal disease carry a high risk of relapse post-anti-TNF-α therapy withdrawal [40, 42]. For (perianal) fistulizing disease, clinical assessment of remission is often suboptimal, and there may be ongoing subclinical inflammation in the fistula tract despite no fistula output [47]. In a prospective cohort study, it was observed that radiological healing lagged behind clinical remission by a median of 12 months [48]. MRI imaging to document healing should be considered prior to drug withdrawal given potential disabling outcomes including fecal incontinence. Similarly, radiologic investigations should be considered for those with small bowel disease where documentation of mucosal healing may be difficult to achieve with endoscopy alone. Internal fistulizing disease and the need for surgery are markers of an aggressive phenotype [40, 49–51]. Ileocolonic CD was reported in a prospective observational study to be predictive of relapse [52]. This observation was however not replicated by other studies [41, 42, 44, 53, 54].

Disease Activity

Active disease at time of drug withdrawal has consistently been shown to predict relapse [12, 40, 41, 44, 45, 52, 55]. Both clinical assessment and biochemical markers can be useful in predicting relapse (Table 10.2). This includes the presence of a low hemoglobin or elevated leucocyte counts, C-reactive protein concentrations, or a high fecal calprotectin level with some variation in the cutoff thresholds reported by different assays and studies [41, 45, 56]. The STORI trial observed hazard ratios of 6.0 (95% CI 2.2–16.5) for hemoglobin <145 g/L, 2.4 (95% CI 1.2–4.7) for leucocyte counts >6 × 10^9/L, 3.2 (95% CI 1.6–6.4) for C-reactive protein concentrations of ≥5 mg/L, and 2.5 (95% CI 1.1–5.8) for fecal calprotectin ≥300 μg/g [41].

Mucosal healing appears to be the most important prognostic factor for durable disease remission. In the Gisbert meta-analysis of 27 studies on the effects of anti-TNF-α therapy discontinuation in IBD, there was a significantly lower rate of relapse if mucosal healing was achieved prior to anti-TNF-α therapy withdrawal. The risk of relapse in CD patients at 1 year was 26% in those with mucosal healing versus 42% in those who did not achieve mucosal healing. The corresponding risk of relapse was 33% versus 50% for those with UC at 2 years [40]. Duration of remission has also been considered. Most studies attempted anti-TNF-α therapy

withdrawal after a median of 7.5 months to 2 years of treatment. Despite this, 21–45% of patients relapsed at 1 year [41–43, 49, 52, 54, 57]. While mucosal markers of sustained remission have been proposed, they have not been as well validated [58, 59].

Overall, anti-TNF-α therapy withdrawal should only be considered in those who have achieved sustained mucosal healing, and patients should be made aware that even in this scenario, the risk of relapse is still considerable, with one third of patients relapsing at 1 year and with this proportion increasing in the long term.

Treatment Factors

In Table 10.1, data on withdrawal of anti-TNF-α therapy was listed, and importantly, many cohorts received ongoing immunomodulator therapy (Table 10.1). This is important to consider, as Casanova et al. reported preliminary data in a retrospective observational study that ongoing maintenance immunomodulator therapy reduced the risk of relapse after withdrawal of the anti-TNF-α therapy by one third (HR = 0.70; 95% CI = 0.57–0.88) [60]. Although the risk of relapse would expectedly be lower for those in whom the immunomodulator was withdrawn in comparison with those who stopped the anti-TNF-α therapy in the setting of combination therapy, this has not been directly compared. SPARE, an ongoing prospective randomized trial comparing combination therapy to immunomodulator monotherapy and infliximab monotherapy, will hopefully confirm and provide further data on this area [61].

The role of therapeutic drug monitoring in predicting successful anti-TNF-α therapy withdrawal requires further prospective evaluation and validation. Drobne et al. observed in a retrospective study that CD patients on infliximab maintenance therapy who had high infliximab drug levels, defined as >5 μg/mL in this study, versus undetectable infliximab trough levels at time of immunomodulator withdrawal had a 0% versus 86% risk of relapse following immunomodulator withdrawal at median follow-up of 29 months. The median co-therapy duration was 13 months (IQR, 8–23 months). While it is stated that immunomodulators were withdrawn in patients with a durable response (CRP <10 mg/L with a persistent improvement of IBD symptoms), the goal of mucosal healing was not deemed a prerequisite to therapy withdrawal [62]. In contrast, a study by Ben-Horin identified a subgroup of patients with undetectable trough levels of anti-TNF-α who remained in clinical remission after drug withdrawal. Importantly, 95% of these patients had endoscopic or MRE evidence of absence of active inflammation. Rather than suggesting an imminent drug failure, this may represent a subgroup of patients whose clinical status is no longer dependent on anti-TNF-α therapy or may have non-TNF-α-mediated disease. As therapeutic drug monitoring is increasingly used, identification of a subgroup of patients who will not be disadvantaged from anti-TNF-α therapy withdrawal may therefore be possible [63]. Further prospective validation is required into the role of therapeutic drug monitoring in prognosticating patients for

anti-TNF-α therapy withdrawal, and to quote Ben-Horin, "[This] illustrates[s] the need for careful and case-by-case interpretation of drug/anti-drug antibody results, as interpretation may differ substantially depending on the context of the specific clinical situation when the blood test was ordered" [63].

Those with more active disease, requiring dose intensification of anti-TNF-α therapy during a 1-year course of biological therapy, were identified as at greater risk of relapse on therapy withdrawal (OR 12.96; 95% CI = 1.39–120.5) [43]. Further, previous immunomodulatory failure and previous exposure to biologic therapy were at increased risk of relapse following anti-TNF-α therapy withdrawal [43, 52, 64].

Patients with CD of short disease duration (less than 2 years) are more likely to benefit from anti-TNF-α therapies and may also have a lower risk of relapse following anti-TNF-α therapy withdrawal [5, 41, 54, 65–67]. This likely reflects that therapy was commenced before the irreversible immunological and structural damage occurred [68]. In keeping with this, patients with a previous surgical resection are at increased risk of relapse [41].

How to Withdraw Anti-TNF-α Therapy if Necessitated

The STORI trial has suggested that withdrawal of anti-TNF-α therapy is possible with careful risk stratification. Six risk factors were identified as predictors of relapse: male gender, absence of surgical resection, leukocyte counts $>6.0 \times 10^9$/L, hemoglobin ≤145 g/L, C-reactive protein ≥5.0 mg/L, and fecal calprotectin ≥ 300 μg/g. For those with two or less risk factors, the relapse rate was 15% at 1 year [41]. Before a patient is considered for drug withdrawal, they should be in deep remission with absence of clinical, biochemical, and endoscopic disease activity. The patient should lack symptoms of rectal bleeding, abdominal pain, urgency, and increased stool frequency. Laboratory markers/fecal calprotectin/imaging should be normal although validated cutoff points especially for fecal calprotectin are lacking. On endoscopy, there should be an absence of mucosal ulceration with a SES-CD score of <3 for CD [69]. For UC, the Mayo Clinic Score remains the most commonly used with most trials defining mucosal healing as a Mayo score of 0 or 1. A recent longitudinal study suggested that a Mayo score of 0 predicted a lower risk of relapse at 6 months, in comparison with a Mayo score of 1 (9.4% versus 36.6%, $p < 0.001$) [70]. Currently, histologic remission is not considered standard of care.

The minimum duration of deep remission requires prospective validation. The EPACT-II expert panel suggested a stopping rule of 4 years for immunomodulator/anti-TNF-α agent monotherapy for luminal CD patients in clinical remission. This can be shortened to 2 years for anti-TNF-α agent monotherapy if both clinical and endoscopic remission are achieved. For CD patients on combination immunomodulator/anti-TNF-α agents, the anti-TNF-α agent was judged appropriate to be stopped after 2 years if clinical and/or endoscopic remission was achieved [71].

No recommendation was made for fistulizing CD. There is currently no recommendation on the minimal duration of remission for individuals with UC prior to consideration of anti-TNF-α therapy withdrawal. In a systematic review of 14 studies on withdrawal of anti-TNF-α therapy in UC, duration of remission before study entry (minimum 6 months) was only stated in two studies [12].

Rather than withdrawing the biologic therapy completely, there are emerging studies of the use of lower maintenance doses in an attempt to minimize drug exposure and reduce costs. A prospective study on a cohort of 12 postoperative CD patients observed that when infliximab was given at lower doses titrated to endoscopic findings, infliximab doses of 3mg/kg were adequate to achieve mucosal healing [72]. However, this was a selected cohort of patients who underwent surgically induced remission and therefore may require lower circulating drug levels related to a smaller disease burden. Another prospective study on 16 CD patients observed that infliximab intervals of 10 weeks rather than 8 weekly infusions as titrated according to fecal calprotectin were as efficacious and did not increase the risk of loss of response provided that fecal calprotectin levels are within the normal range [73]. Prospective validation of these findings will be required. Down-titration of anti-TNF-α therapies has been studied in other immune-mediated disease such as rheumatoid arthritis. Even though short-term clinical disease activity and functional outcomes are maintained, down-titration is associated with significant radiological progression which may have long-term clinical implications [74].

There are also emerging data to support titrating biologic dose using therapeutic drug monitoring. In the TAXIT trial, it was shown that titrating infliximab dose to achieve a trough level of 3–7 mcg/mL resulted in higher remission rates than those with levels of <3 mcg/mL and also saved costs by allowing dose de-escalation for those with levels >7 mcg/mL [75]. The concept of titrating infliximab according to drug level (aiming for >3 mcg/mL) versus clinical symptoms in active CD was also explored in the TAILORIX trial. While proactive trough level-based dose intensification was not superior to clinically based dose adaptation, the full results of the study are still eagerly awaited [76].

Further prospective studies are required, as disease relapse may still occur following drug withdrawal even in those who demonstrate deep remission with mucosal healing, with a sufficiently long observational follow-up. Importantly, attention should be given to identify those who relapse early and restart treatment promptly. Currently, there is insufficient evidence to recommend whether complete drug withdrawal can be achieved or if a maintenance immunomodulator is always required. Close monitoring for disease recurrence is mandatory although there are no strong recommendations on the interval of monitoring. It has been proposed that fecal calprotectin and serum C-reactive protein should be performed every 8–12 weeks, with a low threshold to reevaluate if the CRP increases beyond 5 mg/L or fecal calprotectin is ≥300 mcg/g [41, 47]. The EPACT group proposed routine ileoscopy to be done at year 1 and year 4 in the absence of clinical symptoms [71]. Imaging modalities should be tailored to disease location and phenotype.

Summary

Based on the current literature, withdrawal of anti-TNF-α therapy is possible in highly selected patients who are in deep remission with a favorable risk profile. However, withdrawal of anti-TNF-α therapy is a decision that requires detailed discussion between the physician and patient, a meticulous assessment of a patient's risk profile, and acknowledgment of the risk of long-term disease relapse. The assessment should take into account disease phenotype, disease activity, treatment history, as well as consideration of specific situations including comorbidity status, patient age, and the presence of recurrent infections, malignancy, or pregnancy. Patients with active disease, younger disease onset, smoking habits, complex fistulizing or perianal CD, and history of intestinal resection or those who were required recent anti-TNF-α therapy dose escalation are considered high risk for relapse. Individualized management, with the patient closely involved in the decision-making process with appropriate counseling of the risk of relapse, and lower re-treatment response rates should be undertaken. Close interval monitoring is strongly recommended to identify early relapse and to provide prompt re-initiation of treatment.

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Chapter 11
Biologic Therapy in Pediatric Inflammatory Bowel Disease

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Over the past several decades, there has been an increasing incidence of pediatric inflammatory bowel disease (IBD) internationally [1]. Pediatric patients often have more severe and extensive disease when compared to adult presentation, with more panenteric and colonic involvement in Crohn's disease and pancolitis in ulcerative colitis, which may impact disease course and response to therapy [2, 3]. Many unique considerations must be taken into account when selecting the optimal therapy for a pediatric patient with IBD, including the effect of therapy on growth parameters, the cumulative or long-term adverse effects of multiple treatments over the course of a patient's life, and the inherently longer duration of treatment given the age of diagnosis. Biologic agents have been used for the treatment of pediatric IBD for more than 20 years, and these therapies have not only improved clinical and histologic evidence of bowel inflammation in patients who have refractory or severe disease but have also led to substantial improvement in the quality of life of these patients.

Infliximab for Pediatric Crohn's Disease

Infliximab, a monoclonal, chimeric antibody which acts as an antagonist to TNF-α, has been used for the treatment of pediatric Crohn's disease (CD) for over 20 years; however, the medication only recently received FDA approval in 2006 for the treatment of moderately to severely active pediatric CD. Initial reports of use in pediatric CD focused on small numbers of patients receiving spot or induction dosing of

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infliximab, with these patients having excellent response rates. Kugathasan et al. reported outcomes of 15 consecutive children with medical refractory CD treated with a single 5 mg/kg dose of infliximab [4]. Fourteen of these patients had improvement after this single dose, and 10 of 15 children were in clinical remission (defined as Pediatric Crohn's Disease Activity Index (PCDAI) ≤ 15) by 10 weeks. Steroid doses were also significantly lower at 4 and 10 weeks. Unfortunately, in a subsequent 52-week follow-up, 11 of the 14 responders experienced clinical relapse, with patients with disease over 2 years having a shorter duration of response. A multicenter study of 21 pediatric patients with moderate to severe CD randomized to receive a single infusion of 1 mg/kg, 5 mg/kg, or 10 mg/kg of infliximab showed similar results with 100% of patients achieving clinical response (≥10-point improvement in PCDAI or ≥70 improvements in modified CDAI) and 48% achieving clinical remission, defined as a PCDAI < 10 or a modified CDAI <150, at some point during the 12-week observation period [5]. Patients who received 5 mg/kg and 10 mg/kg doses of infliximab had higher rates of remission at the 12-week follow-up evaluation compared to those who received 1 mg/kg. Nine patients had endoscopic assessment of disease prior to and 4 weeks after receiving infliximab. Endoscopic lesion severity scores improved by a median of 7%, 69%, and 52% in 1, 5, and 10 mg/kg infliximab groups, respectively. Serum infliximab concentrations were found to be similar in both pediatric and adult populations with duration of detectable levels being proportional with dose—levels were detected through week 4 in 1 mg/kg group and compared through week 8 and week 12 in 5 and 10 mg/kg groups, respectively. While the above studies assessed response to a single infusion of infliximab, Cezard et al. prospectively evaluated the response of 21 children with severe CD, most with corticosteroid-dependent disease, who received induction dosing with 5 mg/kg infliximab on days 0, 15, and 45 [6]. Nineteen children were in clinical remission (Harvey Bradshaw (HB) index <4) at day 4, and steroid use was significantly decreased at 3 months. However, similar to the above studies, response was not durable, and 19 of the patients (90%) experienced relapse despite continuing immunosuppressive therapy, with 37% of relapses occurring before 3 months.

As highlighted above, the optimal frequency of medication administration was not known during the early years of infliximab use in the pediatric population. It was initially hypothesized that children could potentially develop a prolonged response to infliximab compared to adults, obviating the need for regularly scheduled infusions; however, preliminary studies showed frequent relapse after single dose or induction dosing. Episodic on-demand infliximab dosing, i.e., giving additional doses if patient relapsed, was another consideration in pediatric patients. This strategy was further evaluated in a randomized, multicenter, open-label study by Ruemmele et al. [7] Thirty-one children who were in remission after three infliximab infusions (induction dosing) were randomized to scheduled infusions every 2 months or "on-demand" dosing. During the course of the trial, 92% of patients who received episodic infliximab therapy experienced a relapse compared to 23% of patients receiving scheduled infliximab therapy every 8 weeks. Additionally, the time to relapse was shorter in patients who received episodic infliximab infusions with an average time to relapse of 120 days compared to 150 days in the scheduled

infusion study group. At week 60, 61% of patients on episodic infliximab therapy were in remission compared to 83% of patients receiving scheduled infliximab.

The REACH study, a large multicenter, randomized, open-label trial, prospectively evaluated the safety and efficacy of induction and maintenance of infliximab in moderately to severely active pediatric CD and demonstrated superiority of every 8-week maintenance infliximab infusions compared to every 12-week infusion schedule [8]. One hundred and twelve patients with moderate to severe CD despite immunomodulatory therapy received three-dose induction regimen of infliximab 5 mg/kg. Responders were then randomized to receive maintenance infliximab 5 mg/kg every 8 or 12 weeks. After completion of induction therapy (week 10 assessment), 88% of patients had responded, defined as a decrease in PCDAI score of at least 15 points, and 59% of patients were in clinical remission, defined as a PCDAI <10. At week 54, 64% of patients receiving infliximab every 8 weeks had a clinical response, and 56% were in clinical remission without the need for a dose adjustment compared to a clinical response rate of 33% and clinical remission rate of 23.5% in the every 12-week study group. Corticosteroid use significantly decreased, and IMPACT III quality of life scores improved in both 8- and 12-week groups over the course of the study. Sixty participants entered the REACH open-label extension—33 patients receiving infliximab 5 mg/kg every 8 weeks, 12 patients receiving 10 mg/kg every 12 weeks, and 15 patients receiving 10 mg/kg every 8 weeks [9]. In these patients receiving scheduled infliximab for up to 3 years, most had sustained clinical benefit, with approximately 80% having no or mild disease based on the physician global assessment (PGA) at assessments.

Additional studies have evaluated the long-term outcomes of infliximab therapy. In one population-based retrospective study of 66 pediatric CD patients treated with infliximab (five receiving episodic treatment) followed for a mean of 41 months, prolonged clinical response was seen in approximately 70% of patients [10]. However, in patients considered infliximab dependent ($n = 37$), 57% had recurrence of symptoms prior to the 8-week interval, requiring increased dose to 10 mg/kg or shortened infusion intervals to maintain response. In a similar study by Crombe et al. of 120 patients with pediatric CD, 54% had long-term efficacy of therapy; 27% of the entire cohort required dose optimization (shortened interval and/or increased dose) [11]. Forty-two percent of these patients were receiving episodic infusions, which may account for the lower long-term response rate compared to other efficacy studies. Finally, a multicenter cohort study of patients enrolled in the Pediatric Inflammatory Bowel Disease Collaborative Research Registry evaluated long-term outcomes of pediatric CD patients treated with infliximab maintenance therapy [12]. In total, 202 of 729 patients received infliximab; the majority of whom received infliximab early in their disease course, with 60 patients (30%) receiving infliximab within 3 months of their diagnosis, 64 patients (32%) between 3 and 12 months from diagnosis, 47 patients (23%) between 12 and 24 months from diagnosis, and 31 patients (15%) after 24 months from diagnosis. One hundred and twenty eight patients were ultimately included in the outcome cohort with 121 patients receiving continuous infliximab maintenance therapy. After 1 year of infliximab maintenance therapy, 32% of patients had mild disease, and 54% had inactive disease as assessed

by PGA; by 2 years, 21% of patients had mild disease and 67% had inactive disease; and at 3 years of maintenance therapy, 30% had mild disease and 57% had inactive disease. However, almost half (63/128) of the patients required anti-TNF dose adjustments during their course on infliximab therapy. The above results emphasize the long-term benefits and durability of infliximab therapy in pediatric CD, but also the need for dose optimization to maintain response in a substantial proportion of patients. Loss of response has been reported to be as high as 33–50% in pediatric CD patients over a follow-up period of 3–5 years. With so many variables involved in the treatment of pediatric inflammatory bowel disease, attempts have been made to identify predictors of response to infliximab. Grover et al. studied 47 patients with refractory, luminal CD who had an initial response to induction infliximab therapy [13]. Twenty-eight patients (60%) developed a sustained primary response for an average of 2.8 years, and 19 patients (40%) had a loss of response at a median of 11 months. It was found that a loss of response was associated with a lower BMI and lower height *z*-scores prior to infliximab induction and a higher CRP after induction, which may be surrogates for severity of inflammation. Patients were more likely to have a sustained primary response if immunomodulator therapy was continued beyond induction therapy with infliximab, likely related to effects on infliximab drug levels. In this study, duration of disease, time to infliximab therapy, disease severity, disease location, complicating phenotypes, and steroid dependency were not associated with loss of response.

As the incidence of pediatric inflammatory bowel disease has risen, there has also been an increase in early-onset disease in patients younger than 8 years of age. A retrospective study by Kelsen et al. evaluated the safety and efficacy of infliximab in this subgroup of patients with early-onset disease [14]. Thirty-three patients with either CD, ulcerative colitis (UC), or inflammatory bowel disease unclassified (IBD-U) who had initiated infliximab therapy prior to 7 years of age were assessed. After 1 year of infliximab therapy, 10%, 25%, and 0% of patients with CD, UC, and IBD-U, respectively, had a clinical response. Nineteen patients (58%) required either dose escalation or a reduction in interval between infusions. The proportion of patients who were maintained on infliximab steadily decreased over time with 36% on infliximab maintenance after 1 year, 18% after 2 years, and 12% after 3 years. In a subset of patients younger than 5 years of age, only 25% were continued on infliximab after 1 year, and only 10% were maintained on infliximab after years 2 and 3 combined. Ultimately, it was found that children less than 7 years of age with early-onset IBD were less likely to continue infliximab as maintenance therapy compared to older pediatric patients assessed in the REACH trial. These findings may be related to specific pharmacokinetics of infliximab in younger patients or potentially related to the colonic-predominant phenotype seen in early-onset IBD.

Adult studies have demonstrated the efficacy of infliximab for treatment of perianal CD, and several small studies have shown similar benefit of infliximab in pediatric patients with this complicated phenotype [6, 15, 16]. Post hoc analysis evaluated the effect of infliximab in a subpopulation of 31 patients with concurrent perianal Crohn's disease from REACH [15]. In 22 patients that had baseline perianal disease, 41% had complete or partial response after a single dose of infliximab,

with 73% having response at 10 weeks (after completion of induction dosing), and the proportion of patients responding after randomization to 8- and 12-week infusion intervals remained consistent during maintenance infusion (73% at 54 weeks, 1 partial, 15 complete). Nine patients developed perianal disease during treatment with infliximab, but most (78%) had response with additional infusions. Cezard et al. showed similar results in a subset of 12 patients with perianal fistula who received three-dose induction regimen of infliximab, with all patients having closure of fistula by 3 months [6]. However, as 90% of the total study population experienced a relapse during the 12-month follow-up, it is possible that some patients had recurrence of perianal disease without scheduled maintenance infusions. Several factors may be associated with a positive response to infliximab therapy in treatment of perianal disease in pediatric CD including shorter duration of disease (<1 year), number of fistulas (≤1), and baseline HB index (<5) [16, 17]. Prior to initiating infliximab therapy for perianal disease, it is important to assess for complicating factors such as rectal inflammation or complex fistula via colonoscopy and pelvic magnetic resonance imaging (MRI) and/or rectal exam under anesthesia as the combination of infliximab and surgery may lead to improved outcomes [18].

Infliximab for Pediatric Ulcerative Colitis

Infliximab was FDA approved for the treatment of moderate to severe pediatric ulcerative colitis in 2011; however, similar to pediatric CD, this medication was used off-label for pediatric patients with refractory colitis for several years prior to approval based on adult data and smaller pediatric case series demonstrating efficacy of this therapy. A preliminary case series by Mamula et al. showed that seven of nine patients (77%) with moderate to severe UC that was refractory to traditional therapy had a clinical response to infliximab as measured by the PGA, with six of these patients having inactive disease 2 weeks after the infusion [19]. A steroid-sparing effect was seen and 66% of these patients were able to discontinue corticosteroid therapy. Nine patients in this cohort were reevaluated after a minimum of 2 years of follow-up, and 73% of these patients were considered to be responders to the initial dose [20]. Two of these patients lost response within 9 months, and the remaining five responders had a sustained response, three of whom were doing well without ongoing infliximab therapy. A clinical response rate of 88% was seen in an additional eight patients with refractory UC treated with infliximab [20]. In total, 14 of 17 patients (82%) developed a short-term response, and 10 patients (63%) developed a long-term response to infliximab therapy. Another retrospective single-center study evaluated the response to infliximab in 12 pediatric patients with UC, 3 with fulminant colitis, 3 with an acute relapse of disease, 5 with steroid-dependent colitis, and 1 with corticosteroid-refractory colitis [21]. Nine patients (75%) developed a complete short-term response, two had a partial response, and eight patients had a long-term response to infliximab (median follow-up 10.4 months). In this small study, long-term response to infliximab therapy was more likely in patients who

were receiving concomitant mercaptopurine. A larger single-center retrospective series by McGinnis et al. evaluated the short- and long-term response to infliximab induction in 40 pediatric UC patients with steroid-dependent or steroid-resistant disease [22]. Twenty-eight patients (70%) had a clinical response to infliximab, including 9 of 12 patients with steroid-dependent disease and 18 or 27 with steroid-refractory disease. Over the study period, 20% of responders had undergone colectomy compared to 82% of nonresponders. A multicenter cohort, inception cohort study of 332 pediatric patients with UC prospectively evaluated outcomes of 52 patients who received continuous maintenance therapy or episodic treatment with infliximab [23]. Approximately 35% of these patients had corticosteroid-free inactive or mild disease at 3-, 6-, 12-, and 24-month assessments, and 61% were colectomy-free at 24 months. Looking at the subset of patients receiving continuous maintenance therapy, approximately 50% of the patients had inactive or mild disease across these time points, and the likelihood of being colectomy-free was 74% at 24 months, suggesting additional benefit on maintenance dosing. These remission rates were lower than previously reported; however, 50% of this cohort was hospitalized at initiation of infliximab, perhaps suggesting more severe or chronic disease.

Patients with chronic ulcerative colitis refractory to treatment with steroids, immunomodulators, and aminosalicylates may have decreased response to infliximab therapy. Fanjiang et al. retrospectively evaluated response to infliximab in acute UC ($n = 16$), defined as new-onset UC that was refractory to intravenous steroid therapy or an acute exacerbation of nonsteroid-dependent UC, compared to response in chronic, steroid-dependent UC ($n = 11$) [24]. Patients received standard induction dosing followed by every 8-week infusions. Patients with acute UC had lower-average Lichtiger colitis activity index (LCAI) scores at 1 and 2 months after therapy and more durable long term response. Over a mean follow-up of 27 months, 75% of patients with acute UC did not require steroid therapy or colectomy compared to 27% of chronic UC patients.

Based on retrospective analysis of a population-based UC cohort, 28% of children <15 years old require hospitalization for an acute severe exacerbation of their disease, and almost 50% these patients are refractory to intravenous corticosteroids [25]. As demonstrated by colectomy rate in the study by Fanjiang et al. [24], there is some evidence that patients presenting with acute, fulminant, severe colitis may have an improved response to treatment with infliximab compared to those with chronic, steroid-dependent colitis. In a prospective, multicenter study of 128 children with acute, severe colitis requiring intravenous corticosteroid therapy, 37 patients (29%) failed to respond to corticosteroids and required rescue therapy, 33 of whom receive infliximab [26]. Twenty-five (75%) of these patients responded, with 7 patients entering clinical remission and 18 patients being discharged with mild disease severity. At 1 year, 55% of these patients had sustained response (11 receiving maintenance therapy and 7 receiving only induction therapy). Patients with newly diagnosed with UC, shorter duration of disease, and more severe disease activity at admission and after 3 days of IV steroid treatment were less likely to respond to infliximab. A smaller respective cohort of 29 hospitalized patients with a

severe colitis showed that response to infliximab may decrease with time, and dose escalation in this population was commonly needed, occurring in 62% of this cohort [27]. Even after dose escalation, only 39% of these patients remained on infliximab therapy after 1 and 2 years and 29% after 3 years. Lower BMI *Z*-score and serum albumin as well as a higher ESR at baseline were associated with dose escalation, but not infliximab failure.

There has been one randomized open-label prospective study evaluating the efficacy and safety of infliximab in induction and maintenance therapy for moderately to severely active pediatric UC [28]. Results of this study led to FDA approval of infliximab for the treatment of pediatric UC in 2011. Sixty patients with medically refractory, moderately to severely active UC were given 5mg/kg of infliximab at 0, 2, and 6 weeks, and those with response were then randomized to receive infusions either 8 weeks or every 12 weeks. Forty-four patients (73%) responded to induction therapy, and at week 8, 41 patients (68.3%) had achieved mucosal healing. Forty-five patients were subsequently randomized to receive infliximab at 8-week or 12-week intervals. At week 54, 38.1% of patients receiving every 8-week infusions were in remission compared to 18.2% receiving every 12-week dosing; a reduction in corticosteroid use at 54 weeks was observed in patients receiving 8-week infusions, but not in the 12-week infusion group. Similar to previous data, dose escalation was common, and approximately 50% of patients required either an increase in infliximab dose or more frequent infusions, with more patients requiring a step-up in therapy in the every 12-week infusion group. Infliximab concentrations were obtained at multiple points during the course of this study; higher concentrations at week 8 were associated with clinical response and mucosal healing, and higher median week 30 troughs were noted in patients receiving every 8-week dosing, likely accounting for higher proportion of patients in this group who had sustained efficacy [29]. In summary, this prospective randomized open-label study and additional retrospective and prospective observational cohorts clearly indicate that infliximab is an effective therapy for moderate to severe UC with benefits in both corticosteroid-dependent and corticosteroid-refractory disease and may help prevent colectomy in pediatric UC patients.

Adalimumab for Pediatric Inflammatory Bowel Disease

Despite the promising outcomes associated with infliximab in the treatment of pediatric IBD, historically, up to 50% of patients require dose escalation, and approximately 33% of patients discontinue infliximab therapy, most commonly due to loss of response. The need for additional anti-TNF agents was recognized prompting the development of adalimumab, a recombinant, fully human, monoclonal anti-TNF antibody. Compared to infliximab, adalimumab provides an inherently decreased risk of neutralizing antibody formation because of the therapy's strictly human antibody components. Initial reports of adalimumab use in pediatric inflammatory bowel disease focused on patients who had become intolerant to infliximab. Noe

et al. evaluated the response on adalimumab therapy of ten patients (seven CD, three UC) previously treated with infliximab, nine of whom developed a hypersensitivity reaction to this medication [30]. Eight patients responded to adalimumab with decreased PCDAI in patients with CD and decreased LCAI in patients with UC. Seven patients were on concomitant corticosteroids at time of adalimumab initiation, and four patients were able to successfully taper off this medication within a mean of 5.5 months. A second small retrospective study of 14 pediatric patients with CD who had an allergic infusion reaction or decreased response to infliximab despite dose escalation showed less robust response to adalimumab; however, a majority of patients still responded, with 50% having complete response and 14% having a partial response; in the subset of patients with perianal disease, three of five patients maintained fistula closure with this therapy [31]. The differences in the outcomes of these studies may be due to variation of adalimumab dosing, which was not controlled, and patient selection, with the former study focusing only on patients who had an infusion reaction to infliximab rather than including those with suboptimal response. Subsequent larger population-based cohort studies have noted initial response to adalimumab in approximately two-thirds of patients who have failed infliximab therapy [32, 33]. RESEAT, a large, multicenter retrospective evaluation of the safety and effect of adalimumab therapy, examined the outcomes of 115 patients with pediatric Crohn's disease from 12 centers who had received at least one dose of adalimumab [34]. Ninety-five percent of this cohort had previously received infliximab therapy, and most had discontinued therapy due to secondary loss of response (47%) or infusion reactions/delayed hypersensitivity (45%). The majority of patients initially received an induction regimen (160/80 mg or 80/40 mg) followed by 40 mg every other week; 27% of patients required dose escalation, most commonly to weekly administration. Clinical response, defined by a decrease in PGA from moderate/severe to mild/inactive or from mild to inactive, at 3, 6, and 12 months, occurred in 65, 71, and 70% of patients, respectively. Clinical remission rates (PGA inactive) at similar time points were 32, 43, and 49%, respectively. Overall, steroid exposure decreased over the study time points, and 42% of the cohort was in steroid-free clinical remission at 12 months, again highlighting the efficacy of this therapy in pediatric CD.

An initial preliminary prospective observational study by Viola et al. showed a remarkable response to adalimumab therapy in 23 patients with moderate to severe pediatric CD, nine of whom had not received previous anti-TNF therapy [35]. In this study, patients were administered induction doses of adalimumab at 0 and 2 weeks followed by maintenance therapy injections every other week over the course of 48 weeks. The percentage of patients in clinical remission increased from 36.3% after two weeks of adalimumab therapy to 65.2% after 48 weeks of treatment. Clinical response rates also improved from 87 to 91% at these same time points, respectively. The average dosage of corticosteroid, PCDAI, CRP, and ESR levels significantly decreased throughout the course of the study. Overall response and remission rates were higher in this prospective cohort, which may be related to higher dosing regimens, with 65% of the cohort receiving adalimumab maintenance therapy of 80 mg every other week through at least 12 weeks. The IMAgINE

1 study, a multicenter randomized trial, evaluated the safety and efficacy of adalimumab in pediatric CD [36]. Similar to the REACH clinical trial, patients received open-label weight-based induction adalimumab (two doses), followed by double-blind maintenance dosing regimens—high dose compared to low dose (high dose, >40 kg received 40 mg every other week and <40 kg received 20 mg every other week; low dose, >40 kg received 20 mg every other week and <40 kg received 10 mg every other week). One hundred and ninety-two patients with moderate to severe Crohn's disease (PCDAI >30) received induction therapy, and 188 patients were randomized based on clinical response to induction dosing (decrease and PCDAI $\geq$ 15) and prior exposure to infliximab therapy (approximately 44% of study participants). After induction (week 4), 155 patients (82.4%) had a clinical response, and 52 patients (27.7%) were in clinical remission. At week 26, 53.7% of patients had a clinical response, and 33.5% of patients were in clinical remission; 28.2% and 35.1% had a clinical response and were in clinical remission at 52 weeks, respectively. A higher proportion of patients in the high-dose regimen were in remission at both of these time points, although the difference was not statistically significant. Of the 71 patients that were on steroid therapy at baseline, 65.8% of patients in the low-dose group and 84.8% of patients in the high-dose group had successfully discontinued this therapy. The proportion of patients experiencing fistula improvement and closure was also higher in the high-dose group. Finally, in the high-dose group, infliximab-naïve patients had higher remission and response rates at both week 26 and 52 compared to patients who had previously been treated with this therapy.

Analogous to experience with infliximab, in the IMAgINE 1 trial, 50.5% of patients in the low-dose adalimumab therapy and 37.6% of patient in the high-dose adalimumab therapy required dose escalation to weekly therapy after week 12 due to nonresponse or disease exacerbation [36]. Efficacy of dose escalation was evaluated in this subpopulation at 52 weeks [37]. Of the 83 patients who escalated to weekly therapy, 51.8% had a clinical response and 24.1% achieved clinical remission, with a higher proportion of patients in the high-dose group achieving these end points (57.1% and 31.4%, respectively). Patients on immunomodulator therapy and patients randomized to the high-dose group were less likely to require dose escalation to weekly therapy. Long-term efficacy of adalimumab was evaluated in the IMAgINE 2 study [38]. One hundred patients who responded to adalimumab at any time during IMAgINE 1 were enrolled in this open-label extension and followed through 240 weeks. Overall 41% who entered IMAgINE 2 were in remission, and 48% had achieved response at 240 weeks, and for patients who entered IMAgINE 2 in remission, remission was maintained in 45% at week 240. Corticosteroid use continued to decrease during the course of this study, and among patients who were on corticosteroids at time of entry into IMAgINE 1, corticosteroid-free remission increased from 40.5% at enrollment into IMAgINE 2 (week 52) to 63.2% at week 240.

Adalimumab is not FDA approved for the treatment of pediatric ulcerative colitis, and there is limited published data regarding the use of adalimumab therapy in children with ulcerative colitis, but in clinical practice, adalimumab therapy is used

off-label as a second-line biological therapy in refractory pediatric UC. An early report by Noe et al. evaluated the short-term response of adalimumab in pediatric IBD; three patients with UC who had failed infliximab were included in this retrospective, two of whom responded to adalimumab based on decreased LCAI score, and the third patient required colectomy for refractory disease [30]. A slightly larger retrospective review of 11 pediatric patients with UC treated with adalimumab after loss of response or intolerance to infliximab showed similar outcomes with 55% of patients achieving clinical remission at 6 months and through follow-up (mean duration of therapy 21.5 months) [39]. Four patients did require colectomy for refractory disease, and the median time to colectomy was 7 months after initiation of adalimumab therapy. A prospective multicenter randomized double-blind placebo-controlled study evaluating the efficacy and safety of adalimumab in pediatric patients with moderate to severe UC is ongoing (ClinicalTrials.gov identifier: NCT02065557) and will hopefully shed more light on the role of adalimumab in this complicated disease. Overall adalimumab appears to have significant efficacy in pediatric IBD, and based on a single-center study of utilization trends from 2007 to 2012 of anti-TNF in adults and children with inflammatory bowel disease, there has been a rise in the use of this medication; however, infliximab remains the dominant anti-TNF therapy, particularly in the pediatric population [40].

Anti-TNF Therapy Impact on Growth and Bone Health

Growth impairment is a common extraintestinal manifestation of pediatric IBD, particularly in CD. Decrease in height velocity has been reported in pediatric CD prior to diagnosis, and up to 60% of children will have a decrease in height percentiles during their disease course [41–43]. The etiology of growth impairment is multifactorial. Prior to diagnosis, patients may have malnutrition from decreased intake, possibly related to anorexia induced by increased circulating TNF-α, increased losses, and increased metabolic demands from inflammation; additionally, inflammatory cytokines, specifically TNF-α, interleukin 1, and interleukin 6, directly impact the growth hormone axis [43–46]. This combination of factors leads to decreased circulating insulin-like growth factor 1 (IGF-1) and growth impairment. After diagnosis, the use of corticosteroids may further impact growth by inhibition of IGF-1. Restoration and promotion of normal linear growth in pediatric patients are important therapeutic goals.

Multiple studies, including REACH and IMAgINE 1, have reported beneficial effects of anti-TNF in restoring growth by improving height velocity. Walters et al. retrospectively evaluated linear growth in 32 patients with active CD, mostly (59%) in early puberty (Tanner I–III). In the analysis of all patients, height velocity increased from a mean of −0.51 to +2.4 after 12 months of therapy [47]. Height velocity improvement was dependent on pubertal stage, with improvement seen in patients in early puberty compared to no improvement in patients near the end of puberty (Tanner IV–V). Patients in early puberty who achieved complete

symptomatic remission also had more substantial improvement in linear growth compared to those who only had a partial clinical response. A second small retrospective study of 36 children treated with adalimumab demonstrated comparable results with 42% of the cohort demonstrating catch-up growth [48]. Again, improvement in height standard deviation score was seen only in patients in early puberty and was more likely in those patients who had achieved remission. A larger retrospective review of 121 pediatric patients receiving anti-TNF therapy (93 on infliximab, 28 on adalimumab, 93% CD) had similar findings, with disease status (remission) and early pubertal stage predicting improvement in linear growth [49]. One of the primary outcomes in the REACH study was assessment of change in height from baseline to week 54 [8]. In patients with a delay in bone age of at least 1 year, there was significant improvement in height *Z*-scores at both 30 and 54 week, with a mean improvement in *Z*-scores of 0.3 and 0.5, respectively. Although not a primary outcome, significant improvement from baseline to week 26 and week 56 in height velocity *Z*-scores was also observed in both the low-dose and high-dose adalimumab groups in the IMAgINE 1 study [36]. The improvement in linear growth appears to be durable; in one study of 195 patients who received infliximab, patients who were in tanner stage 1 and 2 at induction continue to have increase in height *Z*-score for up to 4 years post initiation of therapy [49]. Anti-TNF therapy does lead to decreased use of corticosteroid effect; however, the corticosteroid "sparing effect" is not the sole reason for growth restoration as improvement in height velocity is seen in both children who do and do not receive corticosteroid therapy [48, 50]. A decrease in inflammatory cytokines that directly impact the growth hormone axis likely plays a role in restoration of growth. Anti-TNF therapy is associated with increase in sex hormones (testosterone and estradiol) at 10 weeks and 12 months post initiation across all tanner stages, and in a small study of adult patients with CD, infliximab therapy led to an increase in IGF-1 levels to a level comparable with controls, suggesting possible reversal of growth hormone resistance seen in active disease [51, 52]. Together, these hormonal changes may lead to improvement in linear growth and progression through puberty in pediatric patients.

Decreased bone mineral density (BMD) is prevalent in pediatric IBD and has been reported in 43% of patients with CD and 39% with UC [53]. Although malnutrition, pubertal delay, decreased weight-bearing activities due to illness, and corticosteroid exposure are contributing factors, inflammation also impacts bone health. As a result, children may not attain and/or maintain their peak bone mass, which may impact future skeletal health. Improvement in bone health and vitamin D homeostasis has been observed with anti-TNF therapy. In the REACH study, 112 patients had markers of bone metabolism including bone-specific alkaline phosphatase (BSAP) and N-terminal propeptide of type I collagen (P1NP), products of osteoblast activity, collected at baseline and at 10 weeks [54]. BSAP and P1NP were negatively associated with baseline PCDAI, and both of these biomarkers of bone formation increased during the 10-week interval. The authors hypothesized that improvement in these markers was due to reversal of TNF-α effects on bone growth, decreased corticosteroid exposure, and improvement in linear growth. Griffin et al. evaluated improvement in bone density and structure by tibia

quantitative computed tomography scans in cohort of 74 patients (aged 5–21) initiating anti-TNF therapy [55]. Trabecular BMD *Z*-scores were lower in IBD patients compared to healthy reference participants at baseline and negatively correlated with PCDAI. Trabecular BMD *Z*-scores and cortical structure improved over the 12-month observation interval; younger age was associated with greater increase in trabecular BMD *Z*-scores, but deficits in trabecular BMD *Z*-scores remained. Vitamin D plays also an important role in bone homeostasis, and suboptimal, insufficient, and deficient vitamin D has been noted in pediatric IBD [56]. A recent study of 87 patients with CD, 80 of whom were aged 5–20, assessed short-term changes in vitamin D and mineral metabolism after anti-TNF induction therapy [57]. Although no changes were seen in 25-hydroxyvitamin D (21-OH D), PTH and 1, 25 dihydroxyvitamin D (1, 25-OH D) increased significantly after induction therapy, indicating improved renal conversion of 25-OH D. Although long-term data is limited, these studies suggest a role of anti-TNF therapy in improving short-term bone health in pediatric patients, which, in addition to improvement in linear growth, nutritional support, correction of vitamin D deficiency, and weight-bearing activities, may positively impact future skeletal health.

Vaccination Strategies in Pediatric IBD on Anti-TNF Therapy

Vaccination for prevention of disease is of utmost importance in the pediatric IBD population given the immunosuppression which results from most therapies, including anti-TNF agents. It is recommended that all IBD patients receiving biologic therapy be administered with routine inactivated vaccines according to the recommended schedule detailed by the American Academy of Pediatrics, the Advisory Committee on Immunization Practices, and Centers for Disease Control and Prevention. This includes vaccination for hepatitis A, hepatitis B, diphtheria, tetanus, pertussis, *Haemophilus influenzae* B, pneumococcus (PCV) (13 valent and 23 valent), polio (intramuscular vaccine), and influenza in early childhood and human papilloma virus and meningococcal disease during school age and adolescents. Administration of live virus vaccines, which include rotavirus; intranasal flu vaccine; measles, mumps, and rubella (MMR); varicella; oral polio; oral typhoid; herpes zoster; and yellow fever, is contraindicated in pediatric IBD patients receiving anti-TNF therapy. If clinical presentation allows, these vaccines should be administered several weeks (≥4 weeks for MMR vaccination) prior to initiating immunosuppression or several months after stopping these therapies. Live virus vaccinations such as MMR, varicella, zoster, and rotavirus are not contraindicated in household members of children with IBD on anti-TNF therapy, but vaccine recipients should monitor symptoms, and if vaccine-related symptoms such as rash or diarrhea develop, the recipient should avoid contact with the patient with IBD if he/she has not been appropriately vaccinated [58].

Ideally, inactivated vaccines should be administered at least 2 weeks prior to initiation of immunosuppressive therapy to improve efficacy; however, several

studies have shown immunologic response to vaccines while on immunosuppressive medications, including anti-TNF therapy, although the response may be attenuated when on anti-TNF therapy alone or in combination therapy with an immunomodulator. In one prospective cohort of 60 children with IBD and 53 healthy controls receiving influenza vaccine, the proportion of patient who achieve serologic protection to influenza A was similar to controls, regardless of whether treated with immunosuppressive therapy [59]. However, the response to influenza B was decreased in the IBD population, and immunosuppression did impact response, but 55% still had immunogenicity. Mamula et al. reported comparable findings in 51 pediatric IBD patients and 29 healthy controls; patients on combination therapy with infliximab and immunomodulatory therapy were less likely to respond to influenza A and B antigens, with serologic conversion rates ranging from 90% for influenza A (H3) to 38% for influenza B [60]. Patients on anti-TNF alone were not evaluated, and therefore, it is unclear if the response would be different in this subgroup. Lu et al. reported a similar level of seroprotection in children and young adults with IBD against influenza A (H1N1, H3N2) and B in immunosuppressed compared to nonimmunosuppressed patients, including those patients receiving anti-TNF therapy. Influenza vaccine timing in relation to infusion (at the time of infusion versus midway between infusions) does not appear to affect immunologic response [61]. With regard to other inactivated vaccines, there has been one study of hepatitis B vaccine status and response of 100 pediatric IBD patients receiving infliximab [62]. Forty-four percent of previously vaccinated children were not immune to hepatitis B at initiation of therapy; of the 36 children who received a booster vaccination, 76% had an anamnestic response indicating adequate immunity postvaccination, but children who received infliximab at more frequent intervals were less likely to respond. There is no specific pediatric data, but adult studies have shown a decreased response to pneumococcal and tetanus/pertussis vaccination in IBD patients receiving anti-TNF therapy alone or in combination therapy compared to IBD patients not on immunosuppressive therapy and healthy controls, with the combination therapy leading to significantly decreased immunogenicity to tetanus and pertussis; however, some patients do still have an appropriate response [63, 64]. Based on these combined results, if possible, pediatric IBD patients should receive this vaccination prior to initiating any immunosuppressants; however, in the real world, this is not always feasible given the severity of disease. In the studies that specifically evaluated safety, inactivated vaccines were generally well tolerated, and therefore, despite the concern of decreased immunogenicity, for patients receiving anti-TNF therapy, the benefits of vaccination outweigh the risk. Clinicians need to monitor these patients closely and have a low index of suspicion for evaluating for these infections and initiating appropriate treatment when available regardless of vaccination status. Despite the recommendation for vaccinating patients with IBD, there remains practice variation in the assessment of immunization status in patients with pediatric IBD. In a survey of 178 pediatric gastroenterologists participating in the ImproveCareNow quality improvement network, only 51% of respondents inquired about immunization status, and

30.9% obtained records at the time of diagnosis, a time where there may be opportunities and strategies available for catch-up vaccination prior to initiation of high-dose immunosuppression [65].

Anti-TNF Therapy and Malignancy in Pediatric IBD

Side effects and risks of therapy, including hypersensitivity reactions, infectious complications, and psoriasis, are similar in pediatric patients and are discussed extensively elsewhere in this publication; however, special consideration should be given to the risk of malignancy as this is often the risk that leads to hesitation and indecision for parents and caretakers. Although malignancies, specifically lymphomas, have been reported with anti-TNF agents, there is a growing evidence that the increased risk may be due to combination therapy with thiopurines rather than anti-TNF therapy alone. The most concerning malignancy is hepatosplenic T-cell lymphoma (HSTCL), which has an aggressive course and is often refractory to standard chemotherapy and stem cell transplant. Several cases were reported in the pediatric literature from 2003 to 2006, and by October 2006, there were eight cases of HSTCL in adolescent and young adults treated with anti-TNF reported to the Food and Drug Administration Adverse Event Reporting System [66]. Initial reports were in patients treated with infliximab, but with time and increased use, additional cases were observed after treatment with adalimumab. A systematic review of 36 IBD patients with HSTCL by Kotlyar et al. investigated clinical factors that may impact risk [67]. All 36 patients who developed HSTCL had received thiopurines, and 20 patients (56%) had received concomitant anti-TNF therapy. Risk factors identified included young age (age 10–35 years), male sex (86% of cases where gender was known), and long-term treatment (>2 years) with thiopurines. Although there may be some reporting bias, no cases of HSTCL have been reported in IBD patients treated with anti-TNF monotherapy; however, HTSCL has been reported in one patient with rheumatoid arthritis while receiving anti-TNF therapy without concomitant thiopurines [68]. A more recent systematic review evaluated the risk of lymphoma with anti-TNF for pediatric IBD [69]. Rates of lymphoma of pediatric patients treated with anti-TNF were compared to nonexposed pediatric subjects and adult IBD patients exposed to anti-TNF agents. Two patients treated with anti-TNF therapy developed lymphoma (absolute risk 2.1/10,000 patient-years of follow-up evaluation), which was comparable to the expected rate of lymphoma in the general pediatric population. Although not statistically significant, the rate of lymphoma was lower than the rate in pediatric IBD patients treated with thiopurines and adult IBD patients treated with anti-TNF therapy. Finally, a recent analysis of the DEVELOP registry, a prospective long-term registry of pediatric IBD patients (5766 patients; 24,543 patient-years of follow-up), found no increased risk of malignancy or hemophagocytic lymphohistiocytosis (HLH) in patients exposed to infliximab compared to those unexposed to biologics [70]. However, a trend toward an increased risk of malignancy was

observed in thiopurine-exposed patients, adding to the growing evidence that this class of medications may be the main risk factor for this significant complication of immunosuppressive therapy.

Other Biologic Therapies in Pediatric IBD

Although pediatric IBD patients generally respond well to anti-TNF therapy, based on current data, 30–40% of IBD patients are primary nonresponders, and still more discontinue therapy with time due to loss of response or intolerance to these therapies. Several biologic agents have been developed that target other mechanisms of inflammation, including integrins and IL12/IL23 pathway. Natalizumab, a humanized monoclonal IgG4 antibody against α4 integrin, inhibits migration of lymphocytes to both the central nervous system and gastrointestinal tract; natalizumab was the first anti-integrin used for treatment of Crohn's disease. Experience in pediatric Crohn's disease has been limited due to concerns regarding the development of progressive multifocal leukoencephalopathy from reactivation of the JC virus that has been reported with this therapy. Early experience in pediatrics showed potential, with one phase 2 single-arm open-label study demonstrating early efficacy in moderately to severely active pediatric Crohn's disease [71]. Thirty-eight adolescent patients received three intravenous infusions of natalizumab 3 mg/kg at 0, 4, and 8 weeks (32 per protocol), and although safety/tolerability was the primary study objective, clinical efficacy was evaluated through week 12. Mean PCDAI significantly decreased from baseline at all assessments, with the most significant decrease occurring at 10 weeks; at this time point, 55% of patients had clinical response (decrease in PCDAI by at least 15 points from baseline), and 29% were in clinical remission (PCDAI <10). Thirty-two patients (84%) reported adverse events, most commonly headaches (10%), CD exacerbation (9%), and fever (8%). Eight patients (21%) developed a serious adverse event most related to hospitalization for complications or symptoms related to CD. Overall the medication was well tolerated and no significant safety events were reported through week 32. A second small retrospective single-center study evaluated maintenance of natalizumab (300 mg every 4 week) in nine patients who had failed one or more anti-TNF therapies [72]. By week 10, 50% (4 of 8) of patients were in remission, and remission was maintained at the time of last follow-up (20–52 weeks), and three of five patients were able to taper off prednisone therapy. No serious adverse events or serious infections were observed during this study; however, the median treatment duration was relatively short at 8.25 months (range 3.5–35), and all patients were transitioned to vedolizumab once this therapy received FDA approval in 2014. Although this data is promising, safety concerns have limited ongoing use in the pediatric population.

Vedolizumab is a humanized monoclonal IgG1 antibody to α4β7 integrin, which selectively inhibits T-lymphocyte adhesion to mucosal addressin cell adhesion molecule-1 (MAdCAM-1) mitigating the concerns of PML from inhibition of CNS T-cell trafficking. Given the favorable safety profile, this medication has become the

preferred anti-integrin for pediatric IBD patients who have failed anti-TNF therapy. Thus far there have been two published studies reporting the early outcomes of 73 pediatric IBD patients treated with this therapy. A multicenter, retrospective study by Singh et al. described the early experience with vedolizumab in 52 patients with pediatric IBD, the majority of whom (90%) had failed anti-TNF therapy [73]. All patients received vedolizumab at 0, 2, and 6 weeks and then every 8 weeks; most patients (75%) received adult dosing of 300 mg, and the remaining received weight-based dosing—11 patients (21%) received 6 mg/kg/dose and two patients (4%) received 5 mg/kg/dose. By week 14, 42% of patients with CD were in remission, while 76% of patients with UC were in remission; however, there was no significant difference in corticosteroid-free remission at this time point between these two patient groups. Corticosteroid use did decrease throughout the course of the study from 56% at the time of vedolizumab initiation to 19% by week 14. Disease phenotype may play a role in response as patients with colonic-only disease were more likely to achieve remission at 14 weeks compared to patients with small bowel involvement, 70% versus 39%, respectively. In the small subset of patients who were TNF naïve ($n = 5$), 80% achieved clinical remission by week 6, and remission was maintained through 22 weeks. A second smaller prospective study evaluated the clinical response to vedolizumab in 21 patients with refractory pediatric IBD, the majority with Crohn's disease. Patients received induction dosing with 300 mg at 0, 2, and 6 weeks and then every 8-week maintenance therapy [74]. There was a significant decrease in both PCDAI and PUCAI at every follow-up interval from baseline to week 14, which persisted to week 22 ($p < 0.05$). Clinical response rates for all patients, defined as a decrease in activity index score by at least 12.5 points in CD patients and 20 points in UC/IBD-U, were 31.6%, 52.6%, and 57.9% at weeks 6, 14, and 22, respectively. At week 14 and 22, 20% of patients (4 out of 20) were in steroid-free remission, compared to 5% at 6 weeks. In both studies, vedolizumab generally was well tolerated and no infusion reactions were reported. In the study by Conrad et al., 12 patients did have serious adverse events resulting in hospitalization, but it was unclear whether these were directly related to vedolizumab or patient's primary disease. A phase 2, randomized, double-blind, dose-ranging study of vedolizumab to evaluate the safety and tolerability of in pediatric inflammatory bowel disease is anticipated to begin enrollment soon (ClinicalTrials.gov identifier: NCT03138655), and a multicenter prospective cohort study is currently underway (ClinicalTrials.gov identifier: NCT02862132).

There is limited experience of ustekinumab, the most recently FDA-approved biologic for treatment of adult Crohn's disease, in pediatric patients. This humanized monoclonal antibody binds to the common p40 subunit of IL-12 and IL-23, inhibiting activity of these proteins. To date, only one case report and one small retrospective chart review of use in pediatric CD have been published [75, 76]. Bishop et al. examined the response of four adolescent patients with CD who had received subcutaneous ustekinumab therapy at 0 and 4 weeks and then every 8 weeks for maintenance therapy; no IV doses were administered [76]. All patients had received both infliximab and adalimumab therapy and were primary responders to their first anti-TNF agent. Two patients had a sustained clinical response, were

successfully tapered off corticosteroids and maintained on ustekinumab therapy. More data is needed to determine the safety and efficacy of ustekinumab in pediatric CD, and a randomized double-blind pharmacokinetic study of ustekinumab in moderately to severely active pediatric CD is ongoing (ClinicalTrials.gov identifier: NCT02968108).

The above paragraphs demonstrate the efficacy of anti-TNF therapy in pediatric IBD for induction and maintenance of remission and for improving linear growth and bone health, as well as review the emerging evidence for use of newer biologics vedolizumab and ustekinumab in this patient population. There have been numerous advances in the understanding and use of biologic therapy in pediatric IBD, which have led to improved patient outcomes. However, significant knowledge gaps still exist, including better identification of patients who would most benefit from early biologic therapy and those who have more risks associated with this therapy and direct comparison of the effectiveness of monotherapy versus combination therapy in pediatric patients. Additionally, cost of therapy, access to infusion centers, and safety of home infusions are additional concerns, and some of these factors may present barriers to care. Biologic therapy will continue to play an increasing role in the treatment of pediatric inflammatory bowel disease, but additional research of these agents remains necessary to help guide patients and their families to optimal therapeutic decisions.

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Chapter 12
Infectious Complications of Biologics

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Abbreviations

CDI	*Clostridium difficile* infection
CI	Confidence interval
CMV	Cytomegalovirus
DNA	Deoxyribonucleic acid
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
HBc	Hepatitis B core
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HR	Hazard ratio
HSV	Herpes simplex virus
IBD	Inflammatory bowel disease
JC	John Cunningham
OR	Odds ratio
PCP	*Pneumocystis* pneumonia
PML	Progressive multifocal leukoencephalopathy
PYF	Patient-years of follow-up

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SIR	Standardized incidence ratio
TNF	Tumor necrosis factor
TOUCH	Tysabri Outreach: Unified Commitment to Health
TREAT	[Crohn's] Therapy, Resource, Evaluation, and Assessment Tool
USA	United States

Introduction

Infection is the most frequently encountered consequence of biologic therapy and a major concern for both patients and healthcare providers. Biologic agents suppress immune function to mitigate aberrant and unregulated inflammatory activity but can also predispose to serious, sometimes fatal, consequences including newly acquired infections, opportunistic infections, or reactivation of latent disease. The risk of such infections reflects a variety of external factors including biologic type and the use of concomitant immunosuppressant medication(s) as well as host-specific variables such as age, inflammatory bowel disease (IBD) severity, underlying nutritional status, medical comorbidity, and history of bowel surgery [1]. Other considerations include history of malignancy, presence of cytopenia (i.e., leukopenia or neutropenia), geographic location, previous infectious exposure(s), and vaccination status, among others. Appropriate screening with identification and stratification of at-risk patients, the use of primary or secondary chemoprophylaxis, and close clinical and laboratory surveillance with early recognition and timely goal-directed therapy for both common and opportunistic infections may optimize patient outcomes and decrease associated morbidity and mortality.

Defining an Immunocompromised Host

Genome-wide association studies have demonstrated increasing evidence of an aberrant immune response in IBD, with susceptibility loci incorporating innate and adaptive immune responses toward diminished diversity of commensal microbiota [2]. Although impaired innate mucosal immunity has been linked to the pathophysiology of IBD, particularly Crohn's disease [3, 4], the population is not considered immunocompromised on this basis alone. A systemic immune defect has not been established in IBD patients except in subjects who become immunocompromised as a result of immunosuppressant therapy or who have predisposing medical comorbidities [1].

While IBD may independently predispose to certain infectious processes, such as primary and recurrent *Clostridium difficile* infection (CDI) and invasive pneumococcal disease (particularly within the first 6 months of diagnosis) [5, 6], immunosuppression in the setting of biologic therapy may also heighten the risk for a variety of infections caused by viral, bacterial, fungal, mycobacterial, or parasitic organisms

including opportunistic infections. Lowered host resistance may not only influence the development of infection but may also allow for advanced progression not otherwise seen in immunocompetent persons. Additional contributory factors including age, malnutrition, total parenteral nutrition, comorbidity, and bowel surgery appear independently associated with infection-related hospitalizations among IBD patients as demonstrated in a large US nationwide inpatient sample [7].

Overview: Biologic Therapy and Infection Risk in IBD

Infection risk is a primary concern surrounding biologic therapy though may be most significant with the use of corticosteroids, particularly in doses equivalent to prednisone >20 mg/day for 2 weeks or more [1]. Serious and opportunistic infection risks appear increased not only with corticosteroid use but also with combination therapy including multiple immunosuppressants or concomitant narcotics [8–11]. Unfortunately, there is currently no functional assay to quantify immunosuppressive effects in patients with IBD. Based on limited data, increased infection risk appears to occur early in the course of biologic therapy. In one study, almost 70% of infections occurred after three infliximab infusions or less [12]. A Danish nationwide analysis found that the risk of serious infections (associated with hospitalization) was significantly increased in IBD patients who received one anti-tumor necrosis factor (TNF) dose (hazard ratio [HR] 1.64, 95% confidence interval [CI] 1.06–2.53) and subsequently decreased in patients who received two or three doses (1.18, 95% CI 0.79–1.78) and four or more doses (1.06, 95% CI 0.66–1.69) [13].

Explicit links between immunosuppressant class and specific infection have not been well described [1, 8, 10]. A study from the Mayo Clinic reported specific infection types related to individual immunosuppressant classes (used as monotherapy). Biologic therapy with infliximab was more commonly associated with the development of fungal and mycobacterial infections; corticosteroid therapy and azathioprine therapy were more commonly associated with fungal (*Candida* species) and viral infections, respectively, although considerable overlap was noted and firm conclusions could not be drawn [10]. Of note, this study included a variety of opportunistic infections occurring on a spectrum of severity, ranging from milder infections such as mucosal herpes simplex virus (HSV) to life-threatening disseminated fungal infections.

Epidemiology of Infection with Biologic Therapy in IBD: Collective Data

Biologic agents exert immune system effects through a variety of mechanisms. Studies regarding infection risk with TNF antagonists have shown inconsistent results, with some reporting an increased infection risk and others reporting findings to the contrary [14–20].

A recent systematic review and meta-analysis (including 49 randomized placebo-controlled studies with 14,590 participants) supported that biologic agents (infliximab, adalimumab, certolizumab, golimumab, natalizumab, and vedolizumab) appear to moderately increase the risk of any infection (odds ratio [OR] 1.19; 95% CI, 1.10–1.29) and significantly increase the risk of opportunistic infections (OR 1.90; 95% CI, 1.21–3.01) but do not influence the risk of serious infections in patients with IBD [21]. Interestingly, serious infection risk appeared significantly decreased with biologic use in studies with a low risk of bias (OR 0.56; 95% CI, 0.35–0.90) [21].

A systematic review and network meta-analysis investigating the safety profile of biologics used in the treatment of ulcerative colitis found no significant difference in adverse event rates among patients treated with infliximab, adalimumab, golimumab, and vedolizumab. The most favorable safety profiles were seen with vedolizumab in the induction phase and infliximab in the maintenance phase [22]. Agents with the highest probability of being safest were vedolizumab in the induction phase and adalimumab in the maintenance phase [23].

The assessment of risk with anti-TNF agents varies [9, 24–27]. A meta-analysis of anti-TNF agents used in Crohn's disease found no increase in the risk of serious infection (requiring antimicrobial therapy or hospitalization) among 21 studies enrolling 5356 patients and 3341 controls over a median follow-up of 24 weeks [24]. This applied to the overall analysis as well as subgroup analysis for short-term induction trials, short- and long-term induction trials, and maintenance trials with randomization after open-label induction [24]. A pooled analysis of primary safety data across ten IBD clinical trials (including five pivotal randomized, controlled phase 3 clinical trials, ACCENT I, ACCENT II, and SONIC trials in Crohn's disease and ACT 1 and ACT 2 trials in ulcerative colitis) conducted among adults treated with infliximab and immunomodulator therapy also found no increase in the risk of infections or serious infections with long-term infliximab treatment (5 mg/kg or 10 mg/kg, with or without azathioprine; $n = 1713$) compared to placebo (with or without azathioprine; $n = 406$) [9]. Patients with ulcerative colitis (but not Crohn's disease) who received immunomodulator treatment (versus treatment without immunomodulator) demonstrated an increased incidence of infections [9].

Infection Risk with Biologic Therapy in IBD: Focus on Specific Agents

Anti-TNF Therapy

Infliximab

In contrast to the aforementioned clinical trial data, a nationwide, register-based, propensity score-matched cohort study from Denmark (2000–2012; final cohort $n = 3086$, with 1543 anti-TNF users and 1543 anti-TNF nonusers) demonstrated a 63% increase in the risk of serious infections (associated with hospitalization) for

anti-TNF users within the first 3 months of treatment compared to anti-TNF nonusers, followed by a subsequent risk decline. Over a 1-year risk period, the HR decreased and was no longer significant [13]. Similarly, increased infection risk was detected in an analysis of prospective observational safety data from the Crohn's Therapy, Resource, Evaluation, and Assessment Tool (TREAT) registry, evaluating 6273 patients with Crohn's disease (3420 who received infliximab with a total of 17,712 person-years and 2853 who received conventional nonbiological medications only [other-treatments-only group] with a total of 13,251 person-years) over a mean follow-up of 5.2 years. This study found an increased risk for serious infection in patients treated with infliximab (HR 1.43, 95% CI 1.11–1.84, $P = 0.006$). Almost 90% of infliximab-treated patients received at least two infusions, a majority (81.5%) of whom were dosed at 5 mg/kg. There was no evidence to support that greater numbers of infliximab infusions or infliximab dose escalation (from 5 mg/kg to 10 mg/kg) influenced serious infection risk [8]. Multivariate regression analysis from the TREAT registry found that moderate-to-severe Crohn's disease activity was the strongest significant predictor for serious infection (HR 2.24, 95% CI 1.57–3.19, $P < 0.001$), while isolated colonic Crohn's disease involvement (compared to both ileum and colon involvement) appeared to be protective against serious infection (HR 0.73, 95% CI 0.54–1.00, $P = 0.046$) [8].

Adalimumab

The overall safety profile of adalimumab in global clinical trials of Crohn's disease (involving 3160 patients representing 3401.9 patient-years of drug exposure) was reported to be comparable to that of other anti-TNF agents used for the same indication. Adverse event rates were similar to those described in other studies of adalimumab used for alternate approved indications covering a clinical follow-up period over 10 years. The most frequently reported serious adverse event was serious infection, most commonly due to abscess (intra-abdominal and gastrointestinal related). The incidence of opportunistic infections including tuberculosis was low [27].

A systematic review and meta-analysis including three randomized controlled trials (conducted from drug inception to January 2015) comparing adalimumab with placebo for moderate-to-severely active ulcerative colitis reported no significant difference in adverse events (over 8 weeks, including infection and tuberculosis) or serious adverse events when comparing induction therapy with adalimumab (dosed 160/80 mg at weeks 0/2 and then 40 mg at weeks 4 and 6) versus placebo [28]. Adalimumab maintenance therapy (40 mg every other week) increased the risk of adverse events (over 1 year) compared with placebo (risk ratio 1.28, 95% CI 1.06–1.54) [28].

Certolizumab

Safety data pertaining to infection risk with the use of certolizumab is limited. Three meta-analyses using randomized controlled trial data for certolizumab suggested that the risk of infection with long-term therapy was not clearly increased [29–31].

A pooled analysis showed that the incidence rate for serious infectious complications was higher in short-term studies of certolizumab treatment versus placebo, but the risk did not heighten with long-term certolizumab therapy (up to 7 years) [31].

Golimumab

Golimumab safety evaluated in the PURSUIT trials revealed that adverse events in golimumab treatment groups appeared similar to those observed with other anti-TNF agents and with golimumab used for other approved indications [32, 33]. Results from the PURSUIT-SC induction study found the overall incidence of adverse events through week 6 was similar for golimumab- and placebo-treated patients, with serious infection reported in 0.5% versus 1.8%, respectively [32]. Overall rates of infections, serious infections, and infections warranting antimicrobial therapy per 100 patient-years of treatment did not increase with continued golimumab exposure [33, 34].

Anti-TNFs: Summary

Although varied reports exist regarding serious infection risk, most data support a potentially increased risk for opportunistic infections with anti-TNF agents. The US Food and Drug Administration (FDA) has issued a boxed warning for the anti-TNF class as presenting a risk for the development of a variety of infections, particularly opportunistic pathogens such as tuberculosis and invasive fungal infections [35, 36]. The anti-TNF agents used for the treatment of IBD appear to have similar risks, although that for certolizumab is less clear. Higher drug doses do not appear to be associated with greater infection risk. While this seems surprising, there may be a threshold effect, or the risk may be minimal and would require larger databases than thus far utilized to display this. The overall risk of serious infection with maintenance anti-TNF therapy among the IBD population appears limited, particularly during follow-up over long-term exposure, and may be fueled by other patient factors influenced by disease state and concomitant medication use (i.e., steroids).

Anti-Integrin Agents

A systematic review and meta-analysis of randomized placebo-controlled trials using anti-integrin antibodies in adults with IBD (including 12 eligible trials, four with natalizumab, six with vedolizumab, and two with etrolizumab) reported no significant difference in the risk of opportunistic infections among patients treated with gut-specific and non-gut-specific anti-integrin antibodies, both compared to placebo [37].

Natalizumab

Natalizumab, a humanized monoclonal antibody against alpha-4 integrin, received initial FDA approval for use in multiple sclerosis but was temporarily withdrawn from the market in 2005 due to the risk of progressive multifocal leukoencephalopathy (PML), a serious opportunistic infection of the central nervous system caused by reactivation of the John Cunningham (JC) virus in chronically treated patients. One case of PML was reported in a Crohn's disease patient on combination therapy with azathioprine [38]. In 2008, natalizumab was reapproved in the USA under a specialized distribution program (TOUCH, Tysabri Outreach: Unified Commitment to Health) and FDA approved for the treatment of active Crohn's disease. Natalizumab-associated risk of PML has been most dramatically demonstrated in the multiple sclerosis literature. Among 99,571 multiple sclerosis patients treated with natalizumab (representing 209,123 patient-years), there were 212 reported PML cases (2.1 cases per 1000 patients); 22% of the affected patients died [39]. The risk of PML was lowest among patients who tested negative for anti-JC virus antibodies (estimated incidence 0.09 cases per 1000 patients, 95% CI 0–48). The highest estimated risk was seen among patients with the following factors (alone or in combination): positive anti-JC virus antibody status, immunosuppressant use prior to natalizumab initiation, and increasing duration of therapy (with greatest risk at 25–48 months and very few infections under 12 months). In the highest-risk subgroup of patients with all three risk factors, the estimated incidence was 11.1 cases per 1000 patients (95% CI 8.3–14.5) [39]. Natalizumab is generally prescribed with reservation due to this risk profile, and the availability of vedolizumab has further limited natalizumab use in IBD.

Vedolizumab

The advent of vedolizumab presented a favorable alternative to natalizumab as a gut-selective anti-alpha-4 beta-7 integrin agent. Integrated safety data from six trials of vedolizumab used in Crohn's disease and ulcerative colitis (2380 patients with 4811 person-years of vedolizumab exposure) found no associated increased risk of infection or serious infection, reinforcing the presumed gut specificity of the therapy [40]. Systemic infections may still be a concern, however, with gastrointestinal infections as a potential risk. Serious infections including clostridial infections, sepsis, and tuberculosis were rarely reported in $\leq$0.6%. Independent risk factors for serious infection were corticosteroid use, narcotic analgesic use and younger age in Crohn's disease, and narcotic analgesic use and prior anti-TNF failure in ulcerative colitis [40]. A retrospective cohort study assessing vedolizumab safety for moderate-to-severe Crohn's disease from seven medical centers (May 2014–December 2015) reported 21 serious infections (requiring antibiotics or resulting in discontinuation of vedolizumab, hospitalization, or death) [41]. There have been no associated reports of PML.

Interleukin 12/23 Monoclonal Antibody

Ustekinumab

Safety data of ustekinumab for induction of remission in Crohn's disease indicated no significant difference in adverse events or serious adverse events when comparing ustekinumab to placebo; based on limited data, the assessment of rare adverse events could not be determined [42]. A multicenter, double-blind, placebo-controlled phase 3 study of ustekinumab for the treatment of moderate-to-severely active Crohn's disease refractory to anti-TNF therapy (741 patients, 51% of whom had previously failed two or more anti-TNFs) reported similar proportions of patients with infections in ustekinumab versus placebo groups. Tuberculosis was not reported to have occurred in ustekinumab-treated patients through week 20 [43].

Infection Risk Linked with Combined Medication Use

The risk of serious opportunistic infections (such as tuberculosis or histoplasmosis) as a consequence of anti-TNF therapy appears to be increased with concomitant immunosuppressants, particularly corticosteroids [8]. Data from the Crohn's TREAT registry with over 5 years of follow-up revealed that factors independently associated with serious infection included prednisone treatment (HR = 1.57, 95% CI 1.17–2.10, $P = 0.002$) and narcotic analgesic treatment (HR = 1.98, 95% CI 1.44–2.73, $P < 0.001$). Moderate-to-severe disease activity was the strongest independent predictor of serious infection and was significantly greater among patients treated with infliximab than among patients treated with other medications [8]. In a pooled analysis, ulcerative colitis patients on combined immunosuppressant therapy with infliximab and azathioprine demonstrated an increased incidence of infections compared with infliximab monotherapy; this was not detected in Crohn's disease patients [9].

A case-control study from the Mayo Clinic demonstrated (univariate analysis) that use of infliximab (OR 4.4; 95% CI 1.2–17.1), azathioprine/6-mercaptopurine (OR 3.1; 95% CI 1.7–5.5), and corticosteroids (OR 3.4; 95% CI 1.8–6.2) was each independently associated with significantly increased odds for the development of opportunistic infections relative to medication nonuse. Multivariate analysis confirmed that the use of any one of these immune suppressants (relative to immunosuppressant nonuse) was associated with increased odds for the development of opportunistic infection (OR 2.9; 95% CI 1.5–5.3), while the use of multiple (two or three) agents profoundly increased the odds for opportunistic infections (relative to immunosuppressant nonuse) with an OR of 14.5 (95% CI 4.9–43). Neither methotrexate nor mesalamine was significantly associated with the risk of developing opportunistic infections [10].

Host Factor of Age: Infection Risks in Pediatric and Elderly Populations

Older age appears to increase the risk of infectious complications with anti-TNF agents and possibly other biologics. A significantly increased risk for opportunistic infections has been associated with advanced age over 50 years among IBD populations [10, 11].

Pediatric

There is a paucity of robust clinical data on the risk for infection with biologic therapy in the pediatric population. A systematic review was performed to quantify the incidence of serious infection among 5528 pediatric IBD patients who received anti-TNF therapy over 9516 patient-years of follow-up (PYF). The rate of serious infection in pediatric patients treated with anti-TNFs (352/10,000 PYF) was similar to that in patients treated with immunomodulator monotherapy (333/10,000 PYF; standardized incidence ratio [SIR] 1.06; 95% CI 0.83–1.36) but significantly lower than the expected rate in pediatric patients treated with steroids or adults treated with anti-TNF therapy [44].

Elderly

Certain infections appear more common among elderly compared to younger populations regardless of IBD or immunosuppressed status. These include reactivation of latent tuberculosis and bacterial infections such as community-acquired pneumonia and urinary tract infections. Viral infections occur less commonly in the elderly with the exceptions of viral gastroenteritis, influenza, and varicella zoster virus [1]. Immunosenescence leading to functional alterations in innate and adaptive immune cells may contribute, although there is limited evidence for a direct relationship [45].

Among IBD populations, advanced age appears to be a significant risk factor for infection-related hospitalizations and inhospital mortality as well as postoperative mortality and complications [46, 47]. A US national inpatient cohort study found that inhospital mortality among IBD patients was increased among elderly patients over 65 years of age compared to younger patients (OR 3.91, 95% CI 2.50–6.11), a difference that persisted after adjusting for medical comorbidities and complications. The highest mortality was noted in the oldest age group and was significantly increased among IBD patients who did not undergo surgery compared to those who did [46].

Specific Infection Risk with Biologic Therapy

Mycobacterial Infections and Invasive Fungal Infections

Pathogen exposure and geographic clustering may heighten the risk for certain endemic infections including granulomatous infectious (such as tuberculosis) or opportunistic fungal infections. Native birthplace and background, residence, and travel to endemic areas are thus important historic elements when considering patients for biologic therapy. Anti-TNF agents, in particular, may prevent an effective granulomatous response [48], leading to susceptibility to mycobacterial infections such as tuberculosis and opportunistic fungal infections including histoplasmosis, coccidiomycosis, and cryptococcus, among others [49].

Mycobacterial Infections

Tuberculosis

The risk of tuberculosis is increased with anti-TNF agents. Infection typically presents within the first few months of initiating anti-TNF therapy but may occur up to 2–3 years later or even following treatment for tuberculosis. Although pulmonary infections are classic, atypical sites can be involved [50, 51].

Detection of latent tuberculosis infection or active disease among patients receiving anti-TNF therapy became an issue of notable importance after the US FDA Adverse Events Reporting System found higher tuberculosis rates among patients exposed to infliximab compared to background population rates [52]. Most patients (56%) had extrapulmonary tuberculosis, and 24% had disseminated disease. Not only did the frequency of tuberculosis infection appear increased compared to other opportunistic infections reported in association with infliximab but also 64/70 cases (91%) manifested in countries with a low incidence of tuberculosis suggesting disease reactivation [52]. The risk of tuberculosis has been confirmed in other studies of TNF-alpha antagonist exposure, particularly with the use of monoclonal antibodies [53, 54].

Not only is the risk for reactivation of latent tuberculosis increased among anti-TNF-treated patients but the disease may also be more severe than in the general population [1]. Active tuberculosis can present in IBD patients undergoing anti-TNF therapy despite negative screening tests for latent tuberculosis and can also be seen in those who have completed tuberculosis treatment or received latent tuberculosis prophylaxis [55]. A recent retrospective study conducted at GETAID centers investigated all IBD patients undergoing anti-TNF therapy who developed tuberculosis despite negative screening tests. Among 44 patients identified, the median interval from initiation of anti-TNF therapy to diagnosis of tuberculosis was 14.5 months (interquartile range 25–75, 4.9–43.3). Tuberculosis involvement included pulmonary site in 57% with extrapulmonary involvement in 91%. Tuberculosis exposure

was thought to be implicated in 32% of the cases. Anti-TNF therapy was re-initiated in 27 patients approximately 11.2 months (interquartile range 25–75: 4.4–15.2) following tuberculosis diagnosis, and infection recurrence was not detected [56].

Generally, standard and complete treatment for latent tuberculosis infection (such as isoniazid for 6–9 months) [57] should be commenced prior to anti-TNF therapy, which should not be initiated until at least 3–4 weeks after introduction of the antituberculosis agent(s). Anti-TNF therapy should be stopped if active tuberculosis is detected and may be resumed after approximately 2 months of antituberculosis therapy [1, 57]. Restarting anti-TNF therapy following adequate treatment for tuberculosis appears safe [56].

Invasive Fungal Infections

Patients undergoing biologic therapy, particularly with anti-TNFs, are at increased risk for the development of invasive fungal infections [58]. The US FDA issued a black box warning in 2008 for the class of anti-TNF agents regarding this serious infectious consequence. Invasive or disseminated fungal infections have been reported among patients treated with anti-TNFs (commonly in combination with other immunosuppressants) across indications and may be associated with severe infections and high morbidity and mortality [1, 58–60]. Histoplasmosis [61–65], coccidiodomycosis [65–70], aspergillosis [71–73], cryptococcus [74, 75], and candidiasis [76] infections have been described and are commonly reported in patients on combination immunosuppression in endemic areas. Ten cases of *Histoplasma capsulatum* were reported with anti-TNF use (nine infliximab, one etanercept); all patients resided in histoplasmosis-endemic areas and were on combined immunosuppressive therapy. Infectious manifestations were noted within 1–24 weeks following anti-TNF initiation; nine of the patients required intensive care unit admission, and one patient died [77]. A multicenter retrospective review (January 2000–2011) of 98 patients on anti-TNF therapy (most commonly with infliximab in 67.3%) identified concomitant steroid use as a predictor of severe infection. Disease outcomes were generally favorable, although the mortality was 3.2%. Resumption of anti-TNF therapy occurred in 33.8% at a median of 12 months (range 1–69 months) and appeared overall safe [78].

Pneumocystis jiroveci (*carinii*)

Immunosuppression is a predisposing factor for the development of *Pneumocystis jiroveci* pneumonia, previously known as *Pneumocystis carinii* pneumonia (PCP). *Pneumocystis* pneumonia (PCP) infection appears increased among IBD patients, particularly in association with combination immunosuppressive therapy including infliximab [79–82]. The mean time from infliximab infusion to pneumonia symptom onset

was 21 ± 18 days ($n = 40$), and patients had an average of 2.1 ± 1.3 infusions ($n = 76$) prior to symptom development. The mortality rate was 27% [82].

Prophylactic treatment for PCP (such as trimethoprim/sulfamethoxazole) should be considered for patients on triple immunosuppression (i.e., corticosteroids, biologic, and immunomodulator therapy). Additional risk factors for the development of PCP that may necessitate prophylaxis include lymphopenia (total lymphocyte count <600 cells/mm) and age over 55 years [83]. Primary chemoprophylaxis is not recommended for fungal infections other than *Pneumocystis jiroveci,* and there are no vaccinations available for disease prevention [1].

Bacterial Infections

Legionella

Patients on anti-TNF therapy appear to be at heightened risk for *Legionella pneumonia* infection, particularly with combination immunosuppressant therapy and among elderly populations aged over 65 years [36]. The relative risk of *L. pneumophila* infection was increased in patients exposed to anti-TNF therapy (relative risk 16.5–21) compared with that in the overall population in France [84]. Cases of legionella have similarly been reported in association with anti-TNF therapy used for the treatment of IBD [6, 85–88]. In 2011, the FDA issued a boxed warning regarding the risk of *Legionella* for the TNF-alpha inhibitor class [36]. Immunosuppressant therapy should be held until the acute infection has resolved. Recurrent *Legionella* infection has also been reported and may influence reintroduction of immunosuppressant therapy [1, 89].

Listeria

Patients on anti-TNF therapy appear to be at heightened risk for *Listeria* infection, particularly with combination immunosuppressant therapy and elderly populations aged over 65 years [36, 90]. Several cases of listeriosis have been reported among patients treated with anti-TNF therapy for IBD [91–96] and rheumatoid arthritis [97, 98]. In 2011, the FDA issued a boxed warning regarding the risk of *Listeria* for the TNF-alpha inhibitor class [36].

Nocardia

The risk of systemic and cutaneous nocardia infection has been recognized in association with anti-TNF therapy [99], particularly with concomitant corticosteroid therapy. A review of the literature (1980–2014) pertaining to nocardial infections among immunosuppressed IBD patients reported nine cases (six associated with anti-TNFs, two associated with prednisone plus thiopurine, one associated with cyclosporine).

Clostridium difficile

CDI has become an epidemiologic phenomenon as a leading cause of hospital-associated gastrointestinal illness [100]. It is well established that patients with IBD, particularly those on chronic immunosuppressive therapy with certain agents such as corticosteroids, are at increased risk for the development of CDI [101]. Furthermore, IBD patients who develop CDI have increased risks for severe infection, gastrointestinal surgery, and greater hospital length of stay compared to IBD patients without CDI along with increased inhospital mortality compared to *C. difficile*-infected patients without underlying IBD and IBD patients without CDI [100, 102, 103].

CDI should be excluded (or empirically treated in some cases) prior to initiation of biologic or other immunosuppressant therapy. No meaningful association linking infliximab with serious bacterial infections including CDI was seen in a large retrospective cohort study involving 10,662 patients with IBD, while corticosteroid therapy was associated with an over threefold increased relative risk for CDI (RR 3.4, 95% CI 1.9–6.1) compared with other immunosuppressants [101]. A subsequent retrospective cohort study of 503 patients with CDI identified IBD patients as 33% more likely than the general population to experience recurrent infection. Among this IBD cohort (n = 110), patients with recurrent CDI were significantly more likely than those without recurrent CDI to have reported exposure to biologic therapy (48.6 versus 40.0%, $P < 0.01$). Infliximab use (compared to nonuse) significantly elevated the risk of recurrent CDI (34.3% versus 17.3%, respectively, $P < 0.01$), while adalimumab use did not. Steroid therapy, recent antibiotic exposure, and 5-aminosalicylic acid use also significantly increased the risk for recurrent CDI, while immunomodulators (azathioprine, methotrexate, and cyclosporine) did not appear to influence this risk [5]. Treatment with two or three immunomodulators increased the risk, independent of disease severity at presentation [104]. Chemoprophylaxis for CDI is not recommended [1].

Streptococcal pneumoniae

An increased risk of *Streptococcal pneumoniae* has been established in association with anti-TNF agents, as demonstrated in several large studies in Denmark and in the USA [6, 105]. The risk of invasive pneumococcal disease appears increased among IBD patients compared to controls, not only following but also in years prior to IBD diagnosis [6]. The risk of invasive pneumococcal disease in IBD versus control groups was increased twofold for Crohn's disease and 1.5-fold for ulcerative colitis; this risk was greatest during the first year after IBD diagnosis and decreased 2–4 years after IBD diagnosis. Exposure to anti-TNF agents did not influence the risk of invasive pneumococcal disease in the IBD population (nor did exposure to oral or topical corticosteroids or 5-aminosalicylates/sulfasalazine) [6]. Anti-TNF treatment, either alone or in combination with immunomodulator therapy, has been associated with diminished antibody response to pneumococcal vaccination [106, 107].

Viral Infections

Influenza

Immunosuppressed patients may be at increased risk for developing complications related to influenza infection [1, 108]. Influenza virus infection may be severe or fatal and may be complexed by secondary bacterial infection(s). Additional risk factors for influenza-related mortality include extremes of age (young and elderly) as well as medical comorbidities [109]. Inactivated trivalent influenza vaccine is recommended for patients undergoing immunosuppressant therapy. Lower immune response rates to vaccination [110–112] and persistence of seroprotection have been detected in IBD populations, particularly in association with anti-TNF treatment [113, 114] or combination immunosuppressant therapy [111, 112, 115]. Timing of influenza vaccination relative to infliximab dosing in pediatric and adult patients receiving maintenance IBD therapy does not appear to influence immune response [116]. Influenza vaccination appears safe and well-tolerated among IBD patients [117] and does not appear to be associated with disease flare [111, 113, 117, 118].

Hepatitis B Virus

The prevalence of hepatitis B virus (HBV) infection among patients with IBD appears similar to that of the general population in some studies [119–121] and increased in IBD patients compared to non-IBD patients in others [122, 123]. Hepatitis B reactivation is an important concern among immunosuppressed populations, widely reported among patients undergoing cytotoxic chemotherapy (particularly for hematologic malignancies) and solid organ or stem cell transplantation and also reported in association with biologic treatments for autoimmune conditions and IBD [124]. Immunosuppressive treatment (e.g., with TNF inhibition) can reduce viral clearance, exhaust HBV-specific T-cell responses, and enhance viral load, leading to immune-mediated liver damage particularly after immunosuppression is withdrawn [125–127]. Reactivation of viral replication and flares of HBV thus reflect immune reconstitution and can occur even after short courses of immunosuppression. Occurrence of this preventable consequence has been associated with significant morbidity and mortality that may be mitigated by the use of prophylactic antiviral therapy among at-risk patients [1, 128].

Testing

All IBD patients should receive HBV serologic testing prior to immunosuppressant therapy to assess HBV exposure or vaccination status. Patients should receive the initial HBV vaccination at least 2 weeks prior to initiation of immunosuppressant therapy. Testing to confirm serologic response may be performed approximately 1–2 months after the final vaccination; levels of hepatitis B surface antibody (HBsAb

or anti-HBs) > 100 international units/liter (IU/L) should ideally be maintained during biologic therapy to achieve adequate protection against HBV [1, 129]. Higher doses of the immunizing antigen or a second HBV vaccination course may be required for patients whose response to the previous series is inadequate [130].

Prophylaxis

IBD patients with active HBV infection should receive treatment, with delay of biologic therapy and/or immunomodulators until acute infection or reactivation (HBV deoxyribonucleic acid [DNA] < 2000 IU/mL) resolves [1]. Patients at moderate or high risk for HBV reactivation should be considered for antiviral prophylaxis prior to the initiation of immunosuppressant therapy according to published guidelines from the American Gastroenterological Association. Patients with positive hepatitis B surface antigen (HBsAg) and positive hepatitis B core (anti-HBc) (+HBsAg/+anti-HBc) serologies or with negative HBsAg and positive anti-HBc (−HBsAg/+anti-HBc) planned to undergo treatment with anti-TNF agents, anticytokine agents (such as ustekinumab), or anti-integrin agents (such as natalizumab or vedolizumab) are categorized as moderate risk for HBV reactivation (anticipated incidence 1–10%), and HBV antiviral prophylaxis is suggested (weak recommendation based on moderate-quality evidence). Patients with positive HBsAg and positive anti-HBc (+HBsAg/+anti-HBc) serologies undergoing treatment with low-dose corticosteroids (<10 mg prednisone/day or equivalent) for ≥4 weeks as well as patients with negative HBsAg and positive anti-HBc (−HBsAg/+anti-HBc) serologies undergoing treatment with moderate-dose (10–20 mg prednisone/day or equivalent) or high-dose (>20 mg prednisone/day or equivalent) corticosteroids for ≥4 weeks are also considered to be at moderate risk for HBV reactivation. Patients at high risk for HBV reactivation (anticipated incidence >10%) in whom HBV antiviral prophylaxis is advised (strong recommendation based on high-quality evidence, respectively) include patients with positive HBsAg and positive anti-HBc serologies undergoing treatment with moderate-dose (10–20 mg prednisone/day or equivalent) or high-dose (>20 mg prednisone/day or equivalent) corticosteroids for ≥4 weeks [128].

Prophylactic antiviral treatment should generally be maintained for a minimum of 6 months following discontinuation of immunosuppressant therapy (as recommended by the European Crohn's and Colitis Organisation) [1]. Patients at low risk for HBV reactivation (anticipated incidence <1%) in whom antiviral prophylaxis is not routinely recommended (weak recommendation based on moderate-quality evidence) include patients with positive HBsAg and positive anti-HBc (+HBsAg/+anti-HBc) serologies or negative HBsAg and positive anti-HBc (−HBsAg/+anti-HBc) serologies undergoing immunosuppressive treatment with azathioprine, 6-mercaptopurine, methotrexate, or any oral corticosteroid dose lasting for ≤1 week; others in this low-risk category include patients with negative HBsAg and positive anti-HBc (−HBsAg/+anti-HBc) serologies undergoing treatment with low-dose (<10 mg prednisone/day or equivalent) corticosteroids for ≥4 weeks.

Hepatitis C Virus

The prevalence of hepatitis C virus (HCV) among patients with IBD appears similar to the general population as confirmed in several studies [119–121, 123]. Biologic therapy does not appear to influence the short-term course or reactivation of HCV. Reports suggest that anti-TNF therapy is generally considered safe with appropriate clinical monitoring in HCV patients [131–136]. The long-term effect of therapy on the course of HCV has not been determined [137].

Cytomegalovirus

The presence of cytomegalovirus (CMV) infection among IBD patients has been described in association with the use of corticosteroid and azathioprine therapy [138]. A prospective observational study of 69 ulcerative colitis patients with moderate-to-severe disease activity under immunosuppressive treatment with steroids and/or other immunosuppressants reported that CMV is frequently reactivated in the setting of acute colitis but often resolves without antiviral treatment [139].

The association of CMV infection with biologic therapy has been less frequently described. Systemic CMV reactivation causing severe infections has been infrequently reported in association with anti-TNF therapy, including retinitis [140], colitis [141], hepatitis [142], and disseminated disease [143]. A prospective observational study investigating the association between colonic CMV reactivation and the use of anti-TNF versus azathioprine therapy among 73 ulcerative colitis patients with 109 flare-ups reported that patients undergoing maintenance therapy with anti-TNF agents were not at increased risk of CMV reactivation compared to patients on azathioprine [144]. CMV reactivation was similarly identified in 35% and 38% of patients receiving anti-TNF agents and azathioprine, respectively [144].

Screening for CMV infection is not necessary prior to initiation of immunosuppressive therapy. However, as CMV may complicate disease course in the setting of severe acute or steroid-refractory colitis, infection should be excluded with colonic biopsy particularly during acute colitis flares and prior to increasing immunosuppressant therapy. Among IBD patients, the prevalence of CMV in colonic tissue has been reported in 21–34% of patients with severe colitis and 33–36% of patients with steroid-refractory colitis [145].

Immunosuppressant therapy may generally be continued in cases of mild CMV reactivation. In cases of CMV gastrointestinal disease associated with steroid-refractory colitis, antiviral therapy should be initiated with consideration for discontinuation of immunosuppressant therapy until acute infection resolves. Immunosuppressant therapy should be discontinued [1, 146], and prompt antiviral treatment with ganciclovir (2–3 weeks) should be initiated in the setting of severe or systemic CMV infection; oral valganciclovir may be considered after 3–5 days to complete a 2–3 week treatment course. Foscarnet may be considered as a treatment alternative in cases of ganciclovir resistance or intolerance [1].

Epstein-Barr Virus

Reactivation of Epstein-Barr virus (EBV) has been reported to be more frequent among IBD patients compared to controls and is influenced by therapeutic regimens. A prospective study of 379 outpatients (treated with 5-aminosalicylates, $n = 93$; azathioprine, $n = 91$; infliximab, $n = 70$; combination infliximab plus azathioprine, $n = 43$; healthy controls, $n = 82$) found that over 90% had previous EBV exposure. Only six IBD patients were undergoing steroid therapy. The overall prevalence of EBV-DNA detected in blood was 35% with a significantly greater prevalence in IBD patients, independent of medication regimen, compared to controls. Infliximab (monotherapy or in combination with azathioprine) compared to azathioprine monotherapy or 5-aminosalicylate monotherapy ($P < 0.05$) was associated with higher EBV prevalence. Age was a risk factor for EBV-DNA positivity (OR 1.021, 95% CI 1.002–1.040); older age (>60 years) was related to EBV positivity with specificity of 92%. Ulcerative colitis was a risk factor for high EBV levels (>1000 and 2500 copies/mL). There was no clinical consequence of this EBV-positive status in the short-term follow-up period of this study [147].

Asymptomatic EBV screening should be considered prior to the initiation of immunosuppressive therapy among inflammatory bowel disease patients and can guide therapeutic management strategies, particularly in deferring thiopurine use among patients unexposed to EBV in whom primary infection has been associated with the risk of lymphoproliferative disorders such as EBV-positive lymphoma [148, 149]. Immunosuppressive therapy should be discontinued in cases of severe primary infection or EBV-mediated lymphoproliferative disorders [1].

Varicella Zoster Virus

IBD patients, particularly those on immunosuppressants, are at increased risk for herpes zoster infection compared to the general population [150]. A large, retrospective cohort study using a US administrative healthcare claims database (January 1997–December 2009) including 108,604 adults (<64 years of age) with IBD (56,403 with ulcerative colitis; 50,932 with Crohn's disease; 1269 with unspecified IBD) matched to 434,416 controls without IBD demonstrated that the risk of herpes zoster was increased in the IBD population compared to controls with an incidence rate ratio of 1.68 (95% CI 1.60–1.76). The risk of herpes zoster infections was highest with combination of anti-TNF and thiopurine therapy (OR 3.29, 95% CI 2.33–4.65) after controlling for comorbidities, healthcare utilization, and other medication use [151].

Immunosuppressants should not be commenced during active infection with varicella or herpes zoster virus. Antiviral agents should be dosed promptly if infection occurs while on immunosuppressant therapy, which should be discontinued in severe cases. Reintroduction of immunosuppressant therapy may be considered once the patient is afebrile and vesicular crusting of lesions has occurred.

Herpes Simplex Virus

Immunosuppressed patients may experience more severe, frequent, and extensive manifestations of primary or recurrent herpes simplex virus (HSV) disease [152–154]. Disease manifestations, including HSV-associated esophagitis [155], encephalitis [156], fulminant colitis [157, 158], hepatitis [159, 160], sepsis [161], and disseminated cutaneous infection [162, 163], among others, have been described in IBD patients on immunosuppressant regimens. Reports of localized HSV, HSV encephalitis, and disseminated cutaneous HSV have been described in association with the use of anti-TNF agents [25, 152, 153, 163–166].

Screening for HSV is not necessary prior to initiation of biologic therapy. HSV is not a contraindication to immunosuppressive therapy, although viral reactivation yielding frequently recurrent oral or genital HSV lesions may require episodic or chronic daily antiviral prophylaxis (e.g., with valacyclovir, acyclovir, or famciclovir). Cases of suspected HSV, especially severe or disseminated HSV infection, should prompt antiviral therapy with discontinuation of immunosuppressant(s) until resolution of the acute infection.

Managing Infectious Risks with Biologic Therapy in IBD

Clinician awareness of infectious risks and individual host variables is paramount when considering initiation of biologic therapy. Due to the potential risk for serious infections associated with biologic therapy, adherence to preventive screening and surveillance guidelines are advised. Vaccinations should be advocated for all IBD patients, particularly for patients early in the disease course who may be particularly susceptible to certain infections and who may promptly require immunosuppressant therapy. Most immunizations, except for live virus vaccines, may be safely administered to IBD patients on biologic therapy. Annual tuberculosis risk assessment should be performed with retesting in high-risk situations [1]. Patients being considered for natalizumab therapy should be enrolled in the TOUCH program; JC virus status should be established prior to initiation of therapy (with treatment if negative) and retested periodically at 4–6 month intervals [167].

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Chapter 13
Tumor Necrosis Factor-Alpha Inhibitors and Risks of Malignancy

Julia T. Hughes and Millie D. Long

Introduction

Tumor necrosis factor (TNF)-alpha plays a role in both the innate and acquired immune response. Furthermore, elevated levels of TNF-alpha have been demonstrated in various immune-mediated disease processes, including inflammatory bowel disease (IBD) [1]. TNF-alpha has been shown to act as a key pro-inflammatory mediator in Crohn's disease (CD), a discovery that prompted the development and utilization of anti-TNFs for the management of CD in the 1990s [2]. Anti-TNFs reduce hypercoagulability and inhibit granuloma formation, which make them useful therapeutic tools in CD [3, 4]. The inhibition of granuloma formation also decreases the ability to clear mycobacterium and other intracellular organisms [5, 6], which raises concerns about immunologic compromise, particularly in the domains of infection and malignancy.

Infection, malignancy, antibody development, and infusion reactions are some of the major adverse reactions associated with anti-TNFs. While infectious complications are well recognized with anti-TNF therapy, particularly due to their relatively higher frequency of occurrence over shorter time periods of therapy, complications of malignancy are not as readily observed or docu-

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mented in the literature. This is likely due to the lower frequency and more insidious development over time of malignant complications.

This review will summarize the evidence, including the limitations of the currently available literature, on various types of malignancy that have been associated with IBD therapies, with a focus upon anti-TNF agents. Additionally, although risks of certain malignancies exist, one must also consider the benefits of using these agents for the treatment of moderate to severe IBD. An approach to discussing the risks and benefits of anti-TNFs with patients will be provided. Finally, we will also emphasize those preventable malignant complications and provide recommendations for three forms of prevention in IBD as they relate to malignancy: primary, secondary, and tertiary prevention.

Risk of Malignancy with Anti-TNFs in IBD

Anti-TNFs have been available for the treatment of CD in the late 1990s and subsequently for ulcerative colitis (UC) in the 2000s. These agents have demonstrated overall safety and efficacy in IBD management. However, concerns have arisen about potential associations with cancers such as non-melanoma skin cancer (NMSC), melanoma, lymphoproliferative and myeloproliferative disorders, hepatosplenic T-cell lymphoma, and other solid tumors. When assessing the risks of anti-TNF therapy, it is also critical to consider the roles of concomitant immunomodulators and corticosteroid therapy that are often used in conjunction with or prior to these medications.

In a population-based cohort in Denmark spanning over 30 years, investigators compared the risks of gastrointestinal (GI) and extraintestinal cancers in IBD patients over time periods prior to and after widespread use of anti-TNF agents for the treatment of IBD. CD was associated with GI malignancies (SIR, 1.2; 95% CI, 1.0–1.4) and extraintestinal malignancies (SIR, 1.3; 95% CI, 1.2–1.4), with a stronger association for hematologic malignancies (SIR, 1.9; 95% CI, 1.5–2.3), smoking-related malignancies (SIR, 1.5; 95% CI, 1.3–1.8), and melanoma (SIR, 1.4; 95% CI, 1.0–1.9). UC was more weakly associated with GI and extraintestinal malignancies (SIR, 1.1; 95% CI, 1.0–1.2; and SIR, 1.1; 95% CI, 1.0–1.1, respectively). Importantly, the risk of gastrointestinal cancers decreased since 1978, without an increase in the risk of extraintestinal cancers over time (Fig. 13.1). This demonstrates that effective treatment of inflammation in the GI tract and/or appropriate surveillance and management of dysplasia may be contributing to an overall reduction in the risk of GI malignancies. Notably, anti-TNF therapies are not concomitantly increasing the overall rate of extraintestinal malignancies in patients with IBD [7].

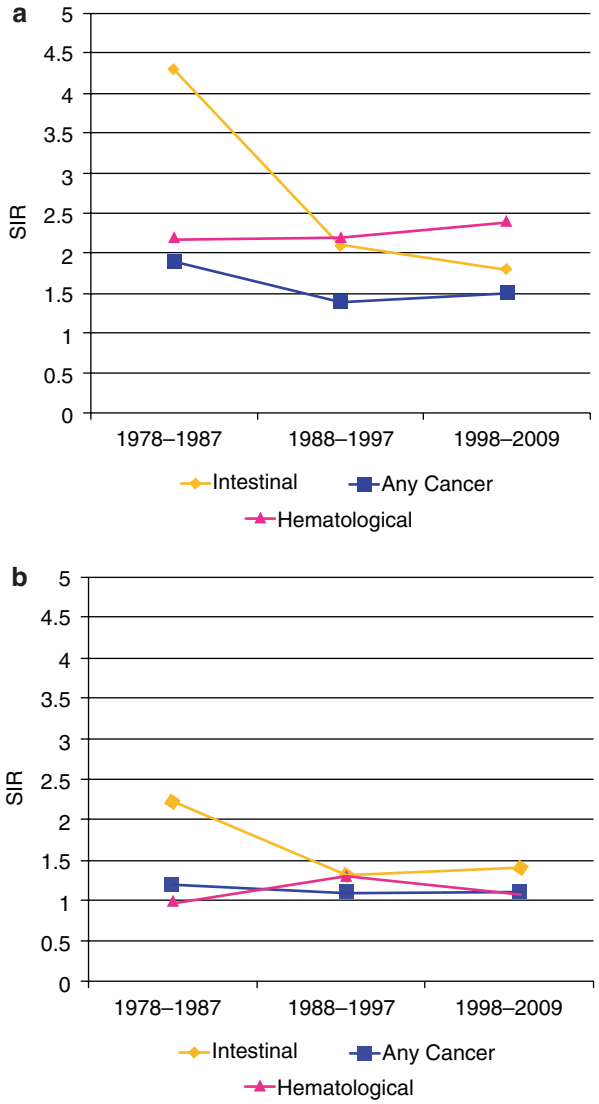

Fig. 13.1 (**a**) Relative risk by decade, Crohn's disease. (**b**) Relative risk by decade, ulcerative colitis

Non-melanoma Skin Cancer

In the USA, NMSC is the most commonly diagnosed malignancy. NMSC includes both squamous cell carcinoma and basal cell carcinoma. Risk factors for the development of NMSC include environment risk factors such as ultraviolet (UV) light exposure or chemical exposures, as well as host risk factors such as human papilloma virus (HPV), genetic susceptibilities, and immunosuppression [8]. In a descriptive analysis of population-based claims, the US Census Bureau, and a population-based cross-sectional survey using multiple US government data sets, NMSC has an estimated overall incidence of 3.5 million [9]. A further increased incidence has been found in solid organ transplant populations [10–12].

Various cohort studies have provided evidence that immunosuppressive therapies used in the treatment of IBD and other autoimmune conditions are associated with an increased risk of NMSC. It is also possible that the underlying immune dysfunction of these autoimmune conditions also plays a role. A retrospective cohort study of NMSC in 26,403 Crohn's patients and 26,934 patients with ulcerative colitis published by Long et al. in 2010 demonstrated a significantly increased risk of NMSC (incidence rate ratio (IRR) 1.64; 95% CI, 1.51–1.78) with an overall annual incidence rate of 733 per 100,000 in the IBD population compared to controls, who had an incidence rate of 447 per 100,000 [13]. A nested case-control study then evaluated the use of immunosuppressive medications in IBD patients. This demonstrated an increased odds of NMSC with recent thiopurine use (within 90 days) (adjusted OR 4.56; 95% CI, 2.81–4.50) or recent biologic use (anti-TNF) (adjusted OR 2.07; 95% CI, 1.28–3.33), as well as persistent/long-term use of thiopurine or biologic therapy. There was some suggestion that longer duration of therapy may further increase risk. Additionally, the overall odds of developing NMSC were found to be highest with combined immunomodulator and biologic therapy (adjusted OR 5.85; 95% CI, 2.62–4.10) [13].

Two other European studies have also evaluated the incidence of NMSC in patients with IBD [14, 15], and both of these studies also showed an increased risk of NMSC in IBD patients. However, these studies were performed prior to the widespread use of biologic therapies. This suggests an innate increased risk in IBD patients independent of biologic use or risks associated with other classes of medications. Factors influencing the development of NMSC may include fair skin, UV light exposure, and impaired DNA repair, likely exacerbated by thiopurine use [16]. Thiopurines have been associated with selective photosensitivity to ultraviolet-A (UV-A) light and oxidative DNA damage [17]. Thus, some of the prebiologic risk of NMSC is likely associated with thiopurine use. As many patients receive thiopurines prior to or in combination with anti-TNFs, it is difficult to determine the independent effects of anti-TNFs on NMSC risk.

The risk of NMSC from anti-TNF therapy with concomitant immunomodulators has been further investigated in a large Quebec claims database study. This study evaluated 19,582 eligible patients regarding the use of thiopurines and biologics and risk of various malignancies: NMSC, melanoma, lymphoma, and

colorectal cancer. There was an increased risk of NMSC with thiopurine treatment for >3 years, and secondary analysis-demonstrated exposure duration >5 years but not 3–5 years was significantly associated with NMSC (OR 2.07; 95% CI, 1.36–3.7). There was an additional increased risk in patients treated with both biologics and thiopurines but not with biologics alone [18]. This points to the fact that while the primary risk of NMSC associated with thiopurines appears to be potentiated by anti-TNF therapy, there does not appear to be the same risk with monotherapy with anti-TNFs.

The more extensive RA literature provides additional valuable data regarding the risks of NMSC in patients treated with biologic therapies. A large cohort study evaluating 15,789 patients with RA and 3639 patients with osteoarthritis (OA) by Chakravarty et al. looked at the incidence rate of NMSC. After adjustment for covariates in Cox proportional hazard models, RA was associated with an increased risk of NMSC, with a HR 1.19, $p = 0.042$. In RA patients, NMSC development was associated with prednisone use (HR 1.28, $p = 0.014$). Anti-TNFs were also associated with an increased, though nonsignificant risk of NMSC development (HR 1.24, $p = 0.89$). Anti-TNF use with concomitant methotrexate use was associated with a statistically significant increase in the development of NMSC (HR 1.97, $p = 0.001$) [19]. Methotrexate has been directly associated with photosensitivity, likely contributing to this increased risk. These findings again indicate a possible amplified effect of anti-TNFs when used in combination with other immunosuppressants.

A large study in the Veteran's Affairs (VA) population compared the risk of NMSC among RA patients on anti-TNFs vs. non-biologic disease-modifying antirheumatic drugs (DMARDs). The incidence of NMSC was found to be 18.9 per 1000 patient-years on anti-TNF agents vs. 12.7 per 1000 patient-years in patients on non-biologic DMARDs. There was a statistically significant increased risk of NMSC for those patients on anti-TNF agents compared to non-biologic DMARDs (HR 1.42, 95% CI), and this was a class effect [20].

Furthermore, a study of the British Society for Rheumatology Biologics Register included 11,881 consecutive patients with RA who were treated with anti-TNF agents, compared to 3629 biologic-naïve patients who received non-biologic DMARDs. There was no evidence that anti-TNF therapy further exacerbated the risk of basal cell carcinoma or squamous cell carcinoma when compared to the risk associated with DMARDs, standardized incidence ratios (SIR) of 1.72 (95% CI, 1.43–2.04) in the anti-TNF group vs. 1.83 (95% CI, 1.3–2.50) in the DMARD group [21].

Based on combined literature from both RA and IBD populations, anti-TNF agents may be associated with a higher risk for NMSC. However, as many patients will first cycle through immunomodulators or DMARDs, respectively, these estimates are likely influenced by use of other agents such as thiopurines or methotrexate, both of which have been associated with increased skin cancer risks through mechanisms of photosensitivity [17]. This NMSC risk attributable to anti-TNF agents appears to be potentiated by both duration of therapy, as well as the combined use of other immunomodulators.

Melanoma

In the USA, melanoma is the fifth most common cancer for men and the seventh most common cancer for women. It is responsible for more than 9000 deaths annually. Overall, the absolute risk of melanoma is much less than that of NMSC, and thus larger populations are needed in order to evaluate specific medication associations. As with other skin cancers, there are significant physical, psychological, financial, and societal costs of melanoma.

The prior literature is limited by the individual sample sizes of many studies.

In a systematic review and meta-analysis, the incidence rate of melanoma in patients with IBD was 27.5 cases/100,000 person-years (95% CI, 19.9–37.0). IBD was associated with a 37% increase in risk of melanoma (12 studies; RR, 1.37; 95% CI, 1.10–1.70). The risk was increased among patients with both CD and UC [22]. This increased risk predated the biologic era, showing that IBD itself may be associated with an increased risk of melanoma.

The Quebec claims database study previously referenced for NMSC also assessed the risk of melanoma. Out of the 19,582 patients who met study inclusion criteria, a total of 102 cases of melanoma were identified. Neither biologics nor thiopurines were found to be associated with an increased risk of melanoma [18]. In contrast, a larger retrospective cohort using LifeLink Health Plan Claims Database in the USA evaluated 108,579 patients with IBD from 1997 to 2009. In a nested case-control study of melanoma in patients with IBD, there were 209 cases of melanoma and 823 matched controls. A total of 26 out of 209 cases of melanoma had documented biologic use (12.4%) vs. 56 out of 823 controls (6.8%). The use of any biologic anti-TNF was associated with melanoma in crude (OR, 2.08; 95% CI 1.24–3.51) and adjusted analyses (OR, 1.88; 95% CI 1.08–3.29), while there was no significant association with any thiopurine or any 5-ASA use. The use, less than 120 days' duration, showed no associated risk of melanoma (crude OR, 0.97; 95% CI, 0.19–4.98). Long-term use, as designated by a surrogate marker of current use of anti-TNF at the time of entry into cohort follow-up, was associated with an adjusted OR of 3.93 (95% CI, 1.82–8.50) compared to patients not using these drugs at enrollment [23].

The link between anti-TNFs and melanoma has been studied more comprehensively in the RA population. A systematic review and meta-analysis by Olsen et al. evaluated six studies. Four of the studies looked at the risk of melanoma in RA patients receiving anti-TNF therapy compared to patients treated with non-biologic DMARDS and found a 1.60 (95% confidence interval, 1.16–2.19) pooled effect estimate. Five of the studies examined the risk of melanoma in RA patients receiving ant-TNFs compared to the general population, and the pooled effect estimate was 1.87 (95% confidence interval, 1.53–2.30). A systematic literature review and meta-analysis of biologic registers demonstrated the relative risk of melanoma to be 1.17 (95% CI, 0.86–1.59) [24]. These findings overall suggest the use of anti-TNFs is an independent risk factor for the development of melanoma in the RA population [25].

Unlike the data on NMSC where the risk may be mediated through alternate concomitant medications (such as thiopurines), anti-TNFs seem to be more directly and independently linked to the risk of melanoma. These findings are echoed in the RA literature. Additionally, this effect does appear to be related to duration of therapy, with longer duration putting patients at higher risk of development of melanoma. The mechanism of this risk is unclear and may not be linked to photosensitivity, as is seen with thiopurines.

Lymphoproliferative and Myeloproliferative Disorders

Lymphomas

There are two broad types of lymphoma: Hodgkin's lymphoma and non-Hodgkin's lymphoma. Within each of these broad categories, there are numerous subtypes. Based on data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program, Cancer Statistics Review (1975–2012), an estimated 788,939 people are living with or are in remission from lymphoma in the USA. Of these, an estimated 181,967 people have Hodgkin's lymphoma, and 609,972 have non-Hodgkin's lymphoma. Approximately 21,270 people are expected to die from lymphoma annually.

A study of 16,023 IBD patients without HIV in the Kaiser Permanente IBD Registry from 1996 to 2009 examined the standardized incidence rate ratio (SIRR) of lymphoma. The most common lymphomas overall were diffuse large B-cell lymphoma (44%), follicular lymphoma (14%), and Hodgkin's disease (12%). For patients with IBD, not receiving anti-TNF or thiopurine therapy, the standardized incidence rate ratio (SIRR) of lymphoma was 1.0. For patients who had received thiopurines alone, the SIRR was 0.3 for past use and 1.4 for current use. For patients receiving anti-TNFs, with or without a concomitant thiopurine, the SIRR was 5.5 for past use and 4.4 for current use. Notably, nearly all of the patients were treated with thiopurines prior to anti-TNF therapy [26].

A review of 3,130,267 reports from the Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) of patients on anti-TNF therapy identified 91 cases (and nine additional cases in a MEDLINE literature search) of T-cell NHL. A total of 28 of these cases were in RA, 36 were in CD, 11 were in psoriasis, 9 were in UC, and 6 were in ankylosing spondylitis (AS). A total of 68% of cases had exposure to both anti-TNF and an immunomodulator, including azathioprine, 6-mercaptupurine, methotrexate, leflunomide, or cyclosporine. The risk for development of T-cell NHL when TNF-alpha inhibitors were used alone was not elevated vs. a fivefold increase in reported risk with anti-TNFs combined with thiopurines and eightfold risk with thiopurines alone. Again, these data highlight the multiple factors contributing to the development of lymphoma in patients with autoimmune diseases, particularly the compounded effect of anti-TNFs when used with immunomodulators.

The risk of lymphoma in patients on anti-TNFs has also been evaluated in the RA population, where thiopurine use is less common. A meta-analysis demonstrated the relative risk of lymphoma on anti-TNF agents to be 0.90 (CI 0.62–1.31), thus leading to the conclusion that anti-TNFs did not contribute to the risk of lymphoma in RA patients [24].

Hepatosplenic T-Cell Lymphoma

Hepatosplenic T-cell lymphoma (HSTCL) is characterized by the infiltration by malignant T cells of the spleen and liver, and it comprises 5% of peripheral T-cell lymphomas. HSTCL is more common in young people, and it is more common in men than women—34 out of 41 cases available in one study were found to be men. Among these patients, 36 out of 45 patients were deceased at the time of data collection, with a median survival of 8 months. Though rare, HSTCL carries a significant risk of mortality [27].

The majority of the data on HSTCL and an association with anti-TNF therapies have been compiled from case reports. The FDA AERS received eight cases of HSTCL in young patients (ages 12–31) using infliximab to treat IBD as of October 5, 2006. A total of seven of these cases were in CD, and one case was in UC. Of these, seven of the patients reported hepatosplenomegaly, and six out of eight cases were fatal. All eight of these patients were using concomitant immunosuppressant therapy with azathioprine, and some were additionally using mesalamine or prednisone. There were 15 additional cases of lymphoma with infliximab use (all indications and ages) which were also reviewed, but it is not clear whether these cases represented HSTCL. There has been only one fatal case of gamma/delta subtype of HSTCL associated with azathioprine and one fatal case associated with mercaptopurine alone. There is no established primary role for infliximab in the pathogenesis of HSTCL, but it does appear evident that there is an association [28].

The above FDA report was later updated to include 15 total cases of biologic-associated HSTCL between 1998 and June 30, 2008. Thirteen of these cases involved the use of infliximab only, while two of these cases represented treatment with infliximab, followed by adalimumab. All patients ranged in age between 12 and 29 years old and were receiving concomitant immunosuppressants, including azathioprine or mercaptopurine in all cases. The authors of this study again concluded that young patients using biologics may be at greater risk for developing HSTCL [29]. Nearly all of these cases were male (14 out of 15 patients), suggesting that there may be a gender-specific risk associated with the development of HSTCL. Additionally, the concomitant use of immunomodulator therapies such as azathioprine or mercaptopurine in all of the cases of HSTCL raises concern about their potential risks when used together with biologics in young, male patients. The review from the FDA AERS system described above also demonstrated a larger number of cases of HSTCL were identified with TNF-alpha inhibitors used in combination with an immunomodulator (29 cases) compared with those with

TNF-alpha inhibitor alone (1 case) [30]. This again echoes the concern for potentiated risk of HTCL with joint anti-TNF and immunomodulator use. Finally, the occurrence of HSTCL has been noted in patients receiving ant-TNF therapy in the RA and psoriasis populations, with four and one cases cited by the FDA AERS study, respectively [30].

Solid Tumors

Prior literature has also investigated the association between anti-TNF use and solid organ tumors. A nationwide cohort of 56,146 patients with IBD in Denmark from 1999 to 2012 focused on the 4553 patients who were exposed to anti-TNFs. The authors found no significant associations between anti-TNF exposure and the development of solid tumors, including those of the lip, oral cavity, pharynx, digestive organs, lungs, breast, and genitourinary system. Additionally, the multivariable relative risks for most cancers were actually decreased after adjusting for azathioprine exposure [31].

The association between anti-TNFs and solid tumors has been studied in the rheumatology literature. The British Society for Rheumatology Biologics Register, a national prospective cohort study, evaluated the rates of solid cancer occurrence in patients with RA receiving anti-TNFs vs. DMARDs. There were 427 solid cancers reported in 52,549 patient-years in the anti-TNF group and 136 per 11,672 patient-years in the DMARD cohort. After adjustment for baseline characteristics, there was no difference in risk of solid cancer for TNF inhibitors vs. DMARDs [32]. A review of the RA literature by Lebrec et al. also did not reveal any association between anti-TNF use and solid tumor development [33]. In fact, an analysis of the Corona RA Registry found a decreased risk of solid cancer associated with anti-TNFs compared to methotrexate [34].

Cervical Cancer

Various factors have been associated with cervical cancer risk in the general population. The most important risk factor is human papilloma virus (HPV) infection. Other associated risks include immunosuppression (such as human immunodeficiency virus), smoking, age, oral contraceptive use, and exposure to diethylstilbestrol (DES). Cervical cancer is relatively rare; the low absolute risk may be associated with detection and treatment of cervical cancer precursors through screening programs [35].

In the IBD population, a population-based Danish cohort demonstrated an increased risk of cervical dysplasia in both CD and UC patients. The risk of cervical cancer was increased only in the CD population. It has been theorized that immunosuppressive medications can lead to increased cervical dysplasia due to impaired

ability clear human papilloma virus (HPV) infections [36]. Kane et al. conducted a case-control study evaluating 40 patients with IBD and their incidence of abnormal pap smears as compared to the control population. Patients with IBD did have a higher risk of an abnormal pap smear as compared to healthy controls. In addition, patients with a history of immunomodulator use were more likely to have an abnormal pap smear associated with high risk strains of HPV (serotype 16 or 18) [37]. However, the outcome of this study was abnormal pap rather than cervical dysplasia or cancer.

Singh et al. evaluated data from the University of Manitoba IBD Epidemiology Database, matching 19,692 women with cervical cytologic or histologic abnormalities on pap smear with 57,898 controls with normal pap smears [38]. While there was no associated risk for abnormal pap smears in patients with UC and CD who had not been prescribed ten or more prescriptions of oral contraceptives, there was an increased risk associated with concomitant corticosteroid and immunosuppressant use. The immunosuppressant medications used among patients in this study were azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, or infliximab. Interestingly, the increased risk was not present with either corticosteroid or immunosuppressant use alone [38]. While there have been conflicting reports about the baseline risk of abnormal cervical dysplasia and cancer in IBD patients, there does appear to be an association with increased immunosuppression use in this population. The limited available data cannot distinguish risks by specific classes of medications.

Colorectal Cancer

It is well established that patients with extensive, long-standing colitis have a higher risk of colorectal cancer (CRC) than the general population [39]. The risk of CRC in patients with UC fluctuates between 0.9–8.8-fold and 0.8–23-fold in patients with pancolitis [40]. There is no statistically increased risk of CRC in CD [41]. However, in patients with long-standing Crohn's colitis, the risk becomes similar to that of UC [42]. TNF-alpha has been identified as a crucial mediator in the development of CRC in IBD. This implies TNF-alpha inhibition may play a role in cancer reduction [40].

Data have shown that CRC risk is linked to the actual histologic inflammatory activity over time. Thus, various medications have been studied that have reduced the risk of CRC and/or dysplasia. A case-control study by Ruben et al. of 141 patients with UC without CRC and 59 matched patients with UC who developed CRC demonstrated an increased risk of CRC with inflammation, as well as a decreased risk of CRC with the use of immunomodulators such as azathioprine, 6-MP, and methotrexate [43]. Classes of medications that have been associated with reduced risk include 5-amino salicylic acid (5-ASA) agents [44] and immunomodulators such as thiopurines [45]. It is also possible that anti-TNF medications similarly reduce this risk through inflammation reduction.

Use of Anti-TNFs in Patients with a Prior History of Malignancy

The safety of anti-TNF therapy in patients with a history of a prior malignancy is important given the chronic nature of IBD. In a retrospective cohort of 333 IBD patients who developed cancer and then subsequently were treated with anti-TNF agents, exposure to an anti-TNF agent or an antimetabolite after cancer was not associated with an increased risk of incident cancer, as compared to those who did not receive immunosuppression [46]. In a subsequent meta-analysis, Shelton et al. also found a reassuring lack of increased recurrence rate associated with anti-TNF use. The authors included 16 studies (10 published, 1 unpublished, and 5 abstracts) looking at 11,702 patients with a history of prior cancer diagnosis who also had RA (9 studies), IBD (8 studies), or psoriasis (1). In the group of patients on no immunosuppression, there were 609 new or recurrent cancers over 12,404 person-years (p-y) of follow-up evaluation, yielding a pooled incidence rate of 37.5 per 1000 p-y (95% CI, 20.2–54.7). Data were significantly heterogeneous with incidence rates ranging from 0 to 62.5 per 1000 p-y. Patients who were subsequently placed on anti-TNF therapy or immunosuppression had a median interval of 6 years to introduction of immunosuppression. The 1753 subjects contributing 5842 p-y of follow-up were exposed to anti-TNF therapy after prior cancer. There were 215 cases of new or recurrent cancer, which gave a pooled incidence rate of 33.8 per 1000 p-y (95% CI, 22.3–45.2). This was similar to what was observed in the no immunosuppression group. There was also no significant difference between the anti-TNF group and the group of patients treated with conventional immunosuppressants. A total of three of the studies looked at combination therapy with anti-TNF + immunomodulator, and the pooled incidence rate was 54.5 per 1000 p-y (95% CI, 29.7–79.3). This was not statistically different than the results of analysis of individual therapy with anti-TNF ($p = 0.23$), other immunosuppression ($p = 0.27$), or no immunosuppression ($p = 0.47$) [47]. This body of information suggests clinicians may cautiously select appropriate patients with a history of prior malignancy for treatment with anti-TNF therapies.

How to Discuss the Risks and Benefits of Anti-TNFs

When considering treatment options for patients with CD and UC, it is imperative to effectively communicate both the risks and benefits of potential medical therapies to patients. Risk communication can be misunderstood, and thus patients may be less amenable to initiating therapies that would be effective at treating their underlying IBD. The communication of the risks of malignancy versus the potential treatment benefits from anti-TNF agents can dramatically influence a patient's ultimate decision. "Rare" means different things to different people, and the way "rare" is portrayed by a clinician can dramatically influence a patient's

decisions. For example, reporting the relative risk without also reporting the absolute risk can skew a patient's perception of the likelihood of an event occurring and may deter someone from utilizing a medication that may offer improved quality of life and potential remission from their underlying disease. It is important to use absolute as opposed to relative numbers and use actual odds rather than percentages (e.g., 5 per 1000 instead of 0.5%). Often, pictures can be used to represent numbers of patients at risk. This can help patients to understand the true absolute risks of malignancy. Comparisons between risks should be presented with a common denominator to avoid confusion. The more specific the clinician can be when describing the likelihood of both risks and benefits, the more likely the patient is to have a well-informed and realistic grasp of their options. Finally, putting together the big picture for the patient in terms of quality of life benefits both long term and on a day-to-day basis as opposed to a cumulative life risk can be invaluable to a patient grappling with the decision to start a biologic or other medical therapy [48].

Prevention of Complications of Immunosuppressive Medications in IBD

There are three forms of prevention: primary, secondary, and tertiary prevention. Primary prevention refers to prevention of development of a disease or complication, such as through vaccination. Secondary prevention refers to the ability to detect disease earlier, when it may be easier to treat or manage, in order to prevent disability. An example of secondary prevention would be screening programs, such as those for colon cancer screening. Finally, tertiary prevention refers to measures that reduce the impact of long-term disease and disability, in order to maximize potential years. Each of these forms of prevention can be addressed for patients with IBD.

For primary prevention of malignancy, there are opportunities to prevent both cervical cancer and skin cancer. Recommendation of HPV vaccine for women age 11–26 can help to prevent cervical cancer. As we know that the mechanism of increased skin cancer risk associated with thiopurines is photosensitivity to UV-A light, recommendation for broad spectrum sunscreen use can help to prevent this complication. For secondary prevention, colonoscopic surveillance based on available guidelines to detect colonic dysplasia in those with long-standing colonic inflammation can help prevent colorectal cancer through early identification of dysplasia. For women, screening pap smears based on the US Preventive Services Task Force (USPSTF) and American College of Obstetricians and Gynecologists (ACOG) recommendations should be performed. Additionally, consideration should be given for skin screening examinations among patients with IBD on known higher-risk medications such as immunomodulators and

anti-TNF agents. Such examinations are recommended in posttransplant populations where risk is also higher. Finally, tertiary prevention refers to treatment of IBD to prevent complications of the disease itself, such as development of abscess or requirement for surgery. By optimizing IBD therapy early in disease course, we may be able to prevent late complications associated with untreated inflammation over time.

Limitations in the Literature and Queries for Future Investigations

While there has been increasing interest and investigation into anti-TNF agents and their associated clinical benefits and risks, including malignancy, data are limited overall. Studies are often retrospective or use administrative data sources which are limited by the risk of misclassification and lack of clinical detail. Long-term cancer risks will need to be assessed as anti-TNF use increases over time, preferably in a prospective fashion. Additionally, the use of novel combinations of medications, such as vedolizumab (anti-integrin therapy) or ustekinumab (anti-p40 IL 12/23 inhibitor) and thiopurines, compared to anti-TNF-containing regimens, will need to be further studied. We also need better detail on combinations of therapy, including methotrexate as an immunomodulator combined with anti-TNF agents. Additionally, the use of anti-TNF agents in patients with a history of prior malignancy is an area that warrants further investigation to help to guide evidence-based treatment recommendations in this group. We anticipate a growing body of literature regarding biologic therapies and malignancy in the coming years, which will help guide both clinicians and patients in selecting therapies to manage IBD.

Summary

Over the past two decades, increasing rates of anti-TNF use in IBD populations have dramatically changed the therapeutic landscape. These agents have allowed patients to reach steroid-free remission and have often allowed for mucosal healing. However, these agents also come with a series of risks, which must be communicated effectively with patients. Risk communication of absolute numbers with common denominators is imperative in order for patients to effectively interpret risk. Importantly, population-based studies have shown that while GI malignancy rates in IBD populations have decreased with more effective therapies and/or improved surveillance techniques, there has not been a concomitant increase in hematologic or other extraintestinal malignancies [7]. This demonstrates that the risk/benefit ratio

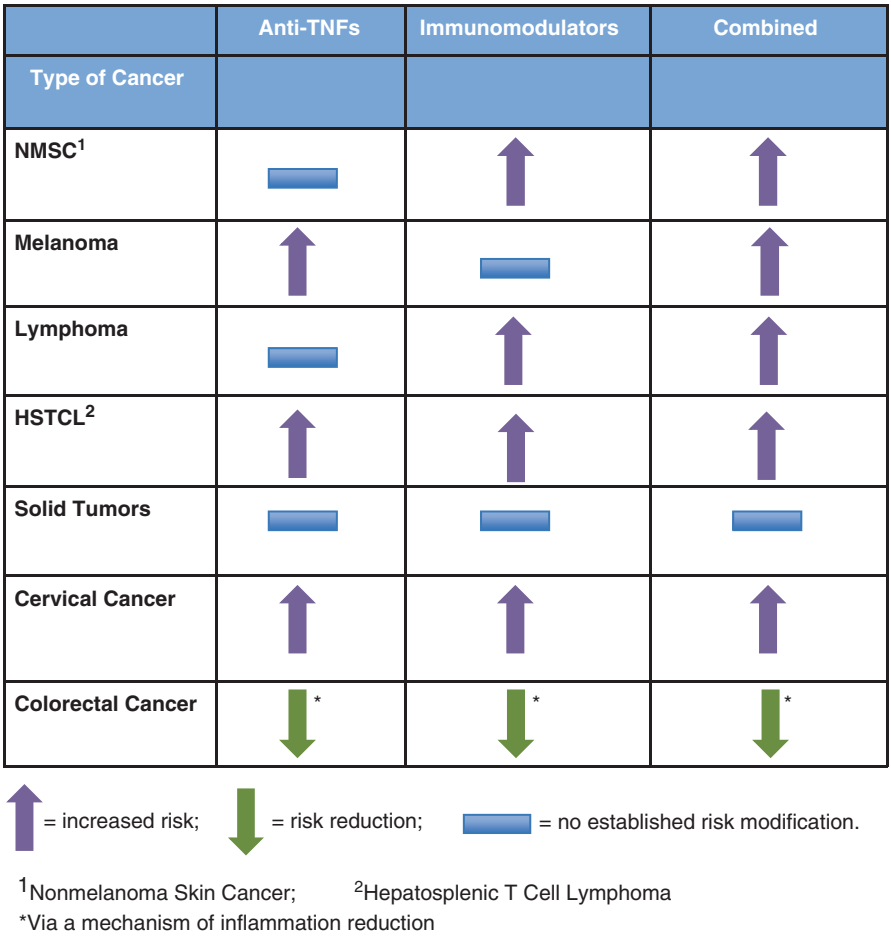

Fig. 13.2 Cancer risk and reduction with anti-TNFs, immunomodulators, and combination therapy

is in favor of benefit at the population level. Risks seem to be focused in three main groups: skin cancer, cervical dysplasia and/or cancer, and lymphoma. There may be benefits of anti-TNF and other classes of medications that allow for mucosal healing and therefore the reduction of colorectal dysplasia and cancer risk. A summary of these risks is shown in Fig. 13.2. Additionally, in populations of patients with prior malignancies, anti-TNF agents have not been associated with recurrence, when carefully selected. As clinicians, we can offer various preventive measures to help to prevent malignant complications in our patients. These efforts focus upon primary, secondary, and tertiary prevention of complications. Overall, a shared decision-making process with appropriate follow-up, monitoring, and continued discussions of risks and benefits of therapies will allow us to effectively and safely treat our patients with IBD.

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Chapter 14
Noninfectious and Nonmalignant Complications of Anti-TNF Therapy

Uni Wong and Raymond K. Cross

Introduction

Biologics, namely, monoclonal antibodies including anti-TNF and anti-integrin agents, are frequently used in the treatment of moderate to severe inflammatory bowel disease (IBD). The noninfectious and nonmalignant complications of biologics include infusion or injection site reactions, psoriasiform and eczematous eruptions, lupus-like reaction, hepatotoxicity, demyelination, and heart failure. In the majority of these cases, the adverse events are reversible with discontinuation of the offending biologic or can be managed with supportive care without discontinuation of therapy. Early recognition and management of these complications is important to minimize suffering from adverse events, to initiate supportive treatment, and to transition to other therapies when needed. This chapter focuses on the clinical presentation, pathophysiology, diagnostic evaluation, and management of the noninfectious and nonmalignant complications of biologics. The majority of our knowledge on the safety of biologics is based on clinical studies on infliximab and adalimumab given their extended use in the treatment of IBD.

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Infusion and Injection Site Reactions

Clinical Presentation

Infusion reactions, both acute and delayed types, are defined as any adverse event related to the drug administration [1]. Acute infusion reactions occur within the first hours after drug administration and can be categorized as mild or severe. Mild acute infusion reactions can be seen in 10–40% of patients receiving infliximab [2, 3]. Symptoms include fever, nausea, vomiting, formation of a wheal, and/or pruritic erythema [1, 2]. Severe acute infusion reactions are less common, occurring in about 8% of patients receiving infliximab [2]. Patients with severe acute infusion reactions can present with fever, hypotension, bronchospasm, dyspnea, generalized urticaria, angioedema, and in some cases anaphylaxis [1, 2].

Delayed infusion reactions have been reported in up to 7% of patients receiving infliximab [3]. Patients with delayed infusion reactions often present with serum sickness-like symptoms including fever, malaise, arthralgia, myalgia, and urticaria 3–14 days after the infusion [1, 2]. Because the symptoms are nonspecific, delayed infusion reactions must be differentiated from other conditions including viral syndromes, drug-induced lupus, and extraintestinal manifestations of IBD [4]. Serum sickness syndrome is typically self-limiting, with symptoms subsiding within days or weeks [1, 2].

Another hypersensitivity reaction patient can experience is injection site reaction localized to the area where the biologic agent is administered. Injection site reactions occur in 8–20% of patients receiving adalimumab [5, 6]. The skin lesions appear within 24–48 h after the injection and are characterized by cutaneous eruptions, erythema, pruritus, tenderness, swelling, and irritation [1, 5]. Injection site reactions are typically self-limiting and resolve after 3–5 days [2].

Risk Factors

Risk factors for developing hypersensitivity reactions to biologics are related to both the patient and the drug [1]. Predisposing factors related to the patient include genetic predisposition (human leukocyte antigen class and presence of genetic defects), age, immune competency, and the presence of other diseases [7]. Risk factors associated with the drug include dose, frequency of dosing, and route of administration [7]. Theoretically, intravenous dosing is less immunogenic than subcutaneous or intradermal dosing; however, this has not been the experience of most providers clinically, and there is no available data to support this theory [7].

Acute infusion reactions are more likely to occur in those receiving episodic or reinitiation of therapy after a drug-free interval due to immunogenicity [3]. Baert and colleagues reported that among 128 patients who were reinitiated on infliximab, 15 patients developed acute infusion reactions, and 10 had delayed infusion reactions, after a median drug-free interval of 15 months [8]. In another study

consisting of 86 adults and pediatric patients receiving episodic infliximab retreatment, Kugathasan et al. found that a drug-free interval as short as 20 weeks is associated with high rates of severe systemic reactions in adults [9].

The level of antibody to infliximab (ATI) correlates with the risk of infusion reactions, especially with acute infusion reactions [10, 11]. In A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment (ACCENT I) trial, among 254 infusion sessions across 64 patients who had positive ATI, 17% (42/254) of the infusion sessions were complicated by infusion reaction [12]. This is in contrast to the infusion reaction rate of 8% (55/656) observed among 656 infusions in 173 patients who had negative ATI [12]. Patients who were on a concomitant immunomodulator were less likely to have ATI (4%), compared to those who were on concurrent steroids (17%) and compared to those who were on neither steroid nor immunomodulator (18%) [12].

Pathophysiology

The immune system is built to detect and eliminate foreign molecules [7]. Drugs, having different structures than endogenous molecules, can also elicit an immune response [7]. The likelihood that a drug is immunogenic depends largely on its structure. Unlike small molecules that are often unrecognized by the immune system as foreign, biologics are typically large proteins with complex structures, thus having an increased risk of recognition by the immune system [7]. Antigen-presenting cells (APCs), T cells, and B cells are involved in immunogenicity. APCs process the biologic agents into peptides that get presented to the T cells via the major histocompatibility complex (MHC) molecules. The peptide-MHC complex binds to a specific T cell receptor, but a T cell immune response is only activated when there is co-stimulation by the molecules on the surface of the APC. Without this co-stimulatory signal, the T cells become anergic or undergo apoptosis. For this reason, biologics that are identical or nearly identical to endogenous proteins are expected to be relatively non-immunogenic [7].

B cell activation and antibody production can occur with or without T cell involvement. Activated B cells produce immunoglobulin (Ig) M initially and, after interaction with antigen-specific T helper cells, switch to productions of IgG or IgE. A subgroup of these B cells matures into long-lived plasma cells. During subsequent exposures to the antigen such as that from the biologic agent, these plasma cells rapidly respond with secretion of large amounts of antibody, representing a memory response [7]. Without interaction with the antigen-specific T helper cells, B cells can still produce anti-drug-antibodies (ADA) in the form of IgM, and these plasma cells are typically short-lived [7].

Hypersensitivity reactions, types I and III, typically occur after IgG or IgE formation, which usually happen 10–14 days after initial exposure [7]. In type I hypersensitivity reactions, IgE isotypes of the ADA are formed during the initial exposure to the biologic agent and bind to mast cells and basophils via the Fc receptors. When

the biologic agent is administered again, it binds to these antibodies, causing rapid release of histamine and other mediators, resulting in anaphylaxis that can be mild to fatal [7, 13]. Another mechanism through which a type I hypersensitivity reaction can occur involves the binding of the IgG isotype of ADA to neutrophils via their Fc receptors. Upon reexposure, the biologic cross-links the surface IgG molecules causing neutrophil activation which results in release of platelet-activating factor. Platelet-activating factor can initiate an atypical anaphylactic response that is 10,000 times more potent than histamine [14, 15].

Immediate type I hypersensitivity reactions are thought to play a role in injection site reaction with release of preformed chemokines, granule-associated mediators, membrane-derived lipids, and cytokines [5]. When an allergen interacts with an IgE that is bound to mast cells or basophils, the allergen-IgE-mast cell complex triggers the release of histamine, leukotrienes, prostaglandins, and platelet-activating factor [16]. As noted previously, platelet-activating factor can initiate an atypical anaphylactic response [14, 15]. Most infusion reactions are not true IgE-mediated type I hypersensitivity events, however [17]. The serum sickness syndrome seen in delayed infusion reaction is due to type III hypersensitivity reactions [18]. In type III hypersensitivity reactions, the biologic-ADA immune complexes are deposited in blood vessels, skin, and joint tissue, eliciting complement activation and inflammation leading to tissue damage [18].

Diagnosis and Management

Mild infusion reactions are often self-limiting and can be managed with supportive care, without the need to permanently discontinue therapy [2]. Management of mild infusion reactions includes temporary interruption of the infusion or decreasing the infusion rate [2]. Additional doses of acetaminophen and diphenhydramine and/or methylprednisolone can be given as well (see Table 14.1). Mild injection site reactions can be managed with cooling, topical corticosteroids, rotation of injection sites, and pain control if necessary [2]. However, it is important to keep in mind that mild infusion or injection reactions may be the first manifestations of immunogenicity against the biologic agent, with potentially worsening of hypersensitivity symptoms with each infusion [2]. Severe infusion or injection reactions with anaphylaxis generally warrant immediate discontinuation of the drug [2]. Delayed infusion or injection site reactions can be managed with supportive care with antihistamine and acetaminophen (see Table 14.1). A short course of oral corticosteroids may be considered in more severe cases [18].

Skin allergy testing can help risk-stratify patients for recurrence of severe hypersensitivity reactions. If a patient who had immediate type I hypersensitivity reaction to a biologic agent had a negative skin test, standard infusion can be continued with premedication [19]. If the patient tested positive on the skin test, then desensitization or change in therapy should be considered [19, 20]. If the patient developed desquamation, skin blistering, or serum sickness with skin testing, avoidance of the medication is recommended [19].

Table 14.1 Clinical presentation and management of infusion and injection reaction

	Acute infusion/injection reactions	Delayed infusion/injection reactions
Timing of onset	Within first hours of dose	3–14 days
Clinical presentation	*Mild*: Fever, nausea, vomiting, wheal formation, pruritus, erythema	Serum sickness-like syndrome: fever, malaise, arthralgia, myalgia, urticaria
	Severe: Fever, hypotension, bronchospasm, dyspnea, urticaria, angioedema, anaphylaxis	
Management	*Mild:*	
	For infusion reactions: temporary interruption of the infusion or decreasing infusion rate, acetaminophen 650 mg po, diphenhydramine 12.5–25 mg po/IV, and/or methylprednisolone 20–40 mg IV	Antihistamine and acetaminophen
	For injection site reactions: cooling, topical corticosteroid, rotation of injection sites, analgesics	
	Severe:	
	Immediate discontinuation of the drug; management of anaphylaxis with maintenance of airway and hemodynamics	Medrol Dosepak or short tapering course of prednisone
Secondary prophylaxis	*Mild:* Acetaminophen 650 mg po, diphenhydramine 25 mg po, and methylprednisolone 40 mg IV or prednisone 40 mg po the day prior and day of infusion	Methylprednisolone 40 mg IV before infusion or prednisone 40 mg po the day prior and day of infusion followed by a Medrol Dosepak after infusion
	Severe: Change of therapy is recommended. If no alternative, desensitization	

Antibody testing, checking for isotypes IgG and IgE, is another way to risk-stratify patients after an episode of infusion or injection site reaction. The presence of IgG is associated with an increased risk of hypersensitivity reactions and decreased effectiveness of the biologic agent [19]. Concomitant use of an immunomodulator such as methotrexate or thiopurine can decrease risk of antibody formation, decrease or eliminate preformed antibodies, decrease risk of infusion reactions, and improve efficacy of the biologic agent [8, 12, 18, 21].

Acute infusion reactions can recur in up to one third of subsequent infusions, so secondary prophylaxis should be considered [18]. To minimize the risk of recurrence of hypersensitivity reactions during subsequent infusions, patients are generally premedicated with a corticosteroid, antihistamine, and antipyretic (see Table 14.1) [19]. Graded dose rechallenge with the drug is thought to be effective, since a smaller test dose theoretically induces smaller quantity of cytokine release correlating to milder reactions [18].

In general, patients who develop severe infusion or injection reactions are recommended to change therapy to another agent [18]. The decision to rechallenge is largely based on the severity of hypersensitivity reactions and potential clinical benefit of further treatment. If no alternatives are available, Lichtenstein and colleagues proposed pretreatment with antihistamine and corticosteroid (prednisone 50 mg every 8 h for 24 h prior to the infusion) or desensitization using graded administration of the offending drug escalating to the target dose that is clinically tolerated [18]. The sequential exposure to low-dose antigen could desensitize mast cells and basophils to the offending drug [18]. Data on desensitization to infliximab is limited to case reports and case series with breakthrough reaction rates of up to 29% similar to the rate observed in those without desensitization, though breakthrough reactions are generally milder allowing for the continuation of therapy [18].

Primary prophylaxis may be necessary in certain selected patient populations, particularly those who have had prolonged drug-free intervals [3, 11, 22]. In a retrospective single-center study, infliximab trough and anti-drug antibody levels were collected from 128 IBD patients that reinitiated infliximab therapy after a median of 15 months (range 6–125 months) [8]. At the time when infliximab was restarted, none of the patients in this study had a detectable ATI [8]. After reexposure to infliximab, ATIs were detected in 40% at week 2 [8]. Ben-Horin et al. also demonstrated that ATI declines to undetectable levels within 1 year after cessation of infliximab therapy in the majority of patients (13/16, 81.3%) [23]. Therefore, in patients who have had a drug-free interval of 12 months or greater, assessment of anti-drug antibodies will not be helpful before reinitiating therapy; however, ATI can be assessed before the next infusion to help predict which patients will develop acute infusion reactions.

Strategies for primary prophylaxis are similar to secondary prophylaxis as described, which include gradual increase of infusion rate, co-administration of an immunomodulator, and premedication with acetaminophen, diphenhydramine, and steroid [18, 19]. Premedication with intravenous hydrocortisone can reduce ATI [24]. In a randomized placebo-controlled trial consisting of 53 Crohn's disease (CD) patients receiving infliximab, only 26% of hydrocortisone-treated patients developed ATI compared with 42% of placebo-treated patients ($p = 0.06$) [24]. Additionally, ATI levels were lower at week 16 among patients treated with hydrocortisone (1.6 vs. 3.4 μg/mL, $p = 0.02$) [24]. Patients treated with adalimumab should first allow the drug to reach room temperature and ice the injection site before administering the injection.

Psoriasiform and Eczematiform Lesions

Clinical Presentation

Development of psoriasiform or eczematiform lesions has been reported in patients treated with anti-TNF therapy [25–28]. Although anti-TNF therapy is used to treat psoriasis, IBD patients can paradoxically develop these immune-mediated

inflammatory skin lesions after initiating biologic therapy [29, 30]. While the timing of these skin lesions occurring after initiation of anti-TNF therapy and their resolution after discontinuation of therapy suggest that they are induced by the biologic agent, in some patients these inflammatory skin lesions may be an exacerbation of pre-existing psoriasis or de novo psoriasis [30].

Psoriasiform Lesions

In a systematic analysis consisting of 1294 IBD patients treated with anti-TNF therapy, 21 (1.6%) of the patients (infliximab = 14, adalimumab = 7) were noted to have drug-induced psoriasis [31]. Others have reported higher incidence of psoriasiform eruptions after initiation of anti-TNF therapy [3, 26, 27, 32]. In a case control study, George et al. found that 18/521 (3.5%) of patients with IBD developed anti-TNF-induced psoriasiform lesions [32]. In a study examining long-term safety of infliximab in patients with IBD, as many as 150/734 (20%) of patients were observed to have psoriasiform eruptions [3]. These inflammatory lesions occur approximately 12 months after anti-TNF therapy, but onset after days to years has been reported [31–34].

Psoriasiform eruptions are characterized by scaly erythematous plaques with pustulosis and possible nail involvement (see Figs. 14.1 and 14.2) [35]. These inflammatory skin lesions have similar histological features as psoriasis: parakeratosis, epidermal hyperplasia, epidermal lymphocytic infiltrates, dilated capillaries, and intraepidermal pustulosis [25, 36]. In a systematic literature review of cases of psoriasis developed during anti-TNF therapy among 41 IBD patients, Collamer et al. found that plaque psoriasis was the most common form, seen in 25/41 (61%), followed by pustular 20/41 (49%) and guttate 2/41 (5%) [36]. In 2011, Cullen et al. published a case series as well as a review of the reported cases in the literature, with a total of 142 cases of anti-TNF-related psoriasis in IBD [34]. These authors have found that the distributions of anti-TNF-related psoriasiform lesions are most common in the palmoplantar and scalp, followed by trunk, flexures, and facial regions [34].

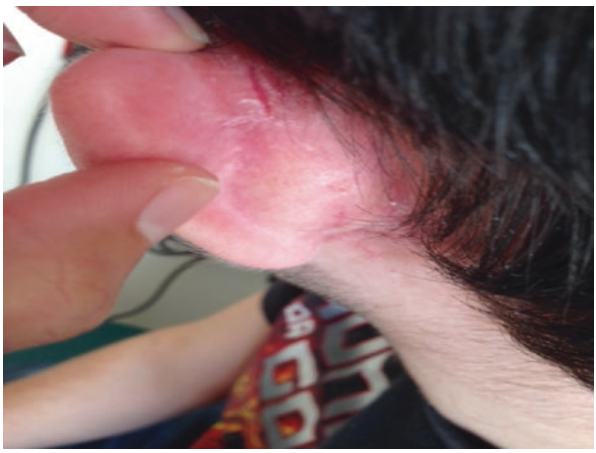

Fig. 14.1 Anti-TNF-induced psoriasiform lesion

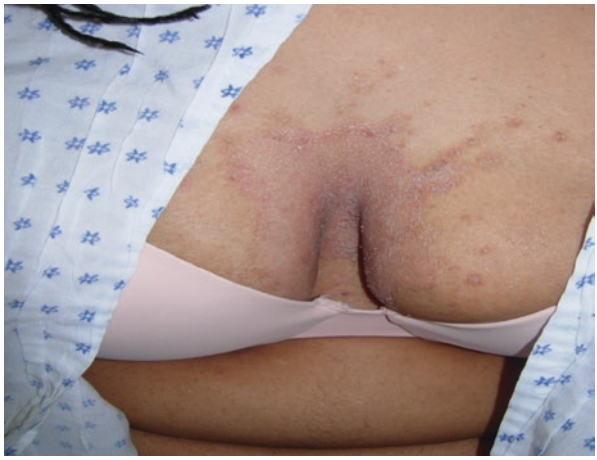

Fig. 14.2 Anti-TNF-induced psoriasiform lesion

Eczematiform Lesions

Eczema-like lesions are characterized by xerosis and pruriginous plaques with erythematous or squamous vesicles [35]. In a retrospective study by Rahier et al., 23 IBD patients were observed to have eczematiform lesions while receiving anti-TNF therapy [25]. Of these 23 patients, 10 had a personal history of atopy, 4 reported a family history of atopy, 1 had a personal history of psoriasis, and 1 had a family history of psoriasis [25]. The observed eczematiform lesions were distributed evenly on the scalp, trunk, face, and flexures [25]. Histological features of eczematiform lesions are similar to those of classic eczema, with intercellular edema within the epidermis and perivascular lymphoid infiltrate [25]. The authors did not find a difference in the development of eczematiform lesion according to the IBD type, disease activity, and the anti-TNF therapy received [25].

Risk Factors for Psoriasiform and Eczematiform Lesions

Psoriasiform lesions that occur after initiation of anti-TNF therapy are thought to be an adverse effect of therapy because the majority of patients do not have a personal or a family history of psoriasis [31]. In a systematic analysis of cases of psoriasis induced by anti-TNF therapy for IBD, only 3/21 (14%) had a first- or second-degree relative with psoriasis [31]. The age at onset of psoriasiform and eczematiform lesions during anti-TNF therapy tends to occur in young adulthood [25, 31, 36], with a median age of 32 years (IQR 24–39) in the psoriasiform group and 31 years (IQR 23–39) in the eczematiform group (see Table 14.2) [25].

The majority of patients who develop psoriasiform and eczematiform lesions are females [25, 31, 32, 34, 36]. In a retrospective study consisting of 85 patients who had new onset or exacerbation of psoriasiform or eczematiform lesions while

Table 14.2 Risk factors for anti-TNF-induced psoriasiform and eczematiform lesions

Young age
Female gender
Smoking
Crohn's disease

receiving anti-TNF therapy for IBD, Rahier et al. found that 42/60 (68%) in the psoriasiform group and 20/23 (87%) in the eczematiform group were females [25]. Guerra et al. and George et al. reported a similar female predominance in their studies, 15/21 (71%) and 14/18 (78%), respectively [31, 32]. Similarly, in a systematic literature review consisting of IBD patients who developed psoriasis during anti-TNF therapy, 21/41 (64%) of the cases were females (see Table 14.2) [36]. This finding may be confounded by the fact that autoimmune diseases are generally more common in females and these inflammatory skin lesions are thought to be immune-mediated [31].

Cigarette smoking has been linked to the development of idiopathic psoriasis [37], and a similar association is thought to exist between smoking and anti-TNF-related psoriasiform lesions (see Table 14.2) [32, 38]. In a case control study consisting of 373 cases with new onset of plaque psoriasis, Wolk et al. found that smoking was associated with 70% increased risk for onset of psoriasis [37]. The ingredients in cigarettes are thought to be pro-inflammatory which can lead to immune dysregulation and the development of idiopathic psoriasis [37]. However, Guerra et al. found that smokers and nonsmokers were equally likely to develop anti-TNF-related psoriasiform lesions in their cohort [31]. In a retrospective case control study consisting of 18 anti-TNF-treated patients with psoriasiform lesions and 70 anti-TNF-treated patients without skin lesions, smokers were numerically more likely to develop psoriasis than nonsmokers, 7/18 [38.9%] vs. 13/70 [18.6%] ($p = 0.13$) [32]. Similarly, in a large retrospective cohort study where 42 cases of psoriasis were recorded among 402 anti-TNF-treated IBD patients, smoking was found to be an independent predictor of psoriasis (HR 2.37, 95% CI, 1.36–4.48; $p = 0.08$) [38].

Psoriasiform lesions may be more common in patients with CD than ulcerative colitis (UC) (see Table 14.2). In a case series by Guerra et al., 17/21 (81%) of patients with anti-TNF-related psoriasis had CD [32]. Rahier et al. also noted that majority of patients who developed psoriasiform or eczematiform lesions during anti-TNF therapy had CD, 52/62 (84%) and 17/23 (74%), respectively [25]. A similar finding was observed in a cross-sectional study by Hellstrom et al. where nearly 80% of patients who had eczema or psoriasiform lesions (new onset = 8, exacerbation of existing lesions = 6, existing lesions not worsened = 11) had CD [26]. In a retrospective case control study comparing demographic and clinical characteristics between 18 anti-TNF-treated patients with psoriasis and 70 anti-TNF-treated patients without psoriasis, those with upper tract CD were more likely to have psoriasis during anti-TNF therapy (39% vs. 5%, $p = 0.001$) [32]. This association may be confounded by the fact that patients with CD, particularly those with upper GI tract involvement, are more likely to receive an anti-TNF than patients with UC.

Psoriasiform and eczematiform lesions appear to be reactions to the class of drugs rather than to the individual anti-TNF agent as these reactions have been reported with infliximab, adalimumab, and certolizumab pegol [25, 29, 31, 33, 39]. When analyzing more than 13 million reports from the Food and Drug Administration (FDA) Adverse Event Reporting System between 2004 and 2011, Kip and colleagues noted a total of 5432 cases of anti-TNF-related psoriasis (infliximab = 1789; adalimumab = 3475; certolizumab pegol = 168) [29]. The control drugs they selected in their analysis were propranolol and lithium, due to their recognized risk of psoriasis, and mesalamine [29]. Compared to control, the proportional reporting ratios of psoriasis for infliximab, adalimumab, and certolizumab pegol were 6.61, 12.13, and 5.43, respectively ($p < 0.0001$) [29]. As a class, the proportional reporting ratio of psoriasis for these TNF antagonists was 9.24 ($p < 0.0001$) [29].

Other reports have also demonstrated an association between various anti-TNF agents and inflammatory skin lesions [25, 39]. Of the 1004 IBD patients who were exposed to anti-TNF therapy, Afzali et al. identified 27 patients who developed psoriasiform lesions (infliximab = 8, adalimumab = 10, and certolizumab pegol = 9) [39]. In the Rahier study described previously, 62 patients had psoriasiform lesions (infliximab = 45, adalimumab = 15, certolizumab pegol = 2) and 23 patients had eczematiform lesions (infliximab = 15, adalimumab = 5, certolizumab pegol = 3) [25]. Adverse inflammatory skin lesions are likely seen more commonly with infliximab and adalimumab because of their increased market share compared to certolizumab pegol [25].

It remains unclear whether there is a dose-dependent risk between TNF antagonist and the development of dermatologic adverse events. Among 71 IBD patients who were receiving stable maintenance infliximab therapy, 9 (12.7%) were noted to have dermatologic adverse events (psoriasis = 2, non-psoriatic skin eruptions = 7) [40]. The median infliximab trough level in patients with dermatologic adverse events was higher compared to those without skin adverse events (13.3 μg/mL [IQR 8.8–17.4 μg/mL] versus 6.6 μg/mL [IQR 3.2–12.7 μg/mL]), respectively, ($p = 0.058$) [40]. However, in another retrospective cohort study where 264/917 (26%) of IBD patients on maintenance anti-TNF therapy developed dermatologic adverse reactions, trough infliximab levels were similar in patients with (4.2 μg/mL [IQR 2.6–5.8 μg/mL] and without lesions (4.0 μg/mL [IQR 1.6–5.9 μg/mL] [41].

Pathophysiology

Paradoxical de novo formation or worsening of psoriasiform lesions that occur during anti-TNF therapy is thought to be due to dysregulated interferon-α (IFN-α) production via plasmacytoid dendritic cell precursors (PDCs) [42, 43]. While there are certain genetic predispositions that are linked to classic psoriasis, including HLA-Cw6, HERV-K, as well as LCE3C and LCE3B deletions, it remains unclear which genetic pathways are responsible for anti-TNF-related psoriasiform skin lesions [44, 45]. In homeostatic conditions, TNF-α and IFN-α behave as opposite

vectors in many innate immune responses [46]. When both cytokines are in balance, the result is an equilibrium allowing protective immunity [46]. TNF-α blockade results in uninhibited PDC production of IFN-α [29, 31, 33, 36, 43, 46]. When compared to primary plaque psoriasis, patients with anti-TNF-related psoriasis have been noted to have increased PDCs and IFN-α signaling demonstrated on histologic specimens [31, 42, 43, 47–49]. Furthermore, psoriasiform lesions have been shown to develop or worsen after injection of recombinant IFN-α [42]. IFN-α also heightens the expression of chemokine T cell receptors CXCR3, which increases T cell homing to the skin [31, 36, 43, 50]. Recruitment of CXCR3 T cells to the skin results in a T cell-mediated immune response with cytotoxic skin reactions that leads to the development of psoriasiform skin lesions [31].

Diagnosis and Management of Psoriasiform and Eczematiform Lesions

Diagnosis of anti-TNF-related psoriasiform skin lesions requires a thorough history, physical exam, and possible skin biopsy. It is crucial to exclude trauma, mechanical stressors, infection, and other medications including beta-blockers, lithium, nonsteroidal anti-inflammatory drugs, tetracycline, and antimalarials as causative agents [33, 51]. Skin lesions that arise during anti-TNF therapy should be evaluated by a dermatologist. Lesions that arise in unusual locations such as on the face or at flexor surfaces may warrant skin biopsy [33]. Biopsies with immunohistochemical staining from the anti-TNF-related psoriasiform lesions show increased concentration of IFN-α in perivascular lymphocytic infiltrate and dermal vasculature [36]. Other histological findings include epithelial hyperplasia with acanthosis and hyperkeratosis with increase cell turnover, parakeratosis, lymphocytic infiltration of the epidermis, and dilated capillaries (see Fig. 14.3) [30, 31, 33].

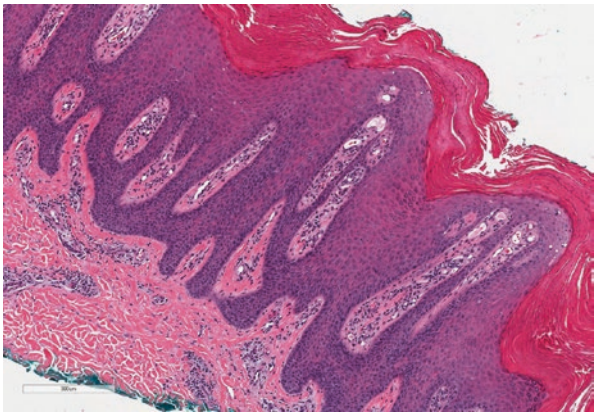

Fig. 14.3 Psoriasiform lesion on histology characterized by epithelial hyperplasia, hyperkeratosis, and lymphocytic infiltration of the epidermis. *Image was provided by Meghan Gloth, MD*

Management of anti-TNF psoriasiform lesions generally does not require cessation of anti-TNF agent [36]. For mild disease with lesions encompassing less than 5% of total body surface area, the anti-TNF agent can be continued [31, 33, 36]. Treatments of mild psoriasiform lesions include topical corticosteroid, emollients, keratolytic therapy, vitamin D analogs, and/or ultraviolet phototherapy [31, 33, 36]. In the case series of Guerra et al., 17/21 patients (81%) continued the anti-TNF agent and had resolution of psoriasiform lesions using topical corticosteroid with or without ultraviolet phototherapy [31]. Duration of therapy before response typically ranges from 1 to 3 weeks [31]. In a systematic review consisting of 222 cases of anti-TNF-related psoriatic lesions, Denadai et al. found that 64/87 (74%) had resolution of psoriatic skin lesions without having to withdraw the anti-TNF agent [33].

In refractory disease or in cases of severe disease with greater than 5% of total body surface area involved, discontinuation of anti-TNF agent may be necessary [31, 33, 36]. In a retrospective study consisting of 85 patients (69 with CD, 15 with UC, and 1 with indeterminate colitis), 29 (34%) patients discontinued anti-TNF therapy due to uncontrolled skin lesions [25]. In a review published by Denadai et al., 86 patients had their anti-TNF agent discontinued, and a large number of these patients, 71/86 (83%), subsequently had resolution of their skin lesions [33]. In addition to topical therapies and phototherapy as described above, systemic treatments such as retinoids, methotrexate, or cyclosporine may also be necessary in these complicated cases [31, 33, 36].

Recurrence of psoriasiform lesions can occur after reinitiating or switching anti-TNF therapy [27, 31, 33]. In the case series by Guerra, 4/21 (19%) patients had their anti-TNF therapy discontinued: One patient had complete response after discontinuation and no recurrence of psoriasis after reintroduction of the same anti-TNF therapy. The other three patients had partial response after discontinuation of the drug (two patients had discontinued anti-TNF therapy permanently; the third patient who had palmoplantar psoriasis was managed with topical corticosteroid and then had mild recurrence after anti-TNF therapy was reintroduced, and the psoriasiform lesions were successfully controlled with topical corticosteroid) [31]. In a single-center observational retrospective study, 59/583 (10.1%) IBD patients had psoriasiform lesions emerge on anti-TNF therapy [27]. Twenty-one of 59 patients (35.6%) switched to another anti-TNF therapy and over half of these patients (12/21, 57%) had recurrence of psoriasiform lesions [27]. Similarly, in the review published by Denadai et al., of the 29 patients who switched anti-TNF agents, 21 (72%) had recurrence or aggravation of their psoriasiform lesions [33].

Early recognition and prompt initiation of therapy is essential in management of anti-TNF-associated psoriasiform lesions. Except in cases where the psoriasiform lesion is severe or extensive, topical treatment is the therapy of choice, and discontinuation of the biologic agent may not be necessary. Patients who are rechallenged with the same or a different anti-TNF agent need to be monitored closely as recurrence of psoriasiform lesions frequently occur (see Table 14.3) [33].

Table 14.3 Management of anti-TNF-induced psoriasiform lesions

Mild	Severe
Topical corticosteroid	Discontinuation of anti-TNF therapy
Emollients	Topical therapy (as for mild disease)
Keratolytic therapy	Phototherapy (as for mild disease)
Vitamin D analogs	Retinoids
Ultraviolet phototherapy	Methotrexate
	Cyclosporine

Lupus-Like Syndrome

Clinical Presentation

Lupus-like syndrome (LLS), a rare autoimmune disorder, is a recognized adverse reaction to anti-TNF therapy in IBD patients [52]. Compared to systemic lupus erythematosus (SLE), patients with LLS tend to be older with mean age of 46–51 years, and with slight female predominance [53–55]. LLS is generally characterized by arthralgia, myalgia, fever, arthritis, and serositis [52, 55]. While malar rash, photosensitivity, and oral ulcers are less common in LLS [55], skin involvement and photosensitivity are common in patients who develop LLS after anti-TNF therapy [54, 56, 57]. However, central nervous system and renal involvement are rarely seen in LLS [55, 56].

Patients who have received anti-TNF therapy are at high risk of developing autoantibodies [57, 58], but the rate of LLS is generally low at 0.5–1% [59, 60]. In the ACCENT I trial consisting of 573 patients randomized to placebo or infliximab, positive antinuclear antibodies (ANA) and double-stranded (ds) DNA were more common in patients on infliximab than those on placebo, 56% and 34% vs. 35% and 11%, respectively [12]. However, only two patients in the infliximab groups with positive autoantibodies developed LLS [12]. Similarly, in a multicenter, longitudinal, observational study where 286 patients had autoantibodies assessed both before and after at least 6 months of infliximab treatment, only one patient (0.35%) in this cohort was diagnosed with LLS [57].

Autoantibodies are also common after treatment with adalimumab. In a case series consisting of 180 IBD patients treated with an anti-TNF therapy (infliximab or adalimumab, or infliximab and adalimumab consecutively), 44.4% were found to have antinuclear antibody (ANA) titers ≥1:240, and 15.6% had dsDNA serum levels ≥9 U/mL [52]. Only 1.1% of these patients, however, had severe LLS requiring immediate discontinuation of anti-TNF therapy. Severe LLS was defined as severe arthralgia including joint swelling and/or additional LLS-related symptoms requiring immediate discontinuation of anti-TNF therapy and initiation of corticosteroids and/or immunosuppressive therapy [52]. Biegel et al. observed that the ANA and dsDNA titers positively correlate with clinical severity of LLS [52].

Onset of LLS has been reported to range from 10 days to 54 months after initiation of anti-TNF [60]. In a case series of 92 patients who developed SLE or LLS after anti-TNF therapy (infliximab = 40, etanercept = 37, and adalimumab = 15), the mean latency of onset was 41 weeks after anti-TNF therapy [54]. Clinical and immunologic data were available in 72 of these patients: 68 (94%) had positive autoantibodies, 57 (79%) with positive ANA, 52 (72%) with dsDNA antibodies, 8 (11%) with antiphospholipid antibodies, and 7 (10%) with anti-Smith antibodies [54]. Sixty-four (89%) patients had cutaneous features, 28 (39%) had musculoskeletal manifestations, and 21 (29%) had systemic symptoms including fever, malaise, and asthenia [54]. SLE cutaneous features including malar rash, photosensitivity, and/or discoid lupus were seen in 48 (67%), arthritis in 22 (31%), cytopenia in 16 (22%), serositis in 9 (12%), and nephropathy in 5 (7%).

Risk Factors

Patients who develop autoantibodies and LLS tend to be older and of female gender [53–55, 61, 62]. When Beigel et al. examined factors associated with the development of LLS in IBD patients treated with an anti-TNF therapy, they found that increased age is a risk factor for developing ANA titers ≥ 1:240 (odds ratio 1.06, 95% CI 1.03–1.09, $P < 0.001$) and for developing LLS (odds ratio 1.08, 95% CI 1.03–1.13, $P = 0.002$) [52]. Moulis et al. analyzed 39 LLS cases associated with anti-TNF therapy, the majority of patients who were affected were females with a female to male ratio 10:1 [62]. Similarly, in the case series by Ramos-Casals et al. where epidemiologic data was available for 62 patients who developed LLS after anti-TNF therapy, there was a female to male ratio of 5:1 [54]. These findings are similar to the female to male ratio in patients with SLE. A meta-analysis consisting of 16 studies with a total of 11,934 SLE patients demonstrated an average female to male ratio of 9:1 [63]. SLE is more prevalent in women because of differences in the metabolism of sex hormones [64].

The two antibodies ANA and dsDNA, part of the immunologic criteria for SLE, have been examined as potential predisposing factors for the development of LLS [52, 54]. In the case series by Ramos-Casals et al., 72 patients with anti-TNF therapy-related lupus met SLE criteria; 57 (79%) and 52 (72%) of these patients were found to have positive ANA and dsDNA, respectively [54]. However, the threshold titers used for positivity of these two antibodies were not reported [54]. In another case series published by Biegel et al. consisting of 180 IBD patients treated with an anti-TNF therapy, dsDNA antibody values ≥9 U/mL were shown to be associated with the development of LLS ($P = 0.02$) [52]. In this cohort, no association was found between ANA titer ≥ 1:240 and development of LLS [52].

Given the low incidence of LLS and limited data, it remains unclear whether concomitant immunomodulator is protective against autoantibody formation and development of LLS. In the case series published by Biegel et al. described previously, concomitant immunomodulator was shown to be protective against ANA

formation ($p = 0.05$) and LLS development ($p = 0.04$) [52]. Others have found that ANA and dsDNA can be detected in CD patients despite being on concurrent immunomodulator while receiving infliximab, but how this rate compares to those who are not on concurrent immunomodulator is unclear [12, 58].

Pathophysiology

The pathophysiology of anti-TNF therapy-induced LLS is not clearly defined, but several hypotheses have been proposed on the development of autoantibodies. Anti-TNF therapy induces apoptosis in inflammatory cells; the release of antigenic particles during this process may stimulate autoantibody formation in susceptible individuals and may lead to the development of LLS [60, 65]. This hypothesis is supported by the finding of increased plasma nucleosome levels after infliximab treatment [66]. Another hypothesis is that patients on anti-TNF therapy are prone to infection which would activate polyclonal B lymphocytes to stimulate autoantibody production [60]. A third potential mechanism by which TNF antagonists could induce autoantibody formation is by humoral autoimmunity activation via inhibition of cytotoxic T-lymphocyte response [60].

Diagnosis and Management

Diagnosis of LLS requires early recognition of a constellation of symptoms including arthralgia, joint swelling, myalgia, rash, erythema, fever, and/or serositis in patients treated with anti-TNF therapy [52, 55]. In patients with only joint manifestations, the differential diagnosis includes delayed hypersensitivity reaction to infliximab, type 1 or 2 arthritis related to underlying IBD, and other causes. Oral ulcers and classic malar rash associated with SLE are less common in LLS, but patients with LLS can present with an erythematous purpuric rash and photosensitivity [54, 56]. LLS rarely involves the central nervous or the renal systems [55, 56]. Although there are no diagnostic criteria for LLS, the diagnosis of LLS is generally made based on clinical features as described previously, the presence of ANA and anti-dsDNA autoantibodies, and notable improvement of symptoms within days or weeks after the offending drug is discontinued. The ANA and anti-dsDNA titers used in the report by Biegel et al. for the diagnosis of LLS were ≥1:240 and ≥9 U/mL though different thresholds for autoantibody positivity have been used in other studies [52, 58].

Autoantibody formation is common after treatment with anti-TNF therapy. As such, there is a subgroup of patients who develop drug-induced autoimmunity in the form of elevated autoantibody titers without clinical symptoms [53]. It is not recommended for these patients to have their anti-TNF withdrawn, because few actually progress to develop LLS [53]. As such, we do not recommend that providers serially monitor ANA and dsDNA levels in patients being treated with anti-TNF agents.

Management of anti-TNF therapy-associated LLS involves withdrawal of anti-TNF therapy with or without the addition of steroids or an immunosuppressive agent. In the report by Ramos-Casals et al., 72/77 (94%) cases had withdrawal of anti-TNF therapy, 31/77 (40%) of patients were treated with corticosteroids, and 7/77 (12%) received immunosuppressive agents (3 methotrexate, 1 cyclophosphamide, 1 leflunomide, 1 mycophenolate, and 1 azathioprine). All but one patient was noted to have improvement [54]. It is important to keep in mind that despite improvement in clinical symptoms after drug discontinuation, the elevated serological markers may persist [53].

With resolution of symptoms after anti-TNF therapy is withdrawn, it is unclear whether it would be safe to continue treatment with a different anti-TNF therapy [60]. Our current knowledge on patient's tolerance of alternative anti-TNF therapy is limited to case reports [59, 60, 67]. Kocharla and Mongey reported a case where a patient with CD developed infliximab-related LLS and was rechallenged with adalimumab with no recurrence of LLS after 9 months of follow-up [67]. In a retrospective review by Wetter et al., 4 (80%) of 5 patients demonstrated no adverse effects after treatment with a different anti-TNF therapy after developing LLS while being treated with infliximab [59]. Three of these patients tolerated adalimumab as an alternative treatment for 6 months, 8 months, and 42 months, respectively [59]. The other patient tolerated etanercept for 41 months [59]. The fifth patient in this cohort tolerated etanercept for 2 months following discontinuation of infliximab. However, the LLS reemerged 9 months after infliximab was reintroduced despite the use of corticosteroid premedication before each infusion; there was also recurrence of LLS after switch from infliximab to adalimumab [59].

As the use of anti-TNF therapy becomes more common, it is essential for clinicians to promptly recognize symptoms and serological markers associated with LLS. In most cases, withdrawal of drug results in resolution of LLS; however 40% of patients will need a course of prednisone, and 12% will need an immune suppressant to resolve the symptoms [54]. Given limited data on clinical outcomes after patients with LLS are rechallenged with an alternative anti-TNF agent, clinicians should use caution with introduction of an alternative anti-TNF, especially as more therapies become available for the treatment of IBD.

Hepatotoxicity

Clinical Presentation

Hepatotoxicity is a rare complication of anti-TNF therapy [68–71]. With lack of population-based studies, the majority of our knowledge comes from case reports and case series [68–71]. The true incidence of anti-TNF-related hepatotoxicity is unknown but is estimated to be less than 1% [68, 69, 71]. Rodrigues et al. reviewed medical records of over 600 patients undergoing anti-TNF therapy; they found only seven patients who developed hepatitis with autoimmune features during anti-TNF

therapy [69]. When identifying cases of drug-induced liver injury (DILI) caused by anti-TNF agents in Iceland from 2009 to 2013, Bjornsson et al. noted that DILI developed in 1 of 120 patients who received infliximab, 1 in 270 who received adalimumab, and 1 in 430 patients who received etanercept [71].

Clinical symptoms of anti-TNF-associated hepatotoxicity can vary. Some patients can be asymptomatic with abnormal liver enzymes discovered on routine laboratory monitoring [69, 72]. Others may present with jaundice, nausea, and/or fever [70, 71]. In examining six cases of hepatotoxicity associated with anti-TNF therapy, Ghabril et al. found that the median latency of onset from initiation of infliximab to hepatotoxicity was 16 weeks (range, 2–52 weeks) [70]. The pattern of hepatic injury was mainly hepatocellular; one patient had significantly impaired coagulation (international normalized ratio [INR], 3.5). None of these patients had ascites or signs of hepatic failure [70].

Combining the six cases above with the 28 cases from the DILI network, Ghabril et al. noted that the peak alanine aminotransferase (ALT) ranged from 140 U/L to 2250 U/L and the bilirubin level ranged from normal to 27.7 mg/dL [70]. Similarly, Bjornsson et al. found that majority of patients (8 out of 11) with DILI from anti-TNF therapy had a pattern of hepatocellular injury, though a cholestatic pattern was also seen [71]. The mean peak ALT, aspartate aminotransferase (AST), alkaline phosphatase, and bilirubin were 704 U/L, 503 U/L, 261 U/L, and 47 μmol/L, respectively [71].

Risk Factors for Anti-TNF-Induced Hepatotoxicity

A number of anti-TNF agents have been associated with drug-induced hepatotoxicity. Among the 34 cases described by Ghabril et al., 26 were due to infliximab, 4 from etanercept, and 4 from adalimumab; there were no reported cases from golimumab or certolizumab pegol [70]. Infliximab-associated hepatotoxicity is most frequently documented, likely because of its earlier approval and widespread use [70, 71]. Due to limited data, it remains unclear whether there is cross-reactivity between different anti-TNF agents in regard to hepatotoxicity. However, in the rheumatology literature, there have been case reports of patients with infliximab, etanercept, or adalimumab-associated hepatotoxicity who subsequently tolerated a different anti-TNF therapy without recurrence of hepatotoxicity [71, 73–75].

Duration and dosing of anti-TNF therapy do not appear to affect the likelihood of its associated hepatotoxicity. Hepatotoxicity has been noted to occur, on average, 14–18 weeks after initiation of therapy [68, 70, 71]. However, drug-induced liver injury associated with infliximab has been reported after just one infusion [76]. Based on the available data, there does not appear to be a dose-dependent hepatotoxicity with anti-TNF therapy. In a case control study, patients who developed ALT elevation were noted to be on a lower dose of infliximab than the controls (5.7 vs. 6.7 mg/kg, $p = 0.02$). Similarly, in a case series consisting of eight IBD patients with anti-TNF-associated hepatotoxicity, Rodrigues et al. noted that all patients were on a standard dose of infliximab (5 mg/kg) and adalimumab (40 mg every other week) [69].

The majority of reported cases of hepatotoxicity associated with anti-TNF agents have been in women [69–71]. The mean age of patients with anti-TNF-associated hepatotoxicity ranges from 32 to 46 years [68, 70, 71].

Pathophysiology

The pathophysiology of anti-TNF agent-induced liver injury has not been clearly defined [71]. Liver biopsies in these cases often reveal hepatocellular injury with features of autoimmunity [70, 71]. Proposed mechanisms include increase in the number of autoreactive immune cells leading to autoimmune hepatitis; induction of an immune system imbalance due to cytokine blockade; a selective effect on T helper cell subsets and immune complex formation, exposing an underlying disease in a patient with genetic susceptibility; or a break in self-tolerance following the exposure of hidden antigens [69].

Diagnosis and Management

Diagnosis of hepatotoxicity associated with anti-TNF therapy requires exclusion of other underlying causes of liver disease. As discussed previously, hepatotoxicity associated with anti-TNF therapy can occur after just one dose of the anti-TNF agent [76], though the average latency described in the literature is 14–18 weeks [68, 70, 71]. The majority of affected patients presents with progressive elevation in transaminases (ALT or AST > 3x upper limit of normal), although a minority presents with bland cholestasis [70, 71].

When hepatotoxicity is suspected after initiation of an anti-TNF therapy, a thorough history including the use of alcohol and both prescription and over-the-counter medications and supplements should be included in the evaluation. It is crucial to exclude viral infections including acute hepatitis A, acute or reactivation of chronic hepatitis B, hepatitis C, hepatitis E, cytomegalovirus, and Epstein-Barr infections [70, 71]. In addition, autoimmune serology including antinuclear antibody, anti-dsDNA, anti-mitochondrial antibody, and anti-liver/kidney microsomal antibodies should be obtained. Right upper quadrant ultrasound or cross-sectional imaging is recommended to exclude biliary obstruction or structural abnormalities. A liver biopsy should be considered if serology and imaging are unrevealing for other causes of liver injury. Among the 34 patients with hepatotoxicity attributed to anti-TNF therapy, Ghabril et al. noted that 22 had positive responses to ANA and/or anti-smooth muscle antibody or had histological features of autoimmunity on liver biopsy (see Fig. 14.4) [70].

The prognosis of anti-TNF therapy-associated hepatotoxicity is generally good [70, 71]. The majority of patients recover from hepatotoxicity after discontinuation of the implicated anti-TNF therapy, with or without the addition of corticosteroid [70–72]. Among the six subjects from the DILI network who had hepatotoxicity attributed to anti-TNF therapy, all patients recovered and were able to be withdrawn

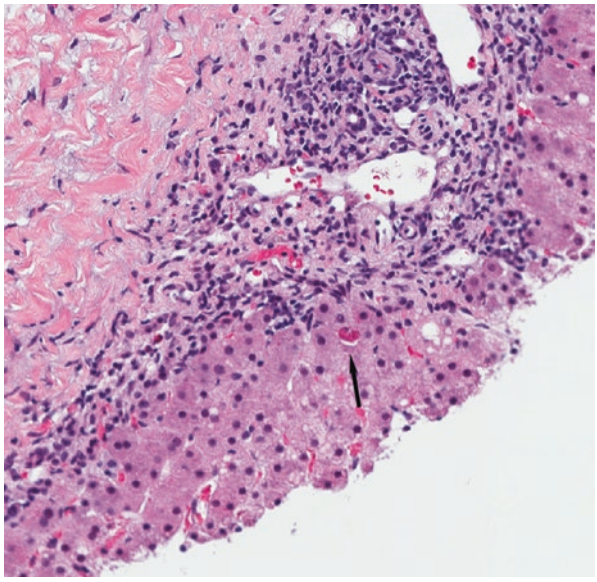

Fig. 14.4 Liver biopsy showing mild mixed inflammation with scattered plasma cells. There is mild interface hepatitis and focal hepatocellular loss (arrow). *Image was provided by William Twaddell, MD*

from corticosteroid therapy [70]. Autoantibodies, particularly ANA, tend to decrease or disappear after corticosteroid therapy [70, 71].

Although there is limited data to guide management, corticosteroid therapy is generally indicated if there is no improvement in liver enzymes within 2 months after withdrawal from the offending agent [71]. There is currently no standard dosing or duration of corticosteroid therapy for treatment of anti-TNF-associated hepatotoxicity. However, an attempt to withdraw corticosteroid should be considered once liver enzymes normalize.

Rechallenging with another anti-TNF therapy may be considered, particularly in case where alternate therapy is not available. In the rheumatology literature, patients who had hepatotoxicity attributed to infliximab or adalimumab subsequently tolerated etanercept [72–75, 77]. In the study by Bjornsson et al., one patient previously treated with infliximab for treatment of CD developed adalimumab-associated hepatotoxicity; the patient was later able to tolerate restarting infliximab without recurrence of hepatotoxicity [71]. More data is needed in guidance on management of anti-TNF-associated hepatotoxicity, particularly in the IBD population.

Demyelinating Diseases

Clinical Manifestation

Demyelinating disease associated with anti-TNF therapy is rare, with prevalence ranging between 0.05 and 0.2% for infliximab, etanercept, and adalimumab [78]. In comparison, the incidence of multiple sclerosis (MS) in the general population is

reported as 3.2 per 100,000 persons per year [79]. Given its high efficacy in treatment of rheumatoid arthritis (RA) and the similarities in pathophysiology between RA and MS, anti-TNF therapy was once studied for use in the treatment of MS. In the first open-label phase I trial, infliximab was used to treat two patients with rapidly progressive MS [80]. Both of these patients had an increase in the number of lesions on brain magnetic resonance imaging (MRI), as well as a rise in leukocytes in CSF and IgG titers [80].

There have been a number of reported cases of brain lesions detected on MRI in patients treated with an anti-TNF therapy [81–84]. The anti-TNF therapies associated with these reported cases include etanercept, infliximab, and adalimumab [81–84]. Among the 19 patients with RA registered in the FDA Adverse Reporting System who developed neurological problems associated with demyelinating lesions of the CNS, 17 of these patients were treated with etanercept and 2 with infliximab [82]. The patients' age ranged from 21 to 56 years, and the average time of onset of neurological symptoms was 5 months after initiating anti-TNF therapy [82].

Patients who develop neurological symptoms after anti-TNF therapy can have a wide range of symptoms. There have been reports of new-onset MS, worsening of baseline demyelinating disease, encephalopathy with residual deficit and/or evidence of demyelination on biopsy, optic neuritis, peripheral neuropathies, and Lhermitte's sign, which is characterized by an electrical sensation that runs down the back into the limbs [85]. In addition, headache, tinnitus, dysarthria, and dysphagia have been reported [86]. The majority of reported cases have partial or complete resolution of symptoms after discontinuation of anti-TNF therapy [81–84].

Risk Factors

Although anti-TNF therapy has been associated with demyelinating disease, patients with one autoimmune disease are thought to be more susceptible to developing another autoimmune condition including demyelinating diseases [87]. In a retrospective cohort and cross-sectional study consisting of 7988 CD and 12,185 UC patients matched with 80,666 controls in the era before anti-TNF therapies, demyelinating diseases were observed more commonly among patients with IBD than those without [87]. Compared to controls, patients with UC had an incidence rate ratio (IRR) of 2.63 (95% CI 1.29–5.15), and patients with CD had an IRR of 2.12 (95% CI 0.94–4.5) [87].

While a number of cases of demyelinating diseases have been reported after anti-TNF therapy [78, 81–84], it remains unclear whether the relationship between anti-TNF therapy and demyelinating disease is coincidental or causal. Patients with demyelinating neurological diseases at baseline are discouraged from using anti-TNF therapy due to concern for exacerbation of existing disease. However, it is not

well understood what other baseline characteristics predispose patients to develop demyelinating disease after anti-TNF therapy.

In a prospective study of 77 patients who were eligible to receive anti-TNF therapy for either RA or spondylarthropathies, all patients underwent a baseline neurological exam and both brain and cervical spine MRI. Two of these patients did not receive anti-TNF therapy due to lesions detected on brain MRI compatible with demyelinating diseases [88]. Neither of these two patients had neurological symptoms after 2 years of follow-up. Among the other 75 patients who received anti-TNF therapy, three patients developed demyelinating diseases with peripheral neuropathy in two and optic neuritis in one [88]. The onset of neurological symptoms occurred between 6 and 25 months after starting anti-TNF in the cohort examined by Kaltsonoudis et al. [88]. It is unclear whether there is an anti-TNF therapy dose-dependent effect on the development of demyelinating diseases. More data is needed to determine whether there is a gender predisposition for this neurologic complication.

Pathophysiology

The pathophysiology of anti-TNF-associated demyelinating disease has not been clearly delineated, but several hypotheses have been proposed. MS is an autoimmune inflammatory condition where T cells react against self-myelin antigens [88]. Experimental autoimmune encephalomyelitis (EAE) is an animal model for MS where animals are injected with an encephalogenic myelin protein and subsequently develop a demyelinating, relapsing illness akin to MS. EAE is mediated by autoreactive myelin-specific T cells [89]. Anti-TNF agents were previously shown to have beneficial effect on animal model of MS [88]. Administration of anti-TNF agents may have local anti-inflammatory effects in tissues such as the joints and intestine. These agents can also upregulate the autoimmune response by activation and survival of peripheral autoreactive myelin-specific T cells which then enter the CNS causing demyelination [85, 88].

Another proposed pathogenic mechanism by which anti-TNF agents cause demyelinating disease is through activation of a latent infection [88]. In the presence of anti-TNF therapy, an unmasked latent viral infection can activate myelin-reactive T cells via molecular mimicry [88]. These activated myelin-specific T cells then migrate into the central nervous system and release cytokines that recruit and activate macrophages as well as more T cells which lead to myelin destruction [88, 90, 91].

While TNF-α could have a detrimental effect on RA and IBD, its exact role in the CNS is unclear. Anti-TNF therapy could inhibit TNF-α-induced interleukin-10 (IL-10) and prostaglandin E2 production resulting in increased IL-12 production. IL-12 subsequently induces IFN-gamma expression which exacerbates MS [85, 90].

Diagnosis and Management

Although the pathogenic mechanism of anti-TNF-induced demyelinating diseases is not yet clearly delineated, all patients should be counseled on this rare potential complication of anti-TNF agents prior to initiation of therapy. Given the variability of onset of these symptoms, patients who are on anti-TNF therapy should be monitored regularly. If demyelinating disease is suspected during treatment with an anti-TNF, the offending agent should be discontinued immediately [82].

A thorough history, physical exam, and neurological exam including a fundus examination for papilledema and optic neuritis, together with a neurology consultation, are warranted for evaluation of patients with suspected demyelinating disease [82]. These patients should also get an MRI of the brain with and without gadolinium; a lumbar puncture to assess for oligoclonal bands and IgG level should be considered in patients with equivocal MRI findings [82]. Multiple periventricular white matter lesions on brain MRI (see Fig. 14.5), elevated IgG level, and positive oligoclonal bands in CSF are characteristics of MS [86]. Nevertheless, other causes of neurological symptoms including Lyme disease, HIV, syphilis, and West Nile virus should be ruled out [83]. As demonstrated in the prospective study by Kaltsonoudis et al., prescreening with brain MRI does not prevent onset of demyelinating disease during anti-TNF therapy [88].

Therapies used in MS including glucocorticoids, IFN-beta, or intravenous immunoglobulin should be considered in anti-TNF therapy-associated demyelinating dis-

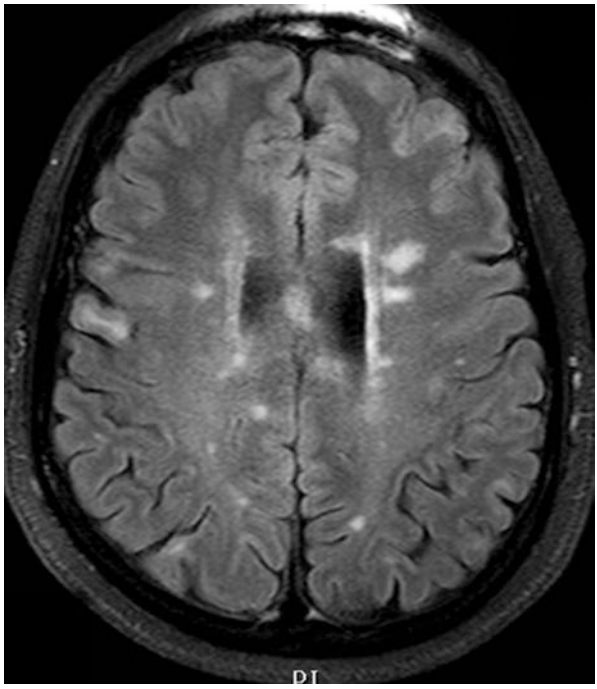

Fig. 14.5 Multifocal T2 hyperintensity in periventricular and deep white matter of both cerebral hemispheres seen on MRI consistent with multiple sclerosis. *Photo courtesy of Fauzia Vandermeer*, MD

eases [82]. The majority of reported cases have complete or near-complete resolution of neurological symptoms after discontinuation of anti-TNF therapy and the addition of glucocorticoid [81, 82, 84, 86]. In the case series by Andreadou et al., all four patients were asymptomatic at 3-month follow-up after discontinuation of the offending drug, treatment with intravenous corticosteroid, and a prednisone taper [86]. Mohan et al. noted that one patient had a positive rechallenge with etanercept [82]. Patients who develop demyelinating diseases while on anti-TNF therapy are not recommended to be rechallenged with the same or a different anti-TNF agent [82, 84].

Heart Failure

Clinical Presentation

Anti-TNF therapy, previously thought to be a potential treatment option for heart failure, has been shown to be associated with new onset or progression of heart failure [92]. More than two decades ago, Levine et al. demonstrated that patients with advanced heart failure, on average, had a higher serum level of TNF-α when compared with age-matched healthy controls [93]. Despite initial data demonstrating short-term safety and clinical improvement in patients with New York Heart Association (NYHA) Class III or greater heart failure [94, 95], large randomized placebo-controlled trials with etanercept were terminated early due to poor clinical outcome and a trend toward increased mortality [96, 97]. Another prospective randomized placebo-controlled trial demonstrated that high-dose infliximab (10 mg/kg) was associated with increased hospitalization and increased risk of death (hazard ratio 2.84, 95% CI 1.01–7.97, $p = 0.04$) [98].

The true incidence of anti-TNF therapy-related heart failure is unknown. The majority of knowledge is based on information obtained from drug monitoring databases and adverse event reporting systems where overreporting, underreporting, or misclassification of diagnosis may occur. Furthermore, the lack of denominators makes it impossible to calculate event rates. In safety analyses of 10,050 RA patients treated with adalimumab, new-onset heart failure was reported in 0.3% and progression of heart failure was reported in 7% of patients [99]. The overall rate of heart failure associated with adalimumab based on these analyses was 0.06 events per 100 patient-years in the post-marketing surveillance [99]. Similarly, in a nationwide comprehensive monitoring system for RA patients treated with etanercept in Sweden, there was a reported heart failure rate of 0.04 events per 100 patient-years [100].

In 2003, Kwon et al. published a case series describing reports of heart failure after anti-TNF therapy, using the FDA's MedWatch program [92]. A total of 38 patients had new onset and nine patients had worsening heart failure after receiving either etanercept or infliximab [92]. The median age among the 38 patients with new-onset heart failure was 62 years (range 17–87 years) and the median age among the nine patients with heart failure exacerbation was 70 years (range 57–74 years)

[92]. Nineteen out of 38 patients (50%) who developed new-onset heart failure had no identifiable risk factor for heart failure [92]. One patient died [92].

The clinical symptoms reported in patients with anti-TNF associated heart failure are similar to those seen in classic heart failure. Patients may present with fatigue, dyspnea, paroxysmal nocturnal dyspnea, lower extremity edema, and/or chest pain [92]. On diagnostic evaluation, decreased left ventricular function on echocardiogram, increased pulmonary pressure on cardiac catheterization, and/or pulmonary congestion on chest radiography are hallmark findings [92].

Risk Factors

The anti-TNF agents most documented to be associated with new onset or exacerbation of heart failure are etanercept and infliximab [92]. However, in 2013, Adamson et al. reported a case of fulminant heart failure in a 51-year-old woman after receipt of the second dose of adalimumab for treatment of polychondritis [101]. The duration of treatment does not appear to be a predisposing risk factor for new onset or exacerbation of heart failure. In the case series described by Kwon et al., new-onset heart failure and exacerbation of heart failure can occur as early as 24 h after administration of anti-TNF therapy or as late as 2 years after initiating treatment [92].

The effect that anti-TNF therapy has on exacerbation of heart failure may be dose-dependent. In a prospective trial, 150 patients with NYHA class III and IV heart failure were randomized to receive placebo, infliximab 5 mg/kg or infliximab 10 mg/kg. Patients randomized to 10 mg/kg infliximab had an increased risk of hospitalization for heart failure and increased risk of death through 28 weeks follow-up [98]. A correlation between heart failure and dose of anti-TNF therapy has not been confirmed in other reports.

Lastly, it appears that the traditional risk factors of heart failure may not be present in patients with anti-TNF therapy-associated heart failure. In the case series published by Kwon et al., new-onset heart failure after anti-TNF therapy was reported in the same number of patients with documented risk factors including cardiovascular disease and diabetes as those without traditional risk factors (19) [92].

Pathophysiology

The pathophysiology of anti-TNF therapy-associated heart failure has not been well delineated. Chronic heart failure is believed to be influenced by over-activation of the sympathetic nervous and neurohormonal systems [92]. A deteriorating heart with hemodynamic overload or myocardial stretch stimulates the immune system and TNF-α production [102]. Unlike in RA and IBD, heart failure is not purely an inflammatory condition. Low TNF-α level confers a cytoprotective effect in the

heart during ischemic injury [103]. Furthermore, TNF-α induces production of nitric oxide which maintains peripheral blood flow in patients with heart failure [104]. A certain physiologic level of TNF-α is likely necessary for tissue remodeling and repair in patients with cardiac injury, including heart failure [105]. Therefore, anti-TNF therapy, with a resultant decrease in TNF-α, may interfere with myocardium repair and remodeling [102], consequently leading to the development of heart failure.

Diagnosis and Management

Anti-TNF therapy should be discontinued when symptoms of heart failure develop [92]. Classic findings on diagnostic evaluation include decreased left ventricular function on echocardiogram, increased pulmonary pressure on cardiac catheterization, and/or pulmonary congestion on chest radiography [92].

Among the 10 patients younger than 50 years of age with new-onset heart failure, 9 of these 10 patients reported discontinuation of anti-TNF therapy [92]. With heart failure treatment, 3 patients reported complete resolution of heart failure, 6 patients had improvement, and 1 patient died [92]. In patients who develop heart failure after receiving anti-TNF therapy, rechallenging with another anti-TNF therapy is not recommended. Anti-TNF therapy should be avoided in patients with NYHA class III or IV [97, 98]. In patients with NYHA class I or II heart failure, providers should consider using an alternative therapy for IBD if possible [106]. If anti-TNF therapy use is considered in these patients, a cardiology consultation and a baseline echocardiography with close monitoring are advised.

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Chapter 15
Biosimilars in Inflammatory Bowel Disease 2017: State of the Science, State of the Art, and State of the Finances

Christina Y. Ha and Asher Kornbluth

Abbreviations

ADA	Anti-drug antibodies
aNDA	Abbreviated new drug applications
AS	Ankylosing spondylitis
AUC	Area under serum concentration
BPCI	Biologics Price and Control Act
CAG	Canadian Association of Gastroenterology
CCFA	Crohn's and Colitis Foundation of America
CD	Crohn's disease
CI	Confidence interval
ECCO	European Crohn's and Colitis Organization
ECL	Electrochemiluminescent immunoassay
EMA	European Medicines Agency
FDA	Food and Drug Administration
IBD	Inflammatory bowel disease
PD	Pharmacodynamic
PK	Pharmacokinetic
RA	Rheumatoid arthritis

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RCT Randomized controlled trial
TNF Tumor necrosis factor
UC Ulcerative colitis
WHO World Health Organization

Introduction

The year 2016 witnessed the FDA approval of the first biosimilar agents for the antitumor necrosis factors (anti-TNF): infliximab (IFX, Janssen) and adalimumab (ADA, Abbvie). Based on a single trial in rheumatoid arthritis (RA) and ankylosing spondylitis, respectively, the biosimilar for IFX, CT-P13 (Celltrion Inc.) was approved, andABP 501 was approved as the first biosimilar for ADA based on a single trial in RA and psoriasis, respectively. Despite patent challenges,Pfizer began sales ofInflectra in December 2016, and despite patent challenges, sales ofABP-501 will soon follow [1]. Considering that the cost of anti-TNF agents has become the largest expenditure in the care of IBD patients, the savings in drug costs will be a major driver in the adoption of anti-TNF biosimilars.

An abbreviated pathway for biosimilar drug developmentwas established as part of the Patient Protection and Affordable Care Act (ACA, also referred to Obamacare), which was signed into law in March 2010. Within the ACA, the Biologic Price and Competition Act (BPCI) was created to facilitate development of biosimilar drugs, aiming forthe introduction ofless expensive drugs with the goal of enhancing greater patient access to costly biologic agents [2]. While the election of Donald Trump has led to efforts to repeal segments of the ACA, there has, to date, not been a public discussion of plans to address the BPCI. The BPCI created an abbreviated new drug application (aNDA), known as the 351(k) pathway for a proposed biosimilar drug. This newly established pathway allows for anew drug application based on a lesser amount of clinical data and instead requires a greater analysis to establish physiochemical, pharmacokinetic, and pharmacodynamic similarity to the originator compound [3].

The FDA definition ofa biosimilar drug is a “biological product that is highly similar to the reference product not withstanding minor differences in clinically inactive components… [with] no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product” [2]. It is important to recognize that the chemical structure of a biosimilar drug, in contrast to generic drugs, is not an identical copy with the same chemical form of the original reference drug. Biosimilars are larger and more complex biological compounds with the potential for immunogenicity similar to originator biologic agents, and may be prone to posttranslational modification, which may potentially influence clinical outcomes and immunogenicity.

The focus of this chapter will be primarily on the biosimilar CT-P13 for infliximab since the randomized controlled trials for this compound have already been

published in full manuscript form [4, 5]. CT-P13 has been marketed as Remsima by Celltrion, Inc., in Europe and other countries around the world, and as Inflectra by Pfizer Inc. in the USA. This chapter will review the complex processes involved in the developmentand manufacturing of these drugs including the physiochemical, pharmacodynamic (PD), and pharmacokinetic (PK) steps and review the evidence presently available on CT-P13 that demonstrated efficacy, immunogenicity, and safety. Included in the discussion will be (1) the stepwise fashion used to demonstrate the "totality of evidence" required by the FDA for the approval of a biosimilar drug; (2) the controversial issue of data extrapolation of the results from the RA and AS trials for CT-P13 and the RA and psoriasis trials for ABP 501 to other disease states; (3) the issues of interchangeability between the originator drug and the biosimilar, which is an important motivating factor for the pharmaceutical and biotechnology industries; and (4) the pharmacoeconomic considerations regarding the use of anti-TNF drugs in IBD.

FDA Guidance for Biosimilar Drug Development

The FDA guidance for biosimilar approval details a stepwise approach requiring demonstration of biosimilarity to the original compound using comparisons of structure, function, animal toxicity, human pharmacokinetics and pharmacodynamics, clinical efficacy, safety, and immunogenicity. This is adequate to provide the totality of evidence that may lead to FDA approval [6]. These factors will determine statistical comparison of PK and PD results,manufacturing processes, dose and route of administration selection between reference and biosimilar products, clinical study design, and long-term follow-up. From a biosimilar study design perspective, the FDA recommends a calculation of a 90% confidence interval for the ratio between the means of the parameters studied to be tested. However, an appropriate limit for the confidence interval may range between 80 and 125% of the ratios comparing the reference and biosimilar product [7]. Features addressing quality standards in biosimilar manufacturing are outlined in Table 15.1.

Table 15.1 Features of quality considerations in demonstrating biosimilarity

1. Expression system
2. Manufacturing process
3. Assessment of physiochemical properties
4. Functional activities
5. Receptor binding and immunochemical properties
6. Measurement of impurities
7. Stability under multiple stress conditions (high temperature, freeze-thaw, light exposure, agitation)
8. Effects of product formulation and packaging

Scientific Criteria for Demonstration of Biosimilarity

Issues in Biosimilar Manufacturing

Many of the synthetic and manufacturing processes involve proprietary techniques to produce a biosimilar of the reference product. Specific manufacturing features are summarized in Table 15.1. A large number of variables exist, among other features, in the choice of the cell vector and cell expression system and cell line and master cell banks. Likewise, conditions for expansion of the cell lines are proprietary, and variables which may be highly controlled are not known to the biosimilar manufacturer and may play into intellectual property concerns after drug approval (Fig.15.1). Differences in synthesis can potentially result in different posttranslational modifications, possiblyaffecting efficacy, safety, and immunogenicity of the product [8]. For both the biosimilars for IFX and ADA, the FDA closely considered

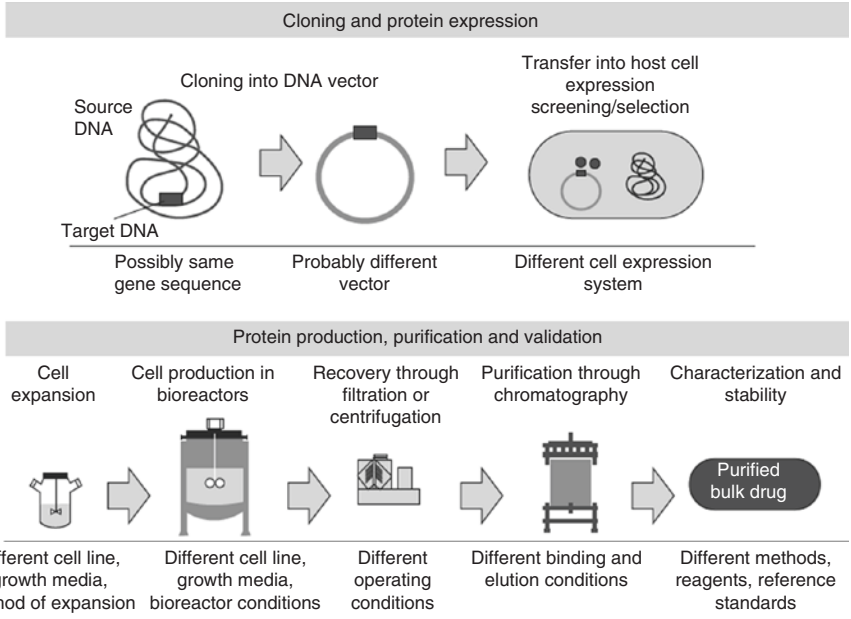

Fig.15.1 Biological drugs manufacturing: reprinted from Ref. [74]

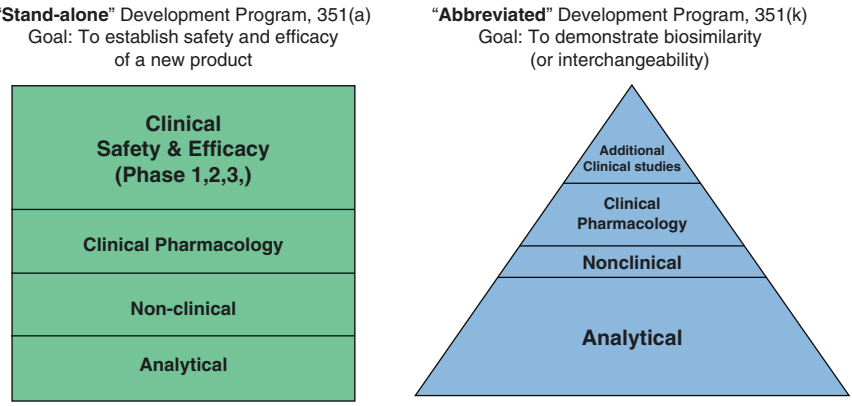

Fig.15.2 Considerations for extrapolation of biosimilarity. Adapted from http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM486171.pdf [75]

whether differences in posttranslational afucosylation may yield to differences in pharmacokinetics and determined that no meaningful differences were present. Differences also can emerge in the design and construction of cell production bioreactors, filtration, and chromatographic purification steps. Notably, theFDA does not require an approach to "independently establish the efficacy and safety of the biosimilar," but rather "a demonstration of the biosimilarity between the proposed product and a reference product." Figure 15.2 depicts the relative weights it places on the different steps in determining biosimilarity.

As a first step, structural analyses are required that the proposed product will encode for the same primary amino acid sequence as the reference product as well as an analysis ofsecondary, tertiary, and quaternary structures. A detailed physiochemical analysis of CT-P13 has been carried out to the reference infliximab. Detailed biochemical techniques used to compare the two are beyond the scope of this chapter and are reviewed in detail elsewhere [9]. Higher-order structures were found to be indistinguishable by multiple assays between the reference infliximab andCT-P13. Importantly,comparable biologic activity of CT-P13 and the reference drug was demonstrated based on its mechanism of action, including invitro TNF neutralization activity, TNF-binding affinity based on ELISA, and cell-based TNF-binding affinity (Fig.15.3a, b). Bridging assays for reference USinfliximab and reference European Union (EU) infliximab demonstrated similar findings between the two products [10].

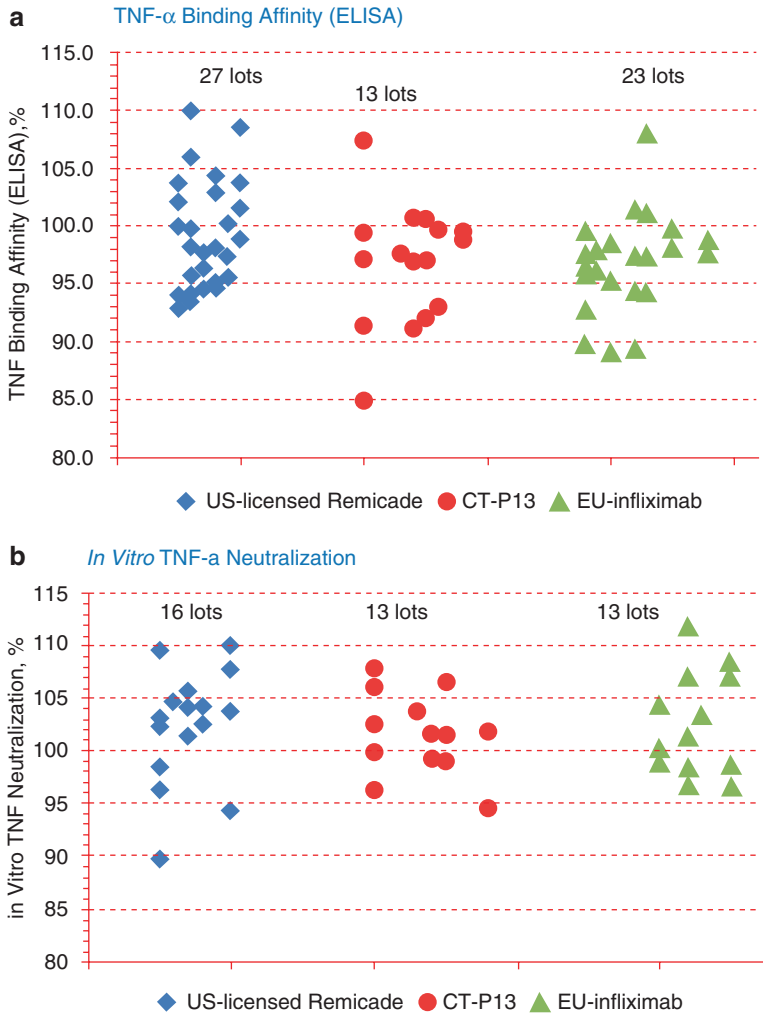

Fig.15.3 (**a**) Comparison of TNF binding by CT-P13,US reference infliximab and European Union (EU) reference infliximab. (**b**) Comparison of TNF neutralization by CT-P13, US reference infliximab and European Union (EU) reference infliximab Source: Ref. [10]

Clinical Criteria for Demonstration of Biosimilarity

Pharmacokinetic Analyses

The pharmacokinetic (PK) properties of CT-P13 were studied in a double-blind, three-arm, parallel-group study of the biosimilar CT-P13 and two formulations of Remicade® using healthy subjects receiving a single infusion dosed at 5 mg/kg of

the biosimilar (n = 70), Remicade® from Europe (n = 71) or Remicade® from the USA (n = 70). All three formulations were essentially equivalent in terms of maximal infliximab concentration (C_{max}), area under the serum concentration (AUC) time curves, and no differences in treatment-emergent adverse events among the 211 study subjects [11].

CT-P13 in Ankylosing Spondylitis

The PLANETAS trial was a phase 1, double-blind, multicenter study of 250 anti-TNF naïve patients with active ankylosing spondylitis (AS) randomized to receive CT-P13 (n = 125) or Remicade® (n = 125) dosed at 5 mg/kg at weeks 0, 2, and 6 then every 8 weeks up to 30weeks [5]. The AS patient population was deemed the immune-mediated inflammatory disorder closest in approximation to healthy volunteers in order to study pharmacokinetics and medication-related safety and efficacy as the goal was to identify differences primarily related to the treatment, not due to disease state [12]. Of note, AS patients with inflammatory or rheumatic diseases were excluded from the study presumably including coexisting IBD diagnoses, present in approximately 5–10% of AS patients [13]. Steady-state PK data, based on AUC and C_{max} values, trough levels, and medication half-life were essentially equivalent for CT-P13 and Remicade®-treated patients at all measured timepoint post-infusions. Clinical response rates at weeks 14 and 30 were 63% and 71% for CT-P13 versus 65% and 72% for Remicade®, with similar changes in baseline activity scores and quality-of-life scores at weeks 14 and 30 [5]. In the PLANETAS study, anti-drug antibodies (ADA) occurred in 9% and 27% of CT-P13-treated patients comparable to 11% and 23% of Remicade®-treated patients at weeks 14 and 30, respectively, with the presence of ADA negatively influencing the PK of both agents [14]. Treatment-emergent adverse event rates at week 30 were 65% for CT-P13 versus 64% for Remicade®, including infusion reactions [5]. Partial remission rates, adverse events, and pharmacokinetic profiles for CT-P13 and Remicade® (AUC and C_{max}) remained equivalent at week 54 [14].

In the subsequent open-label extension study, CT-P13 patients were allowed to either continue treatment with CT-P13 (n = 88), and Remicade®-treated patients were switched to CT-P13 (n = 86) at week 54 and followed for an additional 48 weeks. Notable findings included similar partial remission rates at weeks 78 and 102 between CT-P13-treated patients who continued therapy (70% and 81%) and patients who switched from Remicade® to CT-P13 at week 54 (77% and 77%). However, treatment-emergent adverse event rates were higher for the switch group (Remicade® to CT-P13, 71%) compared to the CT-P13 patients with continued treatment (49%). ADA were present in 22% and 25% of continued CT-P13-treated patients at weeks 54 and 102, respectively, compared to 26% at week 54 and 31% at week 102 for the CT-P13-switched group [15].

CT-P13 in Rheumatoid Arthritis

The PLANETRA trial was a phase 3, randomized, double-blind, multicenter, parallel-group study of CT-P13 in rheumatoid arthritis patients with active disease despite treatment with ≥3 months of methotrexate dosed at 12.5–25 mg weekly [4]. In the PLANETRA trial, eligible RA patients were randomized to receive CT-P13 (n = 302) or Remicade® (n = 304) dosed at 3 mg/kg at weeks 0, 2, and 6 then every 8 weeks with the primary endpoints assessed at week 30 with continued methotrexate administration. The primary aim of the PLANETRA trial was to demonstrate therapeutic equivalence between the two treatment groups defined as 95% confidence intervals (CI) of treatment response within a margin of ±15% at week 30. Week 30 response rates were similar for CT-P13 (60.9%)- and Remicade® (58.6%)-treated patients with the 95% CI range of -6–10%, within the prespecified equivalence margin. Adverse event profiles (CT-P13 60.1%, Remicade® 60.8%) at week 30 and PK data profiles (AUC and C_{max} values) measured after each infusion were also equivalent between the two treatment groups [4]. At week 30, 25.8% of CT-P13-treated patients and 25.4% of Remicade®-treated patients developed anti-drug antibodies using ECL-based assays for ADA detection. Among patients continuing with the PLANETRA study to week 54, remission and response rates, PK profiles, and adverse event rates were again comparable between the two treatment groups. ADA positivity at week 54 was substantially higher than reported during the PLANETAS trials for AS with 52.3% of CT-P13-treated and 49.5% of Remicade®-treated patients having antibodies present by week 54 with lower resultant response rates [16].

In the open-label extension study, beginning at week 54, PLANETRA study patients treated with CT-P13 could continue with scheduled 3 mg/kg dosing every 8 weeks (n = 158), or Remicade®-treated patients could switch to CT-P13 at the same dosing and interval for an additional 48 weeks (n = 144). Clinical efficacy and adverse event rates were comparable between the continued versus switched groups, with the proportions of CT-P13-treated patients with ADA also similar between the patients who continued CT-P13 (49.1% at week 54, 46.4% at week 102) and the patients who switched from Remicade® to CT-P13 (49.3% at week 54, 49.6% at week 102) [17].

CT-P13 in Inflammatory Bowel Disease

There are limited published data commenting on the safety, efficacy, and bioequivalence of CT-P13 for the inflammatory bowel diseases (IBD), Crohn's disease (CD), and ulcerative colitis (UC), consisting mostly of small retrospective studies performed in Korea, Poland, or Hungary (Table 15.2) [18]. One of the larger, prospective observational cohort studies using CT-P13 for IBD included 78 patients (46 CD/32 UC with 28% CD and 16% UC patients having had prior biologic

Table 15.2 Efficacy and safety of CT-P13 in inflammatory bowel disease

Study population	Study design	Sample size	Outcome
CD and UC [20]	Prospective, multicenter, Hungarian nationwide, observational cohort	210 (CD 126, UC 84)	Week 14 response: CD 81%, UC 78%
			Week 14 remission: CD 54%, UC 59%
CD and UC [19]	Prospective, observational Norwegian cohort	78 (CD 46, UC 32)	Week 14 remission: CD 79%, UC 56%
CD and UC [71]	Single-center prospective Hungarian observational cohort	39 (CD 18, UC 21)	Week 8 response: CD 38%, UC 20%
			Week 8 remission: CD 50%, UC 10%
CD and UC [72]	Retrospective, multicenter Korean cohort study	74 anti-TNF naïve (CD 32, UC 42)	Week 8 response: CD 91%, UC 81%
			Week 8 remission: CD 84%, UC 38%
			Week 54 response: CD 88%, UC 100%
			Week 54 remission: CD 75%, UC 50%
CD and UC [73]	Retrospective Korean caseseries	17 (CD 8, UC 9)	Week 8 response/remission: CD 25%, UC 56%

exposure) who received CT-P13 5 mg/kg at weeks 0, 2, and 6, except for three severe UC patients who received either 10 mg/kg due to low albumin/high C-reactive protein or an extra infusion 5–7 days later. Clinical efficacy was assessed at week 14 including clinical activity scores, trough levels, and ADA positivity. At week 14, 79% of CD patients and 56% of UC patients achieved clinical remission with reductions in C-reactive protein and fecal calprotectin values compared to baseline and no unexpected adverse events. Eight patients had undetectable trough levels at week 14, and 7 of these 8 patients had detectable antibodies, but these patients were only treated with CT-P13 monotherapy [19]. Another recently published prospective, nationwide, observational cohort study from Hungary followed 210 IBD patients (126 CD and 84 UC) treated with CT-P13 induction at 5 mg/kg. Reported outcomes included week 14 response and remission rates: CD 81% and 54%, UC 78% and 59% with infusion reactions occurring among 7% of patients, and an adverse event rate of 17% [20].

However, there are no randomized controlled trial data currently available that are equivalent to the PLANETAS or PLANETRA studies to confirm the clinical efficacy, safety, and pharmacokinetic profiles of CT-P13 for the IBD patient population. The influence of IBD-specific diseasestate-related factors on therapeutic efficacy, safety, and pharmacokinetics when considering extrapolation of indications to include IBD patients remains unexplored based on the currently available data. A primary issue of concern pertains to the potential for immunogenicity with the biosimilar product when used interchangeably with the reference product. There are multiple factors influencing immunogenicity aside from just the biosimilar drug itself, including medication dosing, schedule, disease type and severity for which treatment is indicated, and the use of concomitant medications [21].

The two pivotal CT-P13 randomized controlled trials investigated biosimilar outcomes as monotherapy dosed as 5 mg/kg for AS and combination therapy dosed as

3 mg/kg for RA in conjunction with methotrexate 12.5–25 mg weekly. Of note, RA patients tend to have lower rates of anti-drug antibody development presumably due to the use of concomitant methotrexate compared to other disease states such as psoriasis and IBD, which tend to have higher rates of immunogenicity [22–25]. In accordance to recommendations by the World Health Organization (WHO) and the Food and Drug Administration (FDA), in order to extrapolate across indications with efficacy and safety data, immunogenicity risk should be studied in the highest risk patient population for therapy-related adverse events and anti-drug antibody potential [26, 27]. Thus, further investigation with respect to the clinical efficacy and pharmacokinetics of CT-P13 in the moderate to severe IBD patient population may be valuable to add insight to the true bioequivalence in this different immune-mediated disease state [28, 29].

TheNOR-SWITCH study is a randomized, double-blind, parallel-group study of 155 CD and 93 UC patients to evaluate the efficacy and safety of switching from Remicade® to the biosimilar across several disease states including CD and UC [30]. After being in a sustained remission for at least 24 weeks on stable dosing of reference infliximab, patients were randomized to continuing the originator infliximab versus switching to CT-P13. The primary endpoint was disease worsening at week 52 defined as an increase in partial Mayo score of at least 3 points with a minimum score of 5 for UC patients and an increase in the Harvey-Bradshaw Index (HBI) score of at least 4 points with a minimum score of 7 for CD patients. Secondary study endpoints included safety and immunogenicity [30].

For CD patients continuing reference infliximab, 21% of patients experienced disease worsening, compared to 37% of patients switching to CT-P13 (95% CI −29.3%, −0.7%). For UC patients, 9% of patients continuing reference infliximab had disease worsening, compared to 12% of patients who switched to CT-P13 (95% CI−15.2%, −10.0%). There were no statistically significantdifferences for PK drug trough levelsbetween reference drug and CT-P13 for either UC or CD patients. Notably, anti-drug antibodies, adverse events, and serious adverse eventswere similar in both groups. While the strengths of the study included the RCT design, dosing according to standard protocols, and finance of the study by the Norway federal government, limitationswere thatthe study was not powered for non-inferiority within each diagnostic group [30].

There are also two prospective observational studies for CT-P13 in IBD: NCT02539368, CONNECT-IBD, a post-marketing observational cohort of CT-P13 in clinical practice to assess safety, immunogenicity, sustained efficacy, and patient-reported outcomes sponsored by Hospira, and NCT02326155, another observational prospective cohort study of CT-P13 sponsored by Celltrion, the two currently available manufacturers of the infliximab biosimilar [31–33].

Extrapolation

Extrapolation refers to the approval of an approved biosimilar for a condition in which it was not clinically studied, and it is one of the most controversial issues regarding adoption of biosimilars in those countries for which it is approved. The

possibility of gaining approval for extrapolation, as well as for interchangeability, is an important motivator for a biotechnology company to embark on a venture in which large financial risks are taken with an uncertain approval process, an unknown landscape of patent battles, and unknown physician, patient, and payer acceptance. Considerations taken by the FDA in granting approval for extrapolation for each disease state consider the "totality of the evidence." This begins with the establishment of biosimilarity by analysis of primary, secondary, and tertiary structure, posttranslational profile, and in vitro functional characteristics to include TNF binding and neutralization as discussed in the earlier sections of this review. Clinical analysis of the data includes potential differences in mechanism of action (MOA), pharmacokinetic (PK), and pharmacodynamic (PD) data in different patient populations; immunogenicity in different disease states, which may be influenced by different concomitant immunosuppressive agents in the different diseases; and the potential for differences in expected toxicities in different patient populations [26]. Consideration of these same variables and data led to different extrapolation approvals in Canada, the European Union (EU), and the United States (USA).

However, there are a number of potential obstacles in extrapolating from RA and AS to inflammatory bowel disease. Factors which are different between these diseases include different dosages, differences in the use of methotrexate in RA, and the variable patterns of the use of various immunosuppressants in IBD which may affect drug levels, anti-drug antibodies, and resultant differences in clinical efficacy [34–36].

An additional criterion of the FDA scientific guidelines in considering the issue of extrapolation is to "consider whether the tested condition of use is the most sensitive in which to detect clinically meaningful differences and safety and effectiveness [8]." In the case of rheumatoid arthritis, however, the PLANETRA study of CT-P13 versus infliximab trial was designed as an equivalence trial, and the 95% confidence interval for the treatment difference between CT-P13 and infliximab for the primary endpoint was −6–10%, falling within the range of the equivalence margin selected of −15–15%. These confidence intervals contained the *smallest* placebo-adjusted response to infliximab, 8%, previously demonstrated in any disease for which infliximab is indicated [4]. Rheumatoid arthritis may therefore be the *least* sensitive clinical model to detect a potential difference in efficacy between this biosimilar and infliximab in other indications [37]. Another challenge in extrapolating from RA to Crohn's disease is the divergent efficacy for different anti-TNF agents, as well as other biologics in the two diseases, suggesting the possibility of different mechanisms of inflammatory pathways. For example, while anti-TNF agents are effective in both, anakinra, abatacept, and rituximab are effective in RA, but not in Crohn's disease [38–41].

In Canada, Health Canada, the national drug regulatory agency, approved CT-P13 for rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis,based on the PLANETRA and PLANETAS trials [4, 5, 42]. Health Canada also relied on these trials to demonstrate similarity in pharmacokinetic

(PK) parameters, using area under the concentration-time curve over the dosing interval (AUCtau) and maximum serum concentration (Cmax) at steady state. Based on their extrapolation criteria, Health Canada extended approval of CT-P13 for plaque psoriasis and psoriatic arthritis. However, Health Canada, at time of approval, denied extrapolation to adult and pediatric Crohn's disease and UC. This denial was based on the observed differences in degree of afucosylation and FcγRIIIa receptor binding in addition to differences in some in vitro antibody-dependent cell-mediated cytotoxicity (ADCC) assays [42]. In addition, Health Canada observed that the safety profile in rheumatic diseases is different, specifically citing the risk of hepatosplenic T-cell lymphoma in IBD. In the absence of clinical studies in IBD, it was felt that extrapolation was not warranted for CD or UC in adults or pediatric patients [42].

On the other hand, the European Medicines Agency (EMA) and the FDA Arthritis Advisory Committee (AAC) concluded that extrapolation was warranted to all the diseases for which reference infliximab had previously received EMAand FDA approval [10, 43]. The agencies reviewed the data supplied by Celltrion and concluded that the issue of diminished afucosylation and ADCC activity occurred only in the most sensitive experimental in vitromodel using NK cells of patients with high-affinity genotypes. In further examination of efficacy and safety of efficacy in IBD, Celltrion had committed to increase enrollment in a post-marketing surveillance study and plans to conduct an additional comparative trial of CT-P13 versus reference infliximab in active CD.

In summary, the totality of evidence analyzed and considered by the FDA AAC (Table 15.3) resulted in a vote of 21 to 3 in favor of extrapolation,based on the results of the RA and AS trials, to all the indications for which reference infliximab had been approved, including adult and pediatric UC and CD resulting in the FDA approval of CT-P13 for all previously approved indications for infliximab [44]. Similarly,for ABP 501, theFDA granted extrapolation to all indicated diseases for which adalimumab had been previously approved.

Table 15.3 The totality of the evidence leading the FDA to approve extrapolation of the biosimilar to infliximab

• Structural similarity in primary, secondary, and tertiary structure
• Similar posttranslational profiles and in vitro and in vivo functional characteristics
• Similar potency to bind and neutralize TNF, reverse signaling, and Fc region-mediated potential mechanisms of action
• Similar mechanism of action of TNF inhibitors, noting that ADCC is only one of several plausible mechanisms of action, and only found to be altered in the most sensitive of a number of assays
• No clinically meaningful differences between CT-P13 and US-licensed Remicade in bridging studies
• Similarities in PK parameters for US-licensed Remicade in Crohn's disease patients as compared to RA and AS pts
• Similar immunogenicity between CT-P13 in patients with CD

Interchangeability

In January 2017, the FDA issued theirguidance document regarding the critical issue of*interchangeability*, whereby an approved biosimilar can be substituted for a prescribed reference drug without the approval or even the knowledge of the prescribing physician or patient [45]. Beyond demonstrating biosimilarity, the sponsor the biosimilar may request a claim of "interchangeability." According to FDA draft guidance in May 2015**,** the approval of interchangeability allows that the biosimilar "may be substituted for the reference product without the intervention of the prescribing healthcare provider" [46]. In theJanuary 2017 FDA guidance document, the FDA defined the weight of evidence to fulfill the "higher-level" requirement that an interchangeable product "can be expected to produce the same clinical result as the reference product, in any given patient and the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biologic product and the reference product is not greater that the risk of using the reference product without such alternation or switch" [46]. This has become a particularly contentious issue that has been legislated in the USA on a state-by-state basis (Fig.15.4). More specifically, the FDA did not grant interchangeability of CT-P13 with reference infliximab when it approved CT-P13 in April 2016, nor did it grant interchangeability

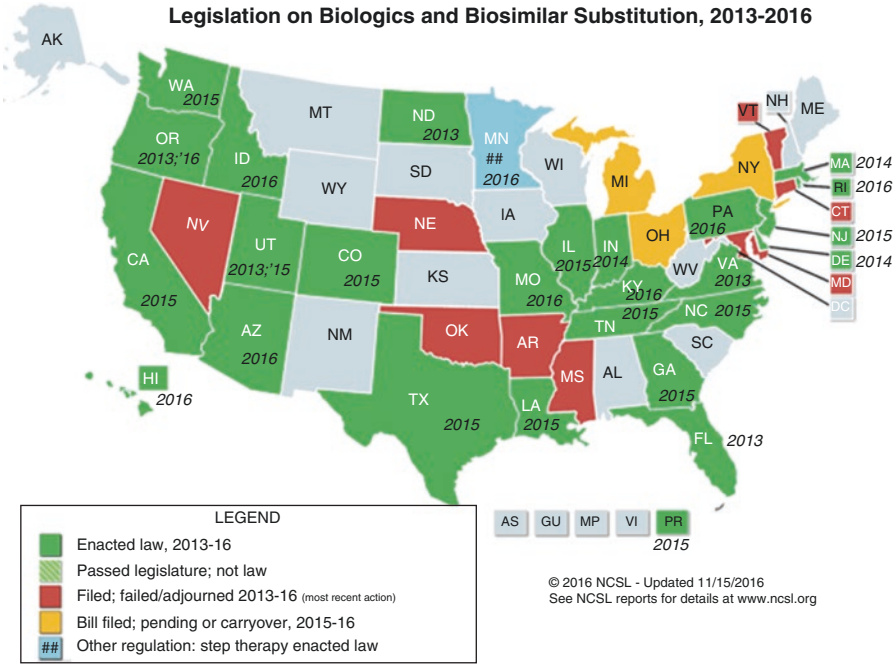

Fig.15.4 Biosimilar legislation throughout the USA. Source: State laws and legislation related to biologic medications and substitution of biosimilars. http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx [76]

for ABP 501 for adalimumab with the approval in September2016, pending additional studies demonstrating their interchangeability [44].

Interchangeability allows substitution of the biosimilar to the reference drug without the intervention of the prescriber, thereby allowing insurance companies to refuse to pay for the originator drug. The FDA requires the approach to begin with the demonstration of biosimilarity for the product with proposed interchangeability. Post-marketing data for the biosimilar in addition to appropriately designed studies-may be used to support interchangeability, but would generally be inadequate to prove interchangeability in the absence of prospective switching studies, since post-marketing data would be unlikely to provide adequate PK and PD data.

The FDA recognizes that if patients experience an immune response or adverse event duringa switching study, it may be difficult to discern whether the event was the result of the reference product or the interchangeable drug. In their consideration of switching studies, the FDA outlines issues in determination of sample size, number, and duration of switches, dosing, and duration of the exposure interval that may be of the greatest concernin terms of generating immune responses with its potentialconsequent effects on safety and efficacy [45]. The design of the study should include a lead-in period of adequate duration to ensure that an adequate steady state of pharmacokinetics has been achieved prior to the randomization to the switching period of the study. The FDA guidance expects that the switching arm incorporates at least two separate exposure periods to each of the two products. In addition, the study should be designed in that the last switching interval is from the referenceproduct to the proposed interchangeable product. An integrated studymay be designed whereby the first phase is designed to demonstrate biosimilarity and the subsequent phase is designed to demonstrate interchangeability. Furthermore the studies may be designed to allow for extrapolation for unstudied indications for which the reference product has been previously approved [45].

In demonstrating interchangeability, several different clinical study designs can be applied such as including a single switch from the reference drug to a biosimilar and monitoring for safety, efficacy, and immunogenicity. An alternative design can entail a switch from reference drug to biosimilar and then back to the reference drug or a switch from the initial use of a biosimilar to the reference drug. An additional issue in designing a crossover study would be to determine the length of the study after the crossover to the biosimilar, considering that a substantial percentage of patients may remain in remission after withdrawal of infliximab in the absence of a follow on biosimilar anti-TNF. In CD, the median time to relapse in patients with a sustained response was 16.4 months after withdrawing infliximab, and 44% of patients relapsed within 1 year. Furthermore, a crossover substitution study would have to control for concomitant immunomodulator therapy and preexisting patient risk factors for early recurrence after anti-TNF withdrawal [47].

Ideally anti-drug antibodies (ADAs) and trough drug levels will need to be determined at the time of the switch, and over time after the switch. Ben Horin reported that ADAs (measured by an ELISA that could detect antibodies in the presence of drug) to reference infliximab recognized and cross-reacted with CT-P13, and these antibodies could similarly interfere with TNF neutralization by either reference

infliximab or CT-P13 [48, 49]. Another infliximabELISAhas been developed that could quantify CT-P13 equally well as with reference infliximab [49]. An additional problem that may arise from interchangeability is the challenge that is introduced in monitoring long-term safety for the biosimilar separate from the originator drug. This issue has been addressed by the consideration of a unique suffix for each newly approved biosimilar, and for CT-P13, the FDA designated it as infliximab-dnnp. Low incidence adverse drug reactions (ADRs) may require large numbers of patients followed for years to determine risk. In Europe the EMA mandated a risk management plan of biosimilar infliximab which includes two patient registries with a total targeted enrollment of 6200 patients in both RA and IBD, with a special focus on serious infections including TB, and is planned to have final submission of data in 2026 [50].

Changesin manufacturing may occur and increase product robustness and physiochemical properties, by the deliberate introduction of new technology or alternative raw materials, or change in production scale or sites to meet changes in market demand [51]. These changes are not uncommon, and there have been at least 36 post-approval changes for Remicade and 21 for Humira [52]. The FDA and EMA have rigorous-defined mechanisms to detect meaningful changes in the pre- and post-change product [53, 54]. For example, for the multiple changes made between 2003 and 2013 in a total of 544 batches for reference adalimumab, comparability exercises revealed a very high level of consistency in multiple parameters including glycan mapping, TNF binding and affinity, and neutralization of TNF.

In summary, key issues that will impact on the legitimacy of interchangeability must address disease-specific design of switch studies, efficacy, and long-term duration of follow-up after switches, serial measurement of drug trough levels and ADAs at appropriately determined time points, and accountability forpossible divergence of biosimilarity over time. These variables have not all been definitively proven to be identical between diseases. Caution must be exercised in considering the issues of extrapolation and interchangeability beyond presumed short-term and unknown long-term cost savings.

Gastroenterologist Concerns: Reintroduction of Biosimilars

In order to prevent confusion regarding adverse eventsdue to originator versus a newly introduced biosimilar,the World Health Organization (WHO) mandated new drug naming in accordance with the international nonproprietary names [55]. The FDA recently published a draft guidance summary regarding the nonproprietary naming of biosimilar agents to avoid confusion and inadvertent assumption of interchangeability due to the biosimilar and reference product having the same proper name, which relates to the chemical structures and pharmacologic features of the product. Currently, the FDA is recommending biosimilars have a core name shared among the related products and a distinguishing suffix consisting of four lowercase letters added to the core name to provide clarification for prescribers, pharmacists,

and patients [56]. In the case of infliximab, for example, the proper name in the case of CT-P13 per the FDA naming system is "infliximab-dyyb [44]."

The American Gastroenterological Association has conducted a survey of 180 members; 91% of respondents noted that they prescribe biologic agents in their clinical practice, with the majority stating the presence of clinical trial-based efficacy data was a key factor in their biologic prescribing for the IBD patients. Although the majority of respondents (72%) reported they would likely prescribe biosimilars if available in the USA, 78% had concerns regarding the safety and immunogenicity profiles of the biosimilars, and 67% were opposed to indication extrapolation for biosimilars in IBD [57]. The consensus across gastroenterology societies, providers, and authorization agencies supports the role of biosimilars for use in the IBD setting with the potential costsavings and increased accessibility across multiple patient groups throughout the world. However, the need for more IBD-centric biosimilar data is consistently emphasized as necessary prior to acceptance for routine clinical practice due to the unique complexities of the disease states and patient populations.

Economic Considerations of Biosimilars

The cost of care of the IBD patient is substantial, and, for many patients, the costs of therapy are rate-limiting factors that ultimately deny patient access to biologic therapies. The annual estimated direct costs for CD patients, *not on anti-TNF therapy,* range up to $18,000/year with approximately $11–15 billion in total economic burden [58]. The annual estimated direct costs for UC patients, *not on anti-TNF therapy*,are up to $11,000/year with approximately $5–9 billion total economic burden [59]. Although the initiation of anti-TNF-α therapies has demonstrated cost-effectiveness and increased quality-associated life-years compared to the non-biologic-based standard of care therapies, the per-person costs are still significant [60, 61]. Remicade® sales globally were over 9.2 billion across the multiple indications in 2014 [62]. In the COIN study performed in the Netherlands, anti-TNF-α therapies accounted for 64% of total costs for CD and 31% of total costs for UC patients, more than hospitalizations or surgeries, which were the primary drivers for high IBD costs of care in the past [63]. Within the EpiCom IBD cohort of close to 1400 IBD patients in Europe, of the total expenditures of almost $6 million, biologic agents accounted for 14% following diagnostic evaluations (38%), surgery (26%), and non-biologic-based treatment (22%) [64].

The intent ofthe congress with the creation of the BPCIA of 2009 was to allow the FDA to create an abbreviatedprocess to expedite the introduction of biosimilars to the market as branded biologics patent approach expiration [65]. Compared to generic medications which cost on average $1–4 million to develop and new biologic medications with an estimated $1.9 billion cost to develop and less than 10% of agents successfully introduced into the market, the biosimilars cost between $100–250 million to produce and take approximately 7–8 years before available for

clinical use [66]. Because of the greater costs and time for research and development for a given biosimilar, the most ideal factors for potential biosimilars are biologic agents with patents near expiration, with the potential for extrapolation across disease states, and with the possibility of interchangeability [62]. However, the complexities of manufacturing the biosimilars according to the FDA-mandated standards, the costs of clinical trials to demonstrate the bioequivalence, the need for post-marketing surveillance or pharmacovigilance to report safety and immunogenicity outcomes, and the uncertainty regarding interchangeability or automatic substitution with branded agents are potential barriers to biosimilar development and encourage corporate partnering or acquisitions, e.g., Pfizer acquired Hospira which held the American rights to CT-P13. Since the release of CT-P13 to the European Market in 2013, the average discounts in cost compared to Remicade® are an estimated 25% with a range of 10–30% savings [67].

Market Financials Influencing Anti-TNF Biosimilars in the USA

The potential cost savings with the use of biosimilar anti-TNFs are enormous considering the 2014 global sales of Humira (Abbvie pharmaceuticals) of $13.0 billion and $10.1 billion for Remicade [68]. However, in the EU market, penetration of CT-P13 varies widely, based on pricing discounts, status of tender nations, and authority of central national payers. In the USA, Pfizer began shipping Inflectra in November of 2016, and estimates of market uptake of CT-P13 range between 15 and 30% over the first 3 years of market availability. Merck, which markets in Europe, sustained a loss of sales of Remicade from $2.3 billion in 2014 to $1.8 billion in 2015 after the introduction of the Remicade biosimilar [69]. Additionally in September 2016,the FDAannounced approval of ABP 501 after positive results in RA and psoriasisand can further serve to discount pricing of anti-TNF agents [70]. In March 2015, Janssen filed for patent infringement by Celltrion on six patents related to Abbvie which has stated that although the composition of matter patent for Humira expires in December 2016, an additional total of 70 patents regarding formulation, manufacturing, and methods of use do not expire until 2022 and announced their strategy of attempting to block the introduction of ABP 501 based on claims of patent infringement.

Conclusions

The approvals of the first anti-TNF biosimilars, CT-P13 and ABP 501 for infliximab and adalimumab, respectively, throughout the world have ushered in a new era of prescribing possibilities for anti-TNF drugs. This approval for IBD was extrapolated to IBD from a single RCT in RA and AS, respectively, for CT-P13,and

RA and psoriasis for ABP 501, without any primary RCT data existing in IBD, though these trials are now underway. Health Canada, on the other hand, denied approval of extrapolation to IBD indications, given their concerns regarding similarity of the mechanisms of action of TNF in the pathophysiology of disease in IBD, compared to RA and AS. The FDA has not issued guidance regarding the issue of interchangeability where substitution of the biosimilar may occur without the consent or even knowledge of the prescribing physician. A number of critical study design issues will need to be established before valid interchangeability trials can be performed. There is already significant resistance by professional societies around the world to the practice of interchangeability in the absence of IBD-specific controlled trials, and the issue of immunogenicity is of significant concern. The biosimilars have the potential for significant cost savings and increasing patient access. However long-term follow-up and randomized controlled trials specifically in IBD will determine whether comparable efficacy, safety, and immunogenicity will lead to patient benefit by reducing cost and increasing access.

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Chapter 16
Anti-integrin Agents in IBD: Efficacy and Risk of Complications

Jimmy K. Limdi and Francis A. Farraye

Introduction

The last two decades have witnessed unprecedented advances in our understanding of the immuno-pathogenesis of the inflammatory bowel diseases (IBD). Conventional management until then typically involved the use of broad-spectrum anti-inflammatory drugs such as aminosalicylates and corticosteroids or immunosuppressants such as the thiopurines or methotrexate, often sequentially with the aim of relieving symptoms and preventing long-term complications [1, 2]. The advent of anti-TNF therapy demonstrating efficacy in the induction and maintenance of remission, corticosteroid-sparing effects, mucosal healing and reduced rates of hospitalisation and surgery redefined treatment paradigms and definitions of disease control [3]. The exciting implications of what can be achieved, through abrogation of immuno-inflammatory events in the inflamed gut, widened the search for other agents to combat IBD-associated gut inflammation. Meanwhile, anti-TNF therapy was not universally effective, with approximately 30–50% of patients being primary nonresponders with further attrition from secondary loss of response as a result of intolerance to therapy or through formation of anti-drug antibodies. In addition, although infrequent, there is a risk of infectious complications attributable to the non-specific inhibition of TNF-mediated immunologic cascades [3–6].

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Tissue injury in Crohn's disease (CD) and ulcerative colitis (UC) occurs in areas heavily infiltrated with subsets of activated lymphocytes that produce an array of inflammatory mediators [1]. These cells are recruited from the bloodstream as a result of increased expression of adhesion molecules on the intestinal vascular endothelium and integrins on lymphocytes and excessive production of chemokines within the inflammatory microenvironment [7]. Evolution in our understanding of the involvement of T-lymphocyte biology orchestrating gut inflammation has led to the development of several agents directed against trafficking of effector T lymphocytes towards the gut mucosa. In this chapter, we discuss the available data on agents that block integrins or adhesion molecules and combat gut inflammation.

The Biological Basis of Leucocyte Trafficking in IBD

Active IBD is characterised by the recruitment of leucocytes into the gastrointestinal mucosa in a highly coordinated, multistep process [8]. As they travel at high speed through the vascular tract, a highly coordinated sequential adhesion pathway is activated, consisting of tethering, rolling, activation, adhesion and migration through the vascular wall [8, 9] (Fig. 16.1). The capture of T cells to the endothelium is mediated through the interaction between selectins (L-selectins expressed by local sites and P- and E-selectins on the endothelium) which act as ligands allowing local sites to slow their speed in the vascular flow and then roll through the vascular wall moving from one selectin to another. Infiltrating leucocytes perpetuate the inflammatory process through the secretion of pro-inflammatory cytokines, further endothelial cell activation and up-regulation of adhesion molecules with enhancement of inflammatory cell recruitment [9]. Adhesion molecules belong to the integrin family (leucocyte cell-surface adhesion molecules), which allow them to stop rolling and start migration through the vascular wall [8, 9].

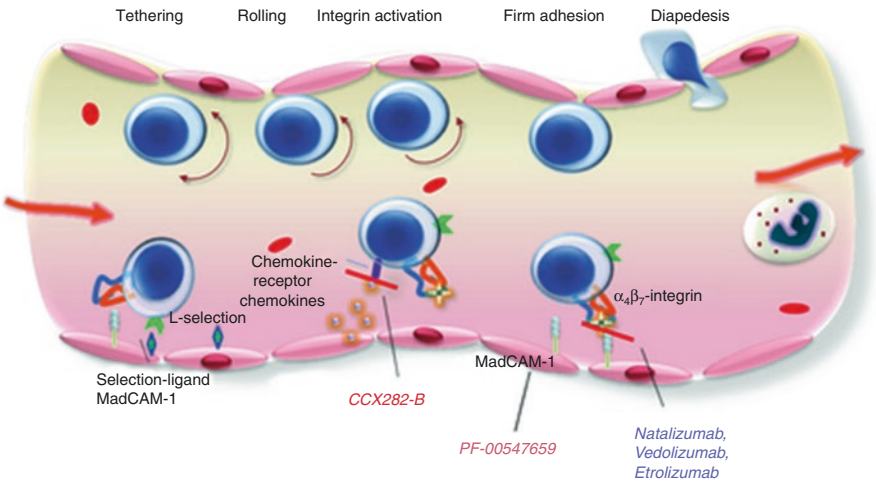

Fig. 16.1 Mechanism of action of adhesion molecules in the intestinal endothelium and their blockage by anti-adhesion drugs

Integrins involved in T-cell migration are leucocyte function-associated antigen 1 (LFA-1 or α 2β2) and the two α4 integrins (α4β1 and α4β7). The subunit α is implied in the specificity and subunit β in signalling pathways [10]. These integrins bind to specific ligands at the endothelium called addressins or adhesion molecules. LFA-1 is expressed on neutrophils and interacts with ICAM-1, which is expressed on leucocytes, dendritic cells, fibroblasts, epithelial cells and endothelial cells [8, 11]. Integrin α4β1 is expressed on most leucocytes but not neutrophils and interacts with VCAM-1. The α4β7 integrin is expressed on lymphocytes in gut-associated lymphoid tissue and interacts with MAdCAM-1. This ligand is expressed on endothelial venues in the small intestine and the colon, especially in the Peyer's patches. The interaction between α4β7 and MAdCAM-1 activates migration of lymphocytes to Peyer's patches; this interaction is gut-specific [8, 11]. Finally, αEβ7 is a member of the β7 integrin family, expressed only in mucosal intra-epithelial T lymphocytes, that binds selectively to E-cadherin on epithelial cells, expression of which is elevated in UC and CD in the active phase of disease [12]. Inhibition of leucocyte trafficking to the gut mucosa during the inflammatory process is now a major therapeutic target, following on from anti-cytokine agents [13]. The predominant targets of this group of biological agents are the integrins α4β1, α4β7 and α2β2, which interact with VCAM-1, MAdCAM-1 and ICAM-1, respectively [13]. They include the monoclonal antibodies natalizumab (anti-α4 integrin), vedolizumab (anti-α4β7 integrin), AMG 181 (anti-α4β7 integrin), etrolizumab (anti-β7 integrin targeting both α4β7 and αEβ7 integrin). Other molecules include AJM300 (inhibitor of the α4 integrin subunit) and alicaforsen, an antisense nucleotide against ICAM-1 messenger RNA [13] (Fig. 16.2).

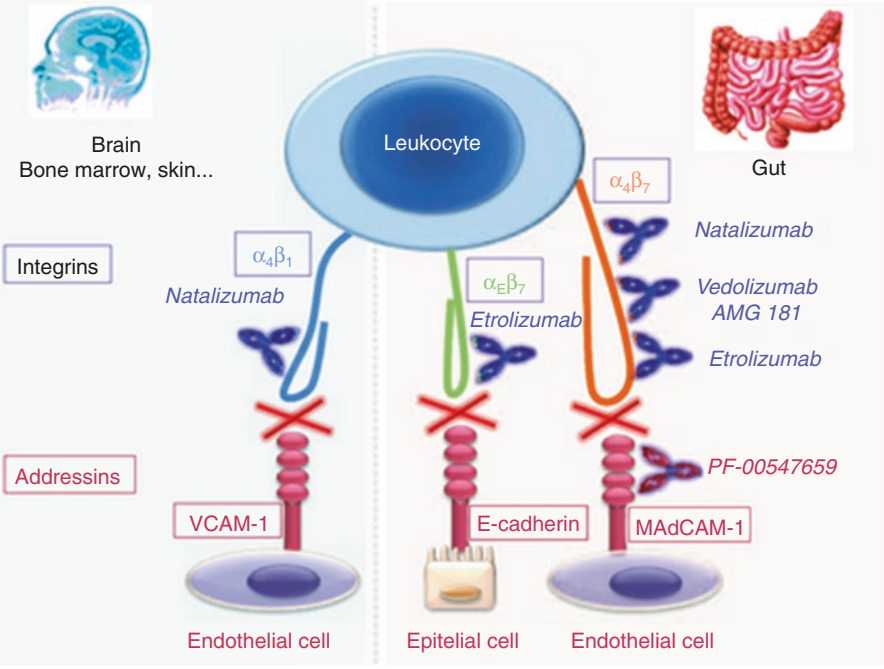

Fig. 16.2 Systemic effects of blocking MAdCAM-1 addressin and α4β1, α4β7 or αEβ7 integrins

Natalizumab

Natalizumab is a recombinant humanised monoclonal IgG4 antibody against the integrin subunit α4 that blocks both α4β7 and α4β1. The α4β7/MAdCAM-1 interaction is gut-specific, whereas the α4β1–VCAM-1 interaction interferes with lymphocyte migration to the central nervous system [9]. Natalizumab was the first monoclonal antibody to be approved for the treatment of relapsing–remitting multiple sclerosis demonstrating considerable and sustained efficacy [14]. Mechanistic support for its use as induction therapy in active IBD came from the finding that VCAM-1 and MAdCAM-1 are increased in gut inflammation and that natalizumab interferes with this interaction [15, 16].

Natalizumab was first assessed in 30 patients with mild to moderate active CD in a randomised double-blind placebo-controlled trial. A single infusion of natalizumab 3 mg/kg showed superior efficacy in inducing remission at week 2 and was well tolerated [17]. The effect was short-lived with majority of patients requiring rescue therapy at a median of 22 days post-infusion.

In a subsequent double-blind, placebo-controlled trial, natalizumab was administered to 248 patients with moderate to severe CD [18]. Patients were randomly assigned to receive one of four treatments: two infusions of placebo, one infusion of 3 mg/kg natalizumab followed by placebo, two infusions of natalizumab 3 mg/kg or two infusions of natalizumab 6 mg/kg. The group receiving two infusions of 3 mg/kg achieved the highest remission at 44% and a high response rate at 71% at week 6 with reduction in CRP and improvement in quality of life [18]. The efficacy of natalizumab to induce remission was evaluated further in the ENACT-1 and ENACT-2 (Efficacy of natalizumab as Active Crohn's Therapy) and ENCORE (Efficacy of natalizumab in Crohn's Disease Response and Remission) trials [19, 20]. In the first trial (ENACT-1), 905 patients were randomly assigned to receive natalizumab or placebo at weeks 0, 4 and 8. Rates of response (56% and 49%, respectively; $p = 0.05$) and remission (37% and 30%, respectively; $p = 0.12$) for drug and placebo were similar at 10 weeks. In the second trial (ENACT-2), 339 patients who had responded to natalizumab were randomly assigned to receive 300 mg natalizumab or placebo every 4 weeks through week 56. Although there was no difference between natalizumab and placebo in the first trial (ENACT-1), continuing natalizumab in patients who had a clinical response resulted in higher rates of sustained response (61% vs. 28%, $p < 0.001$) and remission (44% vs. 26% $p < 0.003$) than placebo at week 36 [19].

The ENCORE study evaluated the efficacy of natalizumab therapy in patients with moderate to severely active CD and elevated CRP concentrations in a randomised, placebo-controlled trial [20]. Of 509 patients enrolled, 48% demonstrated a sustained response at week 8 through week 12 as compared to 32% of patients treated with placebo ($p < 0.001$) while sustained remission was noted in 26% given natalizumab and 16% who received placebo [20].

A recent meta-analysis showed that natalizumab was superior to placebo for the induction of remission in CD (RR, 0.86; 95% CI, 0.80–0.93), being equally

efficacious for anti-TNF-naive (RR, 0.87; 95% CI, 0.75–1.00) and anti-TNF-exposed (RR, 0.86; 95% CI, 0.76–0.99) patients. Anti-α4 integrins were effective in inducing clinical response and improving quality of life, with no significant differences between natalizumab and vedolizumab. Rates of serious adverse events, infusion reactions, infections and treatment discontinuation were similar [21].

Data on the efficacy of natalizumab in UC are limited. In a pilot study evaluating the efficacy of a single infusion of natalizumab (3 mg/kg), a significant decrease in the median Powell-Tuck score was noted at 2 and 4 weeks (7.5 and 6, respectively) compared to median baseline scores of 10. Reduction in median CRP (6 mg/L) was achieved at 2 weeks from pretreatment levels (16 mg/L), but rescue medication was needed for 2 (20%), 3 (30%) and 8 (80%) patients by weeks 2, 4 and 8, respectively [22].

Progressive Multifocal Encephalopathy

Despite data confirming efficacy of natalizumab and also its safety profile, further use in clinical practice was limited by the death of a patient, treated with natalizumab in the ENACT study, from progressive multifocal encephalopathy (PML) [23]. Meanwhile, two other cases of PML occurred in patients with multiple sclerosis receiving concomitant natalizumab and interferon β1a [24, 25]. PML is caused by the reactivation of the latent polyoma JC virus and is related to decreased immune surveillance and impaired diapedesis of lymphocytes across the blood-brain barrier [26]. The earliest clinical manifestations are cognitive impairment and behavioural changes, which progress to visual and language disturbances and also seizures, cortical spinal syndrome and motor weakness [27]. Optic neuritis and spinal cord involvement are rare. Unlike classical PML however, gadolinium-enhancing lesions are observed at presentation in approximately 43% of patients with natalizumab-associated PML; these are diffuse and subcortical and rarely involve the periventricular region [28]. The diagnosis is confirmed by quantitative detection of JCV DNA in the cerebrospinal fluid (CSF) using an ultrasensitive assay [27]. Serum JCV PCR is not a useful test for either screening or diagnosis of PML. Management options for natalizumab-induced PML are limited [29]. Natalizumab must be discontinued at the first clinical suspicion of PML. Plasmapheresis to remove natalizumab followed by accelerated desaturation of the targeted α4 integrin receptor and restoration of leucocyte migration are recommended for up to five sessions. Antiviral therapy with cytosine arabinoside or cidofovir and serotonin receptor antagonists may be considered [29]. Rapid reversal of immunosuppression in cases of natalizumab-associated PML may result in an “immune reconstitution syndrome” which targets JCV in the central nervous system but may result in a paradoxical worsening of PML symptoms for which high-dose corticosteroid therapy may be required [29]. The outcome of PML is dismal, with a reported mortality of 60% in patients with at least 6 months of follow-up [26].

All cases of natalizumab-induced PML occurred in patients who were JCV antibody positive. The seroprevalence of JCV-specific IgG in healthy blood donors is

estimated at 50% by 30 years and 68% by 70 years [30]. The main risk factors for PML in natalizumab-treated patients in addition to JCV virus seropositivity, however, are the duration of natalizumab treatment (more than 2 years) and prior use of immunosuppressive therapy [31]. Further clinical experience with natalizumab has been limited by the PML risk, with approval in the USA, under strict vigilance of the TOUCH programme. It is also available in Russia and Switzerland but not in the European Union [1, 32–35].

AJM300 (Anti-α 4 Integrin)

AJM300 is an orally active and highly specific α4 integrin inhibitor with demonstrated efficacy in a murine model of colitis [36]. Takazoe and colleagues randomised 71 CD patients to receive placebo, oral AJM300 at 40 mg, 120 mg and 240 mg, three times daily for 8 weeks [38]. CDAI reduction at week 4, in AJM300 groups, was higher than in the placebo group, but differences were not statistically significant. The drug was well tolerated at doses of 120 mg and 240 mg three times daily [38]. Yoshimura and colleagues conducted a randomised double-blind placebo-controlled phase IIA trial in patients with moderately active UC [37]. A clinical response (primary endpoint) was achieved in 62.5% in the AJM300 group vs. 25.5% given placebo. Clinical remission rates (Mayo Clinic score ≤ 2 and no subscore >1) were 23.5% and 3.9% in the AJM300 group and placebo groups, respectively (OR = 7.81; 95% CI: 1.64–37.24; $P = 0.0099$), and rates of mucosal healing (endoscopic subscores of 0 or 1) were 58.8% and 29.4% (OR = 4.65; 95% CI: 1.81–11.90; $P = 0.0014$). No serious adverse events including progressive multifocal leucoencephalopathy were observed [37].

Vedolizumab

Vedolizumab is a humanised monoclonal IgG1 antibody which selectively binds to the α4β7 integrin and has been approved for the treatment of patients with moderate to severe UC and CD, by both FDA and the European Medicines Agency [38, 39]. Feagan and colleagues reported the first multicentre, double-blind, placebo-controlled trials of MLN 0002 in two separate studies of similar design [40, 41]. Patients received intravenous infusion of MLN 0002 at 0.5 mg/kg, 2.0 mg/kg or placebo on days 1 and 29. In the UC study with 181 patients, clinical remission at 6 weeks was achieved in 33%, 32% and 14% for the group receiving MLN 0002 at 0.5 mg/kg, 2.0 mg/kg and respectively ($P = 0.03$) [40]. Corresponding clinical response rates were 66%, 53 and 33%, respectively ($P = 0.007$). Endoscopic remission was achieved in 28% of patients receiving 0.5 mg/kg MLN 0002 and 12% of patients receiving 2.0 mg/kg, compared with 8% of those receiving placebo ($p = 0.007$) [40].

In the CD study in 185 patients, the primary efficacy endpoint of clinical response (>70-point decrement in the CDAI score) at 6 weeks was achieved in 53%, 49% and 41% in the 2.0 mg/kg, 0.5 mg/kg and placebo groups, respectively [41]. Clinical remission (secondary endpoint, CDAI < 150) was achieved in 37%, 30% and 21%, respectively. Clinically significant anti-vedolizumab antibody levels (titres >1:125) at day 57 were noted in 12% and 34% of patients in the 2.0 mg/kg and 0.5 mg/kg groups, respectively [41].

The GEMINI phase III studies were each of similar design in the induction phase. Randomised patients received intravenous VDZ 300 mg or placebo at weeks 0 and 2 [42, 43]. A separate open-label group received the same induction regimen. Clinical response was assessed at week 6, and responders were then randomly assigned to continue receiving VDZ (300 mg) every 8 weeks, every 4 weeks or placebo, for up to 52 weeks. All groups included patients with active inflammation despite conventional therapy (corticosteroids, immunosuppressive agents, anti-TNF therapy) and were stratified accordingly.

The GEMINI I study enrolled patients with active UC [42]. The primary endpoint for induction was clinical response at week 6 (a reduction in the Mayo score of ≥3 points and a decrease of at least 30% from baseline, with a decrease of ≥1 point on the rectal bleeding subscore, absolute score 0–1). The primary endpoint for maintenance therapy was clinical remission at week 52. Of 374 patients randomised to VDZ or placebo, clinical response at week 6 was achieved in 47.1% of the VDZ group versus 25.5% of the placebo group (95% confidence interval 11.6–31.7, $p < 0.001$). At week 52, 41.8% of patients assigned to VDZ 8 weekly, 44.8% assigned to VDZ 4 weekly and 15.9% of patients assigned to placebo were in clinical remission (8 weekly and 4 weekly compared with placebo, respectively). A Cochrane systematic review on the efficacy of VDZ included 606 patients from four studies [44]. Vedolizumab was significantly superior to placebo for induction of remission (RR = 0.86; 95% CI, 0.80–0.91), clinical response (RR = 0.82; 95% CI, 0.75–0.91), endoscopic remission (RR = 0.82; 95% CI, 0.75–0.91) and achieving remission at 52 weeks in week 6 responders (RR = 2.73; 95% CI, 1.78–4.18) [44].

The GEMINI II trial enrolled patients with moderate to severely active CD with objective evidence of inflammation (CRP > 2.87 mg/L, colonoscopic ulceration or faecal calprotectin >250 μg/g stool plus evidence of ulcers on imaging) [43]. The co-primary endpoints for induction were clinical remission (CDAI ≤150 points) and a CDAI-100 response (≥100-point decrease in CDAI) at week 6. The primary endpoint for maintenance therapy was clinical remission at week 52. Of 368 patients randomised to induction, clinical remission was achieved in 14.5% on VDZ versus 6.8% on placebo ($p = 0.02$). A CDAI-100 response was achieved in 31.3% on VDZ versus 25.7% on placebo ($p = 0.23$). At week 52, 39% receiving VDZ 8 weekly, 36.4% receiving VDZ 4 weekly and 21.6% receiving placebo were in clinical remission [43]. A Cochrane systematic review found vedolizumab to be superior to placebo for induction of remission (RR, 0.87; 95% CI, 0.79–0.95). Vedolizumab was efficacious for anti-TNF-naive (RR, 0.86; 95% CI, 0.79–0.94) and anti-TNF-exposed (RR, 0.89; 95% CI, 0.78–1.01) patients [21].

The GEMINI III trial enrolled patients with moderately to severely active CD, the majority of who (76%) had failed anti-TNF therapy [45]. The primary endpoint was clinical remission at week 6 in the anti-TNF failure subgroup. Secondary endpoints were clinical remission at week 10 and a CDAI-100 response at week 6 and week 10. Of 315 patients with CD and anti-TNF intolerance or failure, 15.2% on VDZ versus 12.1% on placebo achieved clinical remission at week 6 ($p = 0.433$). At week 10, more patients on VDZ achieved remission compared with placebo (26.6% versus 12.1%; 95% CI, 1.3–3.6; $p < 0.001$) [45]. Taken together, these three trials indicate that VDZ is moderately effective both for UC and CD in a group of patients refractory to conventional therapy including anti-TNF agents. It is noteworthy that the onset of action is relatively slow, often requiring 10 weeks or more of therapy.

Safety and Efficacy

Data on clinical efficacy and safety from prospectively followed cohorts are now available. In a recently reported GETAID study, patients with active IBD (CD = 173 and UC = 121), with an inadequate or loss of response to conventional therapy or at least 1 anti-TNF agent, received standard induction and maintenance doses of vedolizumab [46]. Concomitant use of corticosteroids, thiopurines or methotrexate was permitted. At week 14, 31% of patients with CD were in steroid-free clinical remission, and 51% had a response. Among patients with UC, 36% were in steroid-free clinical remission, and 50% had a response. Severe adverse events occurred in 24 patients (8.2%), including 15 (5.1%) that led to vedolizumab discontinuation (pulmonary tuberculosis in one patient and rectal adenocarcinoma in another). No deaths were reported [46]. Integrated long-term safety data (May 2009–June 2013) from the vedolizumab studies [42, 43, 45, 47, 48] have recently been published and show promising results [49]. Of 2830 patients with 4811 PYs of vedolizumab exposure (median exposure range, 1–1977 days), there was no increased risk associated with vedolizumab exposure. Clostridial infections, sepsis and tuberculosis were reported infrequently (≤0.6% of patients). Independent risk factors for serious infection in UC were prior failure of a TNF-α antagonist and narcotic analgesic use, and in CD these were younger age and corticosteroid or narcotic analgesic use. Eighteen vedolizumab-exposed patients (<1%) were diagnosed with a malignancy including non-melanoma skin cancer, malignant melanoma, colon cancer, breast cancer and renal, liver and lung cancer, with nearly all patients (except one with renal cancer) having had prior exposure to thiopurines and or anti-TNF agents [49]. Vedolizumab demonstrated a favourable safety profile over an extended period [49]. A recent systematic review did not detect any significant increase in either opportunistic infections or malignancy with either non-gut-specific or gut-specific anti-integrin antibodies compared to placebo [50]. Reassuringly, no cases of PML have been reported.

Much of the intrinsic appeal for vedolizumab lies in its gut selectivity without systemic immunosuppression. This was elegantly demonstrated in a randomised

trial showing reduced seroconversion following oral cholera vaccination against cholera toxin but no attenuation of serological response to parenteral hepatitis B vaccination following a single 750 mg dose of vedolizumab [51]. In the GEMINI trials, enteric infections (*Clostridium difficile* in six patients, *Campylobacter* in three and *Salmonella* in one) occurred after vedolizumab but not placebo [42, 43, 45]. Although the real potential for gut-specific immune inhibition to predispose to enteric infection will be borne out in the fullness of time, clinicians must remain vigilant with patients living in or travelling to the tropics and possibly in patients with risk factors for *Clostridium difficile* infection. Until recently there were no data that existed on the transmission of infection by live vaccines in patients receiving vedolizumab. The FDA label indicates that patients receiving the medication should receive live vaccines only if the benefits outweigh the risks. Wichmann et al. recently reported a case of a patient with Crohn's ileocolitis successfully vaccinated against measles virus while on vedolizumab [52]. This anecdotal success with a live vaccine on gut vedolizumab therapy despite making mechanistic sense needs to be studied further.

Practical Clinical Considerations

Vedolizumab has emerged as a viable, efficacious and indeed attractive option in the expanding biological armamentarium for IBD therapeutics. It is crucial for clinicians to understand how this drug will integrate into clinical practice with inevitable comparisons drawn with anti-TNF agents. Bayesian network meta-analyses aim to address this through indirect comparisons with a common comparator but are limited by the heterogeneity of patient populations studied and study design [53–55]. In one network meta-analysis of eight RCTs, the odds ratio for inducing remission in UC was comparable for anti-TNF agents and vedolizumab [55]. One network meta-analysis comparing vedolizumab to other biological therapies in CD found no significant differences [53], whereas another ranked infliximab as the most efficacious agent for induction (86%) and adalimumab for maintenance of remission (48%) [54].

Although induction efficacy of vedolizumab in Crohn's disease at 6 weeks appears to be less compelling, clinicians must pause to consider certain caveats in extrapolating from these results. Indeed, although clinical remission in CD was superior to placebo, no difference in CDAI-100 response or CRP was noted following induction [43]. It seems likely that the timing of assessment was the limiting factor as evidenced by the GEMINI III trial, wherein vedolizumab was superior to placebo for induction of remission at 10 weeks but not at 6 weeks, in patients who had previously failed anti-TNF therapy [45]. For maintenance of remission at 52 weeks, vedolizumab demonstrated superiority over placebo, with a magnitude of effect generally similar to that seen in UC [42, 43, 45]. Thus, although induction data with CD from trials are less compelling, the clearly clinically meaningful effect after 30 weeks suggests that vedolizumab is an appropriate option in well-selected

patients in whom the concomitant use of bridging strategies (such as co-induction with steroids) is possible and where surgery may not be more appropriate. Indeed, it might also be a first-line biologic option in patients where the focus is safety, for example, in young or elderly patients with IBD [56–58]. The role of vedolizumab in treatment of perianal disease is unclear. At 52 weeks in GEMINI II, 41.2% of the vedolizumab 8-weekly group achieved fistula closure compared with 22.7% of the vedolizumab 4-weekly group and 11.1% of the placebo group ($p = 0.03$, $p = 0.32$ versus placebo, respectively) [43]. This borderline significance needs further investigation. Indeed, a higher incidence of perianal abscesses was reported in preliminary data from the GEMINI-LTS extension study [49].

The safety and efficacy profile for UC may be regarded as more favourable, positioning vedolizumab as a potential first-line biologic for induction and maintenance of remission in outpatients with moderate to severe UC, who have failed or had an inadequate response to corticosteroids or immunosuppressant therapy. It cannot be recommended at the present time for the treatment of acute severe UC due to its relative slow onset of action and in the absence of data for this indication. There are no data for the perioperative safety and efficacy of vedolizumab in CD, and although the mechanism of action of vedolizumab, preventing early stages of inflammation, is appealing, clinical trials are needed to provide credible evidence. There are no data in patients with extra-intestinal manifestations of IBD. Although it seems implausible that a gut-selective agent should benefit those manifestations that do not parallel IBD activity (such as pyoderma gangrenosum or ankylosing spondylitis), manifestations associated with gut inflammation (e.g. erythema nodosum and episcleritis) may benefit, and this merits further study.

More promising is the prospect of treating primary sclerosing cholangitis (PSC) affecting 3–10% of IBD patients [59, 60]. Hepatic inflammation in PSC is driven by TNF-α and methylamines in the portal circulation and results in aberrant hepatic expression of MAdCAM-1 and the chemokine CCL25 [60]. This leads to enhanced recruitment of α4β7 and the CCL25 receptor CCR9. Randomised trials of VDZ in patients with IBD–PSC are under way (clinicaltrials.gov NCT00783692 and NCT01316939).

Although vedolizumab has not been associated with an increased risk of malignancy, long-term experience is limited, and indeed patients with prior malignancy were excluded from trials. Diminished gastrointestinal immune surveillance may pose a theoretical concern for colorectal cancer complicating UC or small intestinal adenocarcinoma in CD, given their increased risk relative to the general population. Nonetheless, carcinogenesis is a likely consequence of inflammation, and it is not implausible that control of inflammation by vedolizumab may reduce this risk [61, 62]. More research is needed in this area.

Vedolizumab is a pregnancy risk category B drug with limited data on safety in pregnancy. In a series of 24 women exposed to vedolizumab during pregnancy, there were 12 live births, five elective abortions and four spontaneous abortions [63]. With a half-life of 25 days, any strategy of withholding dosing in the third trimester could result in significant vedolizumab concentration in the foetus and prolonged drug clearance in the neonate potentially extending to 6–12 months, the

consequences of which are presently unknown. This could have implications on vaccination against enteric infections such as rotavirus (an oral vaccine) but possibly not parenteral agents commonly administered in the first year of life. No evidence-based recommendations can be made at the present time, and any intentional use in pregnancy would need to be discussed on a case-by-case basis. Data on vedolizumab use in the paediatric age group are limited to retrospective observational data in largely TNF-exposed patients, suggesting a remission rate of 100% at 14 weeks in three patients with UC, an improvement to the comparative 44% reported in nine Crohn's patients [64]. A phase III study of vedolizumab of patients 15 years and older is currently ongoing (ClinicalTrials.gov:NCT02039505), and a phase III PK/PD paediatric trial is about to start.

Therapeutic Drug Monitoring

The quantification of drug levels and anti-drug antibodies has garnered appropriate attention with supportive evidence for correlation between trough levels and therapeutic outcomes [65]. In the GEMINI studies, a positive correlation was noted between VDZ levels and efficacy [42, 43]. Dosing frequency (q4 or q8 weekly) had no effect on drug levels with both leading to α4β7 saturation in ≥95% serum lymphocytes. Anti-vedolizumab antibodies were noted in 1–4.1% of patients in GEMINI I and II of which 0.4–1% were persistently positive and concomitant immunosuppression was associated with reduced immunogenicity consistent with observations with anti-TNF therapy [65]. No difference in efficacy was noted between monotherapy and combination with immunosuppressive therapy in the GEMINI trials. They were, however, not powered for detection. That said, with much of the present appeal for vedolizumab is in its gut specificity and consequently its safety profile, monotherapy may find more favour in the light of present evidence. The availability of vedolizumab trough and antibody testing in the USA since May 2016 and data on its impact on clinical endpoints and decision making are eagerly awaited.

Head-to-head comparisons between vedolizumab and other biological agents and its role in special situations discussed above are now needed to better position it in current treatment paradigms of active IBD.

AMG 181

AMG 181 is a fully human (IgG2) α4β7 integrin antibody that, like vedolizumab, specifically inhibits binding to MAdCAM-1 but not VCAM-1. AMG 181 has showed in vitro pharmacology and pharmacokinetic and pharmacodynamic characteristics in cynomolgus monkeys rendering the compound suitable for evaluation in humans [66]. Results of phase I studies are not published yet.

PF-00547659 (Anti-MAdCAM-1)

PF-00547659 is a monoclonal IgG2 antibody directed against MAdCAM-1. MAdCAM-1 is expressed on vascular endothelium of the intestinal lamina propria and through its binding to α4β7, it regulates intestinal homeostasis of lymphocytes [8, 11]. In a multicentre, double-blind, placebo-controlled first-in-human study designed to explore the safety and efficacy of PF-00547659 in 80 patients with active UC, subjects received single or multiple (three doses at 4 weeks interval) doses of PF-00547659, 0.03–10 mg/kg, IV/SC or placebo [67]. Overall response and remission rates at 4 and 12 weeks were 52%, 42% and 22%, respectively, with combined PF-00547659 doses as compared to 32% and 21%, respectively, with placebo [67]. Equivalent endoscopic response rates were 50% and 42% vs. 26% and 29%, respectively. The study was not powered to detect statistically significant differences in clinical/endoscopic response or remission rates and biomarkers (secondary outcome measures). PF-00547659 was noted to be safe, well tolerated and devoid of immunogenicity. Although no statistically significant differences were noted, between drug and placebo, some benefits over clinical and endoscopic endpoints were seen. Of note, faecal calprotectin levels were significantly reduced in patients treated with PF-00547659 relative to placebo, lending support to the anti-inflammatory effect of the drug in the colon [67]. Phase II trials on induction (OPERA) and maintenance (OPERA II) in CD and phase II trials on induction (TURANDOT) and maintenance (TURANDOT II) in UC are in progress (http://www.clinicaltrials.gov).

Etrolizumab

Etrolizumab (rhuMAb β7) is a humanised monoclonal antibody against the β7 subunit of the heterodimeric integrins α4β7 and αEβ7. A phase I trial in subjects with moderate-severe UC (Mayo clinic score ≥ 5) suggested it to be safe and well tolerated [68]. The most common adverse effect was headache, followed by fatigue, abdominal pain and nasopharyngitis. Neither enteric nor respiratory infections were increased in the etrolizumab-treated group [68]. In a subsequent double-blind randomised placebo-controlled phase II trial (EUCALYPTUS) that studied the effects of etrolizumab on the induction of remission in patients moderate to severe UC, 124 patients were randomised to receive monthly SC injections, of either etrolizumab at 100 mg or 300 mg plus a loading dose (420 mg SC between weeks 0 and 2) or placebo [12]. After three doses, both dosing levels of etrolizumab were associated with higher rates of clinical remission compared with placebo at 10 weeks. In the 100-mg treatment group, 20.5% achieved clinical remission ($P = 0.004$), and in the 300 mg plus loading dose, 10.3% ($P = 0.049$) achieved clinical remission. None of the subjects (0%) receiving placebo achieved clinical remission. In subgroup analysis, the clinical efficacy of etrolizumab was demonstrated in anti-TNF-naive patients (43.8% and 25% at 100 and 300 mg + loading dose, respectively). Those with an inadequate response to prior anti-TNF therapy (n = 47) did not meet the primary

endpoint of clinical remission at either treatment dose in comparison to placebo (4.3% in the pooled etrolizumab treatment groups). Etrolizumab continued to demonstrate safety and tolerability. No serious infections were reported in the etrolizumab treatment groups, and there was no difference in drug-related adverse effects or adverse effects requiring discontinuation of therapy [12].

Several novel aspects of this trial make it a milestone in trial methodology and indeed IBD therapeutics. Firstly, the percentage of patients on placebo achieving remission at week 10 was zero. Placebo response rates in previously reported trials have ranged between 5.4 and 14.9% [5, 69, 70]. The rigorous use of central reading of endoscopic videos had never been implemented previously in trials of biological therapies but has recently been demonstrated to be of vital importance in correct patient enrollment [12, 71]. The assessment of the primary endpoint at 10 weeks may have contributed to the results and indeed may also have clinical implications for the assessment of response for anti-integrin therapy and the lessons learned from 6-week assessments in the vedolizumab studies [43, 45].

Pharmacodynamic studies of etrolizumab including the analysis of β7 occupancy and expression on T- and B-lymphocyte subsets in peripheral blood and colonic tissue, quantification of αE+ cells and gene expression of cytokines and adhesion molecules have possibly provided the first insights into additional predictive markers for response to treatment [12, 72]. Gene expression studies in colonic biopsies from anti-TNF-naive UC patients treated with etrolizumab showed higher baseline expression of T-cell-associated genes, including αE integrin and granzyme A messenger RNA (GZMA) in clinical remitters and also higher rates of mucosal healing in αE^{high} and $GZMA^{high}$ patients [72]. The potential for predictive biomarkers has exciting implications for further basic science research and indeed for personalised medicine in the complex pathobiology of IBD. Etrolizumab is currently being evaluated in phase III studies in both CD and UC (Clinical trials.gov).

Alicaforsen (Anti-ICAM-1)

Alicaforsen (ISIS 2302) is an antisense oligonucleotide directed against human intercellular adhesion molecule (ICAM)-1 and is expressed at low levels in endothelial cells and leucocytes. Interest in ISIS 2302 as a potential therapeutic agent stemmed from the observation that ICAM-1 is overexpressed in the inflamed intestine of CD patients [73]. In a pilot study of 20 patients with active CD, 13 infusions of different doses of ISIS 2302 or placebo over 26 days, ISIS 2302 demonstrated superiority over placebo for corticosteroid-free remission [74]. A subsequent double-blind, placebo-controlled trial did not show significant efficacy between 2- and 4-week alicaforsen groups compared to placebo (20.2% and 21.2% vs. 18.8%) [75]. Schreiber and colleagues conducted a dose-interval, multicentre, placebo-controlled trial in 75 patients with steroid-refractory CD [76]. The primary endpoint (steroid-free remission at week 14) was only achieved in 2 of 60 (3.3%) alicaforsen-treated patients and none in the placebo-treated group. No further studies have been performed using alicaforsen in CD.

The first evaluation of alicaforsen in UC, a randomised double-blind placebo-controlled escalating dose trial of 40 patients with mild-moderately active UC, evaluated the efficacy and safety of alicaforsen enemas administered in four different doses [77]. Alicaforsen enemas resulted in a dose-dependent improvement in DAI (overall $P = 0.003$). The drug was well tolerated with no major safety issues.

The local and systemic availability of alicaforsen enema, as also its activity when administered once daily, was assessed in UC patients in an open-label study of 15 subjects who received nightly enemas of alicaforsen (240 mg) over 6 weeks [78]. A 46% reduction in mean DAI and a 33% rate of remission as defined by complete mucosal healing were observed at the end of treatment. In an open-label trial in 12 patients with chronic, unremitting pouchitis, treated with 240 mg alicaforsen antisense enema nightly for 6 weeks, alicaforsen appeared to improve the PDAI score, clinical symptoms and endoscopic mucosal appearance [79]. In a recent case series, alicaforsen enemas significantly reduced clinical and endoscopic disease 2–3 months after therapy [80]. The enema formulation is currently being evaluated in a phase III study for chronic antibiotic refractory pouchitis (http://www.clinicaltrials.gov: NCT02525523). Taken together, alicaforsen has shown conflicting data for CD patients but more promising data for UC. The relative lack of efficacy may be due to the non-dominant role of ICAM-1 expression in the inflammatory response in IBD [81].

Conclusion

Anti-adhesion therapies are a welcome addition to the expanding armamentarium of IBD treatment with gut specificity of newer agents being particularly appealing. The potential for predictive biomarkers has exciting implications for further research and holds promise for personalised medicine. Future studies will provide further insights from real-world data on remission and impact on mucosal healing, hospitalisation and surgery. Data in specific patient populations (e.g. pregnancy, extremes of age, prevention of postoperative recurrence and malignancy) are much needed.

Meanwhile, evolving understanding of the complex immuno-inflammatory pathways has already seen the development of a plethora of agents with several others in the pipeline. Targeting adhesion molecules appears to represent a fitting piece in the daunting puzzle of the aetiopathogenesis of IBD. The prospect of further intellectual effort invested in this mechanism being rewarded through clinically meaningful outcomes for our patients is now realistic.

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Chapter 17
Novel Agents in Inflammatory Bowel Disease

Fernando Velayos

Every new treatment for inflammatory bowel disease (IBD) is, by definition, novel at some level. That a treatment is new, of course, does not always equate to the more commonly understood definition of novel: interesting, groundbreaking, or transformative. For nearly two decades, novel therapies for IBD have primarily targeted the same cell signaling cytokine, tumor necrosis factor alpha (TNF-α). TNF is a key cytokine in inflammatory pathways, and dysregulation of TNF production has been implicated in both ulcerative colitis (UC) and Crohn's disease (CD). This strategy has been and continues to be effective but not wholly effective. Nearly a third of patients do not respond to this strategy and others flare despite initial control [1].

This chapter focuses primarily on novel agents other than anti-TNFs that have either been recently released or under late-stage investigation and likely to progress to market. They can be broadly grouped into either (1) inhibitors targeting white blood cells from migrating to areas of injury and perpetuating their local inflammatory effect or (2) inhibitors of the inflammatory cascade. The agents reviewed in this chapter, besides new, are interesting in that they elucidate what pathways and molecules other than TNF are important in IBD and whether the traditional monoclonal antibody strategy is the only viable strategy for treating IBD (Table 17.1). They have the promise of being groundbreaking or transformative either in their efficacy, mechanism of action, or route of delivery. This list of course is not exhaustive and always changing. The chapter focuses less on early stage compounds as their progress into advanced stages of clinical development can be quite variable, dependent on internal data, funding, and other priority factors that may have nothing to do with science.

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Table 17.1 Novel biologic agents by mechanism of action and current status

Crohn's disease	Mechanism	Ulcerative colitis
Vedolizumab (approved)	Anti-integrin	Vedolizumab (approved)
Etrolizumab (phase III)		Etrolizumab (phase III)
PF-00547659 (phase II)		PF-00547659 (phase II)
Ozanimod (phase II)	Sphingosine-1-phosphate inhibitor	Ozanimod (phase III)
Ustekinumab (approved)	Anti-IL12 and/or IL23	Ustekinumab (phase III)
Risankizumab (phase II)		
Filgotinib (phase III)	Janus kinase inhibition	Tofacitinib (awaiting approval)
		Filgotinib (phase III)
Mongerson (phase III)	Anti-SMAD7	Mongerson (phase II)

Leukocyte Trafficking Antagonists

Vedolizumab (Anti-α4β7 Integrin, Monoclonal Ab, IV Route, UC/CD)

Vedolizumab, a monoclonal antibody that targets the α4β7 integrin, was approved by the FDA in May of 2014 for use in UC and Crohn's disease. α4β7 integrin, a cell-surface glycoprotein variably expressed in circulating B and T lymphocytes, interacts with mucosal vascular addressin cell adhesion molecule-1 (MAdCAM-1), its counter-receptor found preferentially in the intestinal vasculature [2]. By blocking the α4β7 integrin, vedolizumab mediates leukocyte trafficking to the gut [3]. The integrins found to be important for the gastrointestinal tract include α2β2, α4β1, and α4β7 [4]. They can, of course, be found in other organs as well besides the gut.

Vedolizumab is not the first anti-integrin approved for the treatment of IBD. Natalizumab, a monoclonal antibody that targets both the α4β1 and α4β7 integrins found in the gut, blocks trafficking not only in the gut but also the brain. α4β1 integrins are also involved in leukocyte trafficking in the brain [2]. Natalizumab was approved by the FDA in January 2008 for use in moderate to severe Crohn's disease. Although efficacy data was compelling [5], reports of a 2.1 per 1000 risk of progressive multifocal leukoencephalopathy (PML) [6], a serious brain infection, relegated its use to second-line salvage therapy. The typical patient is low risk for PML (negative JC virus serology) and has failed TNF therapy [7].

In contrast to natalizumab, vedolizumab more selectively targets the α4β7 integrin receptor, found primarily in gut-specific lymphocytes. It does not target the α4β1 integrin, found in the gut and the brain [8]. Based on this gut-selective mechanism, the lack of reported cases of PML to date [9], and clinical trial data [2, 8], it was FDA approved as first-line therapy for the treatment of moderate to severe Crohn's disease and ulcerative colitis. Specific monitoring for PML or JC virus serology is not required.

Phase III randomized controlled trials provide the evidence base demonstrating the efficacy of vedolizumab. GEMINI I enrolled patients with moderate to severe

ulcerative colitis [2]. After induction, vedolizumab-treated patients had greater rates of response, remission, and mucosal healing at week 6 of the trial compared to placebo. These favorable data persisted at week 52 during the maintenance phase of the trial. The maintenance phase included an every 4 week and every 8 week arm, both which showed similar outcomes. There were no differences in adverse events among the groups and no cases of PML were identified.

GEMINI II enrolled patients with moderate to severe Crohn's disease [8]. After induction, vedolizumab-treated patients achieved a statistical greater rate of remission at week 6, but missed the second co-primary endpoint, reduction in the Crohn's Disease Activity Index by 100 points. However at week 52 in the maintenance trial, vedolizumab-treated patients had greater rates of clinical remission (primary endpoint) as well as other key outcomes (reduction in the CDAI by 100 points and steroid-free remission). No cases of PML were identified; however, the incidence of serious adverse events, infections, and serious infection was noted to be higher in the vedolizumab-treated group. These were not further elaborated in the manuscript and not seen in the ulcerative colitis clinical trial.

GEMINI III was an induction trial focusing on moderate-severe Crohn's patients who failed TNF therapy [10]. Patients received vedolizumab at 0, 2, and 6 weeks and the primary outcome was measured at week 6. Although rates of remission between the vedolizumab-treated group and placebo were similar at week 6, rates of response were higher in the vedolizumab-treated group at this time point. The vedolizumab-treated group achieved greater rates of remission not at week 6 but several weeks after induction, at week 10. There were no differences in adverse events in this induction trial and no cases of PML were identified.

Etrolizumab (Anti-α4β7 and αEβ7 Integrin, Monoclonal Ab, SC Route, UC/CD)

Ertrolizumab is a monoclonal antibody with a dual anti-integrin mechanism of action. It blocks the β7 subunit of both the α4β7 and αEβ7 integrins, resulting potentially in a very novel mechanism of action compared to vedolizumab [11]. Besides inhibiting gut-specific α4β7 lymphocytes from homing and migrating to the gut, etrolizumab uniquely blocks the interaction between αEβ7 and E-cadherin [12]. The E-cadherin gene has been implicated in IBD through genome-wide association studies. Cadherins are important in preserving intestinal barrier function. Thus, etrolizumab can have an additional beneficial effect of controlling inflammation at the mucosal level by inhibiting αEβ7 lymphocytes from entering the epithelium [11, 13].

The data for etrolizumab will be informed by an extensive and novel phase III clinical trial program, for which studies are ongoing. In EUCALYPTUS, a phase II randomized controlled trial, etrolizumab showed to be an effective induction agent for moderate to severe UC [12]. More patients treated with etrolizumab were in remission at week 10 compared to placebo. Adverse events occurred at a similar frequency in the treated and placebo groups. Although no cases of PML were

detected and its mechanism of action should not increase the risk of PML, this was a short-term induction study, thus requiring a larger and longer-term trial to more appropriately assess this outcome.

One milestone of this study was the finding of a 0% remission rate in the placebo group, thought to be in part to the use of central readers and entry criteria [11]. Another interesting post hoc exploratory analysis from the phase II study suggested a possible heterogeneity in treatment benefit or patients with varying αE concentration. The finding that baseline colonic αE expression could improve response to etrolizumab and that treatment reduced αE+ lymphocytes in the epithelium suggests that αEβ7+ lymphocytes contribute to the pathogenesis of UC and that specific blockade of these lymphocytes could provide a novel dual therapeutic approach to treatment [12]. These hypotheses, of course, will need further study and testing in the longer-term phase III trials.

The phase III trial program for etrolizumab includes at least eight studies, including one in Crohn's disease, and is novel for several reasons. Besides using standardized centralized endoscopic scoring, it will also be the first phase III trials to perform head-to-head biologic comparison to anti-TNF therapy (infliximab in one trial, adalimumab in another).

PF-00547659 (Anti-MAdCAM-1, Monoclonal Ab, SC Route, UC/CD)

PF-00547659 is a monoclonal IgG2 antibody directed against mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1) [14]. MAdCAM-1, found in the endothelium of venules, preferentially binds leukocytes expressing α4β7 receptor integrins in the gut and results in migration of lymphocytes from the bloodstream into the intestine and promotion of the inflammatory cascade locally [15]. Thus, while PF-00547659 is similar to vedolizumab and etrolizumab in that it prevents migration of α4β7-expressing lymphocytes from migrating to the gut, it works quite differently by blocking the effector receptor in the intestinal vasculature (MAdCAM-1) as opposed to its α4β7 integrin ligand on the lymphocytes [1].

Phase III clinical trials using this molecule are reportedly planned. TURANDOT, a phase II randomized controlled trial, enrolled patients with moderate to severe ulcerative colitis [14]. This induction study achieved its primary endpoint, clinical remission at week 12. There was no increased incidence of infection, including in MAdCAM-1 bearing tissues (gastrointestinal tract, nasal tissue, spleen, bladder, uterus, and lung). There were no cases of PML in this short-term induction study. Even though mechanistically there is low concern for PML, nonetheless this question is best addressed in longer-term studies. TURNADOT II is the open-label long-term treatment study which is ongoing but no longer recruiting. The estimated completion date is December 2017.

OPERA I, a phase II randomized controlled clinical trial, enrolled patients with moderate to severe Crohn's disease [16]. This induction study missed its primary

endpoint, a reduction of 70 points in the CDAI at week 12, and this was attributed to a high placebo response rate. A statistically significant difference in response to those with an elevated CRP (above 18) suggested that perhaps better identifying those with true inflammation would help in trial design. There were no cases of PML in this short-term induction study. OPERA II is a phase II open-label long-term treatment study that completed in July 2016.

The central nervous system is constitutively devoid of MAdCAM-1; thus the strategy of blocking MAdCAM-1 should not result in cases of PML. As corroborating data that this strategy should not be associated with PML, the TOSCA study performed up to two lumbar punctures in 24 patients with Crohn's who received PF-00547659 after failing TNF therapy [17]. The results showed no change in the CSF lymphocytes, supporting a CNS-sparing mechanism with this drug.

Ozanimod (SIP Receptor 1 and 5 Agonist, Small Molecule, po Route, UC/CD)

Ozanimod is a small molecule inhibitor with a different strategy than other leukocyte anti-trafficking strategies discussed above. Instead of inhibiting circulating lymphocytes from entering injured/inflamed tissue through blockade of the α4β7 integrin or its counter-receptor, MAdCAM-1, ozanimod effectively traps lymphocytes at the earliest phase of trafficking [1]. Besides the novel mechanism of action, this drug is also novel in that it is an oral medication.

Ozanimod traps lymphocytes through internalization and degradation of the sphingosine-1-phosphate receptor (S1P) found on the lymphocytes [18]. Without the S1P receptor, the lymphocyte is unable to respond to S1P expressed along the lymphatic endothelium, a necessary step for activated lymphocytes to leave the lymph nodes. The arrest of lymphocytes in the lymph nodes leads to a reversible reduction of circulating lymphocytes in the blood.

There are five S1P subtypes (S1P1 through S1P5), responsible for regulating multiple immunologic and cardiovascular effects [18]. S1P1–3 are expressed ubiquitously, S1P4 is generally confirmed to lymphoid cells and tissues, and S1P5 is predominantly located in the central nervous system [19, 20]. Ozanimod blocks two of these subtypes, primarily subtype 1 but also subtype 5. Blockade of subtypes 2, 3, and 4 is associated with cardiovascular issues (bradycardia, second-degree AV block), elevated aminotransferases, and macular edema. Blockade of subtypes 1 and 5 in patients with multiple sclerosis showed reduction in brain lesions with minimal effect on heart rate and liver enzymes [18].

A phase III randomized controlled trial is underway in UC. TOUCHSTONE, a phase II randomized controlled trial, recruited patients with moderate to severe UC [18]. This study achieved its primary induction primary endpoint, clinical remission at 8 weeks over placebo. It also achieved its primary maintenance endpoint, clinical remission at week 32 [18]. Treatment with ozanimod at the highest-dose group reduced circulating lymphocytes by 49% with no significant side effects. Even so,

the study was deemed as preliminary by the authors [18]. The reasons were size of the study (around 65 patients per group) and insufficient duration to establish clinical efficacy or assess safety. A phase II study in Crohn's disease is ongoing but not recruiting patients. Estimated completion date is September 2018.

Inflammatory Cascade Antagonists

Ustekinumab (Anti-IL12 and Anti-IL23, Monoclonal Ab, IV then SC Route, UC/CD)

Activated lymphocytes, if allowed to leave the lymph node and enter the gut, will participate in the local and dysregulated inflammatory cascade that includes various cytokines [1]. The traditional anti-cytokine strategy in IBD had been to target tumor necrosis factor α. New data show this is not the only potentially successful target.

Ustekinumab, a monoclonal antibody that targets interleukins IL12 and IL23, was approved by the FDA in September 2016 for use in moderate to severe Crohn's disease. Genome-wide association studies have shown an association between the IL12/IL23 pathway and CD, and the IL12/IL23 pathway is an important driver of inflammation in adaptive immune responses [21, 22]. Ustekinumab, an interleukin inhibitor, blocks the p40 subunit of IL12 and IL23 and prevents their interaction with the IL12Rb1 receptor on the surface of T cells, natural killer cells, and antigen-presenting cells. The result is inhibition of IL12- and IL23-mediated cell signaling, activation, and cytokine production [22, 23].

Phase III randomized controlled trials provide the evidence base demonstrating the efficacy of ustekinumab in additional to a large phase IIb clinical trial. CERTIFI, a phase IIb randomized controlled trial, enrolled patients with moderate to severe Crohn's disease resistant to TNF antagonists [24]. Patients were enrolled in an 8-week intravenous induction and then a 28-week subcutaneous maintenance trial. The study met its primary endpoint response at week 6. There was no difference in remission at week 6; however rates of remission and response were superior at the end of maintenance.

The phase III randomized controlled trials (UNITI) enrolled patients who failed TNF (UNITI-1) or who were biologic naïve (UNITI-2) to receive a single intravenous induction dose of ustekinumab followed by subcutaneous maintenance for 44 weeks (IM-UNITI) [25]. The induction studies met their primary endpoint, clinical response at week 6. The maintenance study also met its primary endpoint, remission at week 52 of the trial (week 44 of maintenance). Adverse effects were similar among the groups.

The formulation and trial are novel in that it involves an intravenous formulation for induction and then a subcutaneous formulation for maintenance and that the trial specifically enrolled and demonstrated efficacy in TNF failures. Previous studies have used the same formulation (intravenous or subcutaneous injection) for both the induction and maintenance phases and permitted TNF failures, but did not

specifically seek this group as a population of interest. A phase III randomized clinical trial in ulcerative colitis is recruiting patients with an estimated primary completion date of April 2018.

Risankizumab (Anti-IL23, Monoclonal Ab, IV Route, CD)

Unlike ustekinumab, which blocks both IL12 and IL23 through a shared p40 subunit, risankizumab, a monoclonal antibody, more selectively blocks IL23 by targeting its p19 subunit. Although no phase III studies are currently registered, a recently completed phase II randomized clinical trial in Crohn's disease showed it met its induction efficacy endpoint, clinical remission at week 12 for its higher dose arm [26]. An open-label, long-term extension safety study is ongoing but not recruiting participants. Its estimated completion date is October 2019. The FDA has granted the drug orphan status for the investigational treatment of pediatric Crohn's disease [27].

Tofacitinib (Anti-JAK1-3, Small Molecule, po Route, UC)

There are four known Janus kinase subtypes, JAk1, JAK2, JAk3, and TYK2. Tofacitinib inhibits three of the subtypes, primarily JAK1 and JAK3 and to a lesser extent JAK2 [28]. When cell-surface receptors for various cytokines interact with JAKs, signal transduction pathways are activated (JAK-STAT pathway), resulting in the selective production of messenger RNA and synthesis of critical proinflammatory cytokines, primarily interleukins [28, 29]. Inhibition of the JAK-STAT pathway through the use of JAK inhibitors such as tofacitinib downregulates these various inflammatory mediators.

Phase III randomized controlled trials provide the evidence base demonstrating the efficacy of tofacitinib. The OCTAVE phase III clinical trial program enrolled patients with moderate-severe ulcerative colitis [30]. OCTAVE 1 and 2 were 8-week induction studies and met the endpoint of clinical remission at week 8. Increased levels of serum lipids and creatinine kinase were observed in patients treated with tofacitinib. In the maintenance trial, OCTAVE Sustain, the primary endpoint, remission at week 52, was met [31]. There were no new adverse events. There were more frequent infections in the tofacitinib group, a dose-dependent increase in herpes infections, and no intestinal perforations, and there were changes in lipid and creatinine kinase profiles, consistent with results from prior studies. The drug is currently under FDA review. Two phase IIb randomized control trials in Crohn's disease were negative for both induction and maintenance [32].

The novel aspects of these trials and this agent are that central readers were used to assess mucosal inflammation and that this therapy is oral, a significant advance in ease of administration compared to infusions and subcutaneous injections.

Filgotinib (Anti-JAK1, Small Molecule, po Route, UC/CD)

Similar to tofacitinib, filgotinib is an oral small molecule directed against the JAK-STAT pathway. Unlike tofacitinib, which is a pan JAK kinase inhibitor, filgotinib is a JAK1 selective inhibitor, with 30–50x greater affinity to JAK1 than JAK2 or JAK3 [33].

A phase III randomized controlled trial is underway in CD and UC. FITZROY, a phase II randomized controlled trial, recruited patients with moderate to severe CD [33]. This study achieved its primary induction endpoint, clinical remission at week 10 over placebo. Patients were then followed for an additional 10 weeks to assess safety. At 20 weeks, filgotinib-treated patients had higher rates of serious infections. Filgotinib-treated patients also had some elevations in lipids (both LDL and HDL), similar to what was observed with tofacitinib. Longer-term safety data are needed to more accurately determine if more selective JAK inhibition reduces the risk of infection.

This study and molecule is novel and important in suggesting that selective Janus kinase inhibition may not completely protect against infection. Also notable and perplexing is that this study showed filgotinib was effective for treating Crohn's while another JAK kinase inhibitor, tofacitinib, was not.

Mongerson (Anti-SMAD7, Small Molecule, Oral Route, UC/CD)

Mongerson is an oral Smad7 antisense oligonucleotide that normalizes activity of transforming factor (TGF-β1), an immunosuppressive cytokine [34, 35]. Gut inflammation reduces TGF-β1 activity, thereby suppressing an important counter-regulatory cytokine. This is due to increased levels of SMAD7, an intracellular protein that binds the TGF-β receptor and prevents TGF-β1-associated anti-inflammatory signaling. Mongerson hybridizes to SMAD7 messenger RNA, mediating degradation and downregulation of SMAD7 and normalizing TGF-β1 activity [36].

A phase III randomized clinical trial in Crohn's disease is underway based on a very promising phase II randomized clinical trial. In a phase II induction trial, the primary outcome was met, clinical remission at day 15 with maintenance of remission for at least 2 weeks. The novelty of this study and this compound goes beyond the simple novelty of not being an anti-TNF [37]. For one, it is an oral compound, which is quite attractive as a treatment delivery system. Second, it targets the counter-regulatory processes of Crohn's by restoring the body's natural anti-inflammatory cytokine, TGF-β1. In contrast, anti-TNF strategies and the other cytokine-based targets presented in this chapter target the proinflammatory cytokine pathways. The third is the unprecedented rate of remission after only 2 weeks of therapy, between 55 and 65%, for the two highest-dosing groups. Fourth is that the

drug appears to work locally and not bioavailable systemically. Last, and perhaps most novel, is that clinical remission was maintained for almost 3 months even though the drug was administered for only 14 days.

Phase III studies are critical, more than for other compounds to confirm these results [37]. The inclusion criteria in the phase II trial used only symptoms and not more objective criteria for active disease, such as endoscopy. The median level of C-reactive protein was low and 39% of patients did not have an elevated level. Finally the endpoint also used only symptoms and did not include more objective markers such as mucosal healing or normalization of fecal calprotectin or C-reactive protein. These more objective inclusion criteria and endpoints are part of the current phase III randomized control trial. The current trial is designed also to better assess safety.

Of all the novel agents discussed in this chapter, this agent is potentially the most transformative. Based on the available data and its mechanism of action, this agent presents a possibly novel approach to treatment: short cycles of mongerson to restore immunoregulatory processes and bring about a durable remission without continuous maintenance therapy. A phase II randomized controlled trial in ulcerative colitis is currently ongoing but not recruiting patients.

Conclusion

It is clear from the number and breadth of recently approved or late-stage development agents that the treatment of IBD is expanding beyond anti-TNF therapy. These novel agents are not novel because they are new but because they are interesting, groundbreaking, and transformative. From novel strategies and mechanisms of action to reduce inflammation, to introduction of oral therapy, to introduction of possible intermittent therapy with antisense oligonucleotide therapy, each new agent educates us on what are the key molecules in IBD and potentially one step closer to a cure.

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Chapter 18
Quality, Safety, and Practical Considerations of Using Biologic Therapies

Leilei Zhu and Gil Y. Melmed

Introduction

Biologic medications including anti-TNF, anti-integrin, and anti IL12/IL23 therapies represent an important step in the treatment of inflammatory bowel disease (IBD), as these drugs induce remission and achieve clinical response [1]. Although generally safe, biologics may place the patient at a small increased risk for developing infections and malignancy, the latter likely more relevant when in combination with thiopurines [2]. The US Food and Drug Administration (FDA) added "boxed warnings" about the increased risk of serious infections and malignancy for the entire class of anti-TNF agents [3–6], although subsequent experience and research have demonstrated that these medications are generally safe when used appropriately. Successful and safe use of biologic therapies requires an understanding of contraindications, appropriate patient education, screening and baseline lab testing, and vaccination schedules prior to initiation or during biologic therapy. In addition, drug selection, proper administration, safety monitoring during treatment, and monitoring after treatment discontinuation are important to understand the appropriate use of these medications. The purpose of this chapter is to provide quality, safety, and practical considerations when using biologic therapies in patients with IBD (Fig. 18.1).

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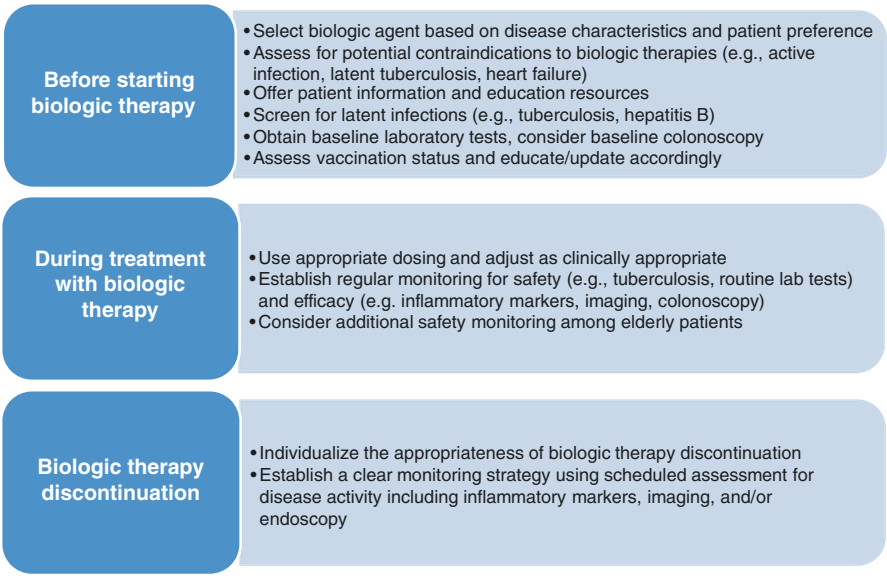

Fig. 18.1 Practical strategies for improving safety of biologic therapies

Choice of Biologic Agents

There are eight FDA-approved biologic agents to treat IBD, generally indicated for patients with active disease despite conventional therapy or corticosteroids, or for those patients at increased risk for disease complications [7, 8], including five anti-TNF agents. These agents include infliximab (Remicade®) for CD and UC, adalimumab (Humira®) for CD and UC, certolizumab pegol (Cimzia®) for CD, golimumab (Simponi®) for UC, and one biosimilar to infliximab (Inflectra®); two integrin receptor antagonists, including natalizumab (Tysabri®) for CD and vedolizumab (Entyvio®) for CD and UC; and one anti IL12/23 agent, ustekinumab (Stelara®) for CD. Anti-TNF-α agents are the most widely used first-line biologic agents, although vedolizumab is an appropriate first-line biologic treatment for UC [7]. The positioning of ustekinumab for CD has yet to be determined in guidelines and clinical practice. The uptake of natalizumab has been limited by an associated small increased incidence of PML. There are no head-to-head prospective, randomized trials of biologic agents to guide decision-making for positioning one anti-TNF over another on the basis of safety or efficacy [9]. The mode of the administration and cost of therapy have become important factors to be considered when choosing a biologic agent. The number and frequency of injections or infusions, the type and ease of injections, access and time for intravenous therapies, and insurance company formulary restrictions can all impact the decision of which biologic to start. Another consideration for distinguishing among biologic therapies is the availability of commercial assays for drug and antidrug antibody assays. Thus, in addition to safety and efficacy considerations, patients should be informed of the advantages

and disadvantages of the different options and be involved in the decision as to which biologic may be best for them [10].

Notably, over one-third of patients do not respond to the initial anti-TNF-α agents at all, and among those with an initial response, 23–46% of patients lose response over time [11]. In cases of loss of response to anti-TNF-α therapy, reduction in interval between doses or dose escalation may be appropriate strategies before switching to another agent [12]. Measurement of drug concentration and antidrug antibody levels has been shown to be a cost-effective strategy given the ability to optimize biologic therapies [13]. The use of therapeutic drug monitoring to guide decision-making [14] is beyond the scope of this chapter and is discussed elsewhere (Chap. 8).

Appropriate Administration

Currently, all biologic agents for IBD are administered either by intravenous (IV) infusion or subcutaneous injection. Infliximab is given through IV infusion over 2 h; adalimumab, certolizumab pegol, and golimumab are administered by subcutaneous injection; natalizumab and vedolizumab are given through IV infusion over 30 or 60 min; and ustekinumab is administered via single intravenous loading dose followed by subcutaneous maintenance doses. Quality control around drug handling and administration is critically important for the safe use of biologics. Product mishandling includes exposure to extremes of temperature or pH, agitation, pumping operations, freeze-thawing, and exposure to light, which can cause protein aggregation, potentially triggering immunogenicity in a patient after months of successful treatment, and may contribute to the loss of response and infusion reactions to biologic agents. Thus, clinical staff in infusion centers must carefully follow the product instructions to minimize product degradation [15]. Subcutaneously administered agents also require proper training to patients and/or their caregivers on the right way to prepare and inject these agents. Patients should be comfortable and confident with their ability to self-administer injections at home and to comply with manufacturer instructions regarding the need for appropriate temperature control, light exposure, and undue manipulation/shaking of biologic products.

Before Starting Biologic Therapies

Appropriate Patient Selection

Before starting biologic therapy, contraindications should first be considered. A thorough history should be obtained to exclude any active untreated infection, untreated latent tuberculosis, known hypersensitivity to the biologic agents, and congenital or acquired immunodeficiency [16]. Anti-TNF should not be used in patients with moderate-to-severe heart failure (New York Heart Association

Table 18.1 Checklist of contraindications to assess before starting biologic therapy

Contraindications	Anti-TNF	Anti-integrin	Anti IL12/IL23
Any active untreated infection	X	X	X
Untreated latent tuberculosis	X	?	X
Moderate-to-severe heart failure (NYHA class III/IV)	X		
Personal history of multiple sclerosis or optic neuritis	X		
Known hypersensitivity to biologic agents	X	X	X
Present or prior malignancy or history of lymphoma	?	?	?
Have or have had progressive multifocal leukoencephalopathy (PML)	?	X	?
Have reversible posterior leukoencephalopathy syndrome (RPLS)	?	?	X

[NYHA] functional class III/IV) or a personal history of multiple sclerosis or optic neuritis [3–6]. Integrin receptor antagonists are contraindicated in patients who have or have had progressive multifocal leukoencephalopathy (PML) [17, 18]. Ustekinumab, approved for moderate-to-severe Crohn's disease, binds to p40, a common subunit of the IL12 and IL23 receptors, and should not be used in those with reversible posterior leukoencephalopathy syndrome (RPLS) [19] (Table 18.1).

Patient Education

Due to the potential serious risks and significant cost of biologic therapies, it is important for patients to make an informed decision after thoroughly understanding potential risks, the benefits to their disease and quality of life, and the high cost associated with these therapies.

Patients should receive adequate education on the expected course of their disease state without biologic therapy, the anticipated benefits to disease activity from appropriate treatment, potential benefit to their quality of life from biologic therapy, and the risks of therapy [20]. Clinicians play a critical role in patient education about the risks of their disease and the benefits and risks of therapy, to facilitate decisions that are in line with their personal preferences for treatment [21]. In addition, patients should be familiar with the medication administration, prescribed regimen, and the importance of treatment adherence. Furthermore, financial implications of treatment should be discussed, given the expense of treatment and the need for maintenance therapy; these can be contrasted to the costs of uncontrolled disease and potential complications [22].

Patient education can take many forms, including face-to-face discussions with the physician and/or nurse, provision of educational materials [20], referral to professional organizations such as the Crohn's & Colitis Foundation of America (CCFA, http://ccfa.org) and European Crohn's and Colitis Organisation (ECCO,

https://www.ecco-ibd.eu), and reputable Internet sites. Although patients can get reliable and easily understandable information about almost all aspects of IBD from these resources, they should be encouraged to discuss questions and concerns with their prescribing healthcare provider.

Screening Tests

Prior to starting biologic therapy, appropriate screening to identify active and latent infections should be performed. When any active or latent infection such as *Clostridium difficile* (*C. difficile*), *Cytomegalovirus* (CMV), or Epstein-Barr virus (EBV) is identified, biologic therapies should generally be deferred until appropriate treatment has been initiated or until clinical resolution of the active infection.

Anti-TNF Therapy

Before starting anti-TNF therapy, screening for latent tuberculosis (TB) and hepatitis B virus (HBV) should be performed, and doing so is an indicator of good quality of care [23]. In addition, screening for other infections should be considered based on patient-specific factors (i.e., travel to endemic areas for various infectious) and geographic risk (i.e., histoplasmosis in high-risk regions) (Table 18.2).

Risk factors for latent TB include a prolonged stay (>3 months) in a high TB incidence area, close contact with patients with active TB, radiological evidence of

Table 18.2 Suggested checklist of screening and baseline tests before starting biologic therapy

• Appropriate screening to identify active and latent infections as clinically warranted
• Anti-TNF therapy screening tests
– Latent tuberculosis (TB)—PPD[a] skin test or IGRA[b]test, CXR as indicated for higher-risk individuals
– Hepatitis B virus (HBV)—HBsAg, HBsAb, HBcAb
• Anti-integrin therapy screening test
– Anti-JCV antibody test (prior to initiation of natalizumab)
– Screening of TB (according to the local practice before vedolizumab)
– Screening of HBV and other hepatitis viruses (provider discretion)
• Anti-IL12/IL23 (ustekinumab)
– Latent tuberculosis (TB)—PPD[a] skin test or IGRA[b]test, CXR as indicated for higher-risk individuals
• Baseline tests before all biologics
– Complete blood counts, chemistries with liver enzymes, inflammatory markers (sedimentation rate, CRP, with or without fecal calprotectin)
– Consider colonoscopy and/or small bowel imaging, as clinically warranted

[a]Purified protein derivative
[b]Interferon-γ release assays

previous TB infection or having undergone previous treatment for active TB or latent TB infection [24]. There are no 100% specific or 100% sensitive methods for diagnosing latent TB infection. All patients should have a tuberculin skin test (TST) or interferon-γ release assay (IGRA) test and a chest X-ray as indicated for higher-risk individuals. It is important to recognize that concurrent immunosuppressive therapies such as corticosteroids are associated with anergy and false-negative skin test results can occur [25]. It is generally recommended to replace the TST with IGRA, which is more specific and sensitive [24]. Patients screening positive for latent TB should begin a 6-month course of antituberculosis therapy prior to initiation of biologic therapy, and while the duration of treatment for latent TB prior to initiation of anti-TNF therapy has not been definitively defined, common practice suggests at least 1 month of antituberculosis therapy prior to anti-TNF therapy is prudent in most cases.

Anti-TNF therapy may increase the risk of reactivation of HBV in patients who are chronic carriers of this virus. Guidelines recommend screening all patients for HBV prior to starting anti-TNF therapy. Serologic assessment for HBV should include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb) with levels, and hepatitis B core antibody (HBcAb). If active HBV is found, it should be treated and controlled before anti-TNF initiation. In HBsAg + carrier patients, prophylactic antiviral treatment is recommended and ideally started at least 2 weeks prior to the introduction of anti-TNF therapy and continued for at least 6 months after its cessation [23, 26] to reduce the risk of HBV reactivation.

Anti-integrin Therapy

Clinical trial data suggest that anti-integrin therapies overall have a favorable safety profile, with low rates of serious infections over an extended treatment period [27]. However, the occurrence of progressive multifocal leukoencephalopathy (PML) due to reactivation of John Cunningham (JC) virus in approximately 1:1000 patients treated with natalizumab both in clinical trials and in post-marketing surveillance has limited the uptake of natalizumab for Crohn's disease. Risk factors for PML include positive JCV antibody status at baseline, concomitant immunosuppression, and more than 2 years of exposure to natalizumab [28]. Therefore, testing for JCV prior to starting natalizumab can identify those patients at lowest risk (i.e., negative antibody status) for subsequent PML. Furthermore, patients treated with natalizumab should not be on concomitant immunosuppressives, and those on concomitant steroids should be weaned off of steroids within 6 months of initiation of natalizumab [17].

Although natalizumab and vedolizumab are both anti-integrins that prevent leukocyte adhesion via blockade of α4 integrin, vedolizumab is more selective due to additional β7 inhibition which is specific to leukocyte trafficking to the gut. To date, no cases of PML have been reported in patients receiving vedolizumab [29], and JCV testing is not indicated prior to initiation of vedolizumab therapy.

With regard to tuberculosis, active TB has infrequently occurred in vedolizumab-exposed patients, and all cases occurred in endemic regions. Therefore, while there is likely no TB reactivation risk on vedolizumab, screening for TB should be considered according to the local practice [18], and patients should be asked about exposure to tuberculosis. There were no cases of HBV reactivation in the vedolizumab pivotal trials; however, due to the potential risk of hepatotoxicity among vedolizumab-treated patients [18], screening of HBV and other hepatitis viruses before vedolizumab initiation may be prudent.

Anti-IL12/IL23 (Ustekinumab)

Ustekinumab should generally be avoided in patients with active infections, with special concern for patients at risk for mycobacterial infections and those with *Salmonella* infection due to increased infection risks among patients genetically deficient in IL12/IL23 [19]. Testing for latent tuberculosis should be performed prior to initiation of ustekinumab.

Baseline Tests

Complete blood counts, chemistries with liver enzymes, and inflammatory markers (sedimentation rate, CRP, with or without fecal calprotectin) should be assessed to establish baseline values prior to starting therapy and periodically during the course of treatment for response and safety [2, 30]. Oftentimes a baseline colonoscopy may be useful to establish disease activity, with a follow-up colonoscopy approximately 6 months later to determine treatment response especially when clinical symptoms do not clearly correlate with endoscopic disease activity [31] (Table 18.2).

Vaccination Strategies

Vaccinations can effectively prevent or reduce the risk of certain infections, particularly among patients with IBD patients treated with immunosuppressive therapies. However, this appears to be significant underutilization of recommended immunizations in the adult IBD population [32, 33].

All patients being considered for biologics should have their vaccination status thoroughly assessed. Inactivated influenza vaccination is recommended annually, and updated guidelines suggest pneumococcal vaccination with both the 23-valent polysaccharide and the 13-valent conjugate vaccines 8 weeks apart [34, 35]. All adults should also undergo vaccination with tetanus toxoid every 10 years [36]. Hepatitis B vaccination should be offered to at-risk nonimmune individuals, and levels of anti-HBs >100 IU/l are advisable to achieve adequate seroprotection when

Table 18.3 Checklist of recommended vaccinations before starting biologic therapy

• Non-live vaccines (can be given before or during therapy) – Inactivated influenza vaccination (during "flu" season) – Pneumococcal vaccination with both the 23-valent polysaccharide and the 13-valent conjugate vaccines, per guidelines – Tetanus toxoid (if not in prior 10 years) – Hepatitis B (if not immune) – HPV (age appropriate)
• Live vaccines (should generally not be administered while on biologic therapy) – Varicella – Herpes zoster – Live inhaled influenza vaccine – Measles/mumps/rubella (MMR)

anti-TNF treatment is planned [37]. In addition, HPV vaccination in women and men ≤26 years should be considered, due to increased frequency of abnormal Pap smears in women with IBD on immunosuppressive therapy [38]. Other vaccinations should be administered based on recommended intervals and specific indications, and evaluation of antibodies to some infectious diseases (e.g., varicella) might be performed to determine if specific vaccines are required. In general, live virus vaccines (such as varicella, herpes zoster, measles, mumps and rubella vaccines, BCG vaccine) should be generally avoided while on any biologic therapy [39, 40] (Table 18.3).

A clinical trial found vedolizumab did not affect antibody titers after administration of injected hepatitis B vaccine, but it did reduce the humoral response to orally administered cholera vaccine. The impact on other oral vaccines and on nasal or mucosal vaccines in patients is unknown but is theoretically impaired among patients receiving vedolizumab [41].

One study in patients with psoriasis showed that non-live T-cell-dependent (tetanus toxoid) and T-cell-independent (pneumococcal polysaccharide) vaccines were not impaired among patients receiving ustekinumab relative to placebo [42].

During Treatment with Biologic Therapies

Safety Monitoring

Due to the risks associated with biologic agents, safety monitoring during the biologic therapy is recommended. Patients should be followed up closely and be evaluated for risk factors or presence of systemic or local infections and other adverse events at the time of regular visits. A high index of suspicion for rare but potentially serious events should be maintained throughout the treatment period [43]. Although there are currently no accepted monitoring guidelines for biologic therapy, several tests are generally accepted as appropriate care depending on patient-specific factors (Table 18.4).

Table 18.4 Checklist of suggested safety monitoring during biologic therapy

• Annual tuberculosis screening among high-risk patients[a]
• Liver function tests (LFT) and complete blood counts (CBC) regularly
• Age-appropriate cancer screening
• HBV reactivation (among those treated with anti-TNF and with latent HBV)

[a]That is, travel to a TB endemic region, known contact with active TB

Annual tuberculosis screening during maintenance therapy with anti-TNF agents should be performed among patients at high risk, for example, those traveling to endemic areas for TB or with occupational exposure, including patients who tested negative for talent TB prior to initiating therapy. Tuberculosis should also be considered in the differential diagnosis of a newly developed infection, especially in patients who have previously or recently traveled to countries with a high prevalence of TB or who have had close contact with a person with active TB [3–6, 18].

Liver function tests (LFT) and complete blood counts (CBC) are recommended every 3 months for the first 12 months of biologic therapy or as frequently as the clinician deems necessary during the course of therapy to assess opportunistic infections, malignancies, and liver abnormalities [43, 44]. The most appropriate frequency and duration of routine LFT and CBC monitoring for patients on long-term treatment are unclear but should be additionally prompted by clinically important changes in health status [44]. For patients in deep remission on biologic therapies, these authors recommend routine laboratory monitoring every 3–6 months.

A small incremental risk of malignancies attributable to biologic therapies has been demonstrated in some studies but not others [45, 46]. Specifically, lymphoma [47] and melanoma [48] have been identified as particular cancers potentially attributable to anti-TNF therapy, although lymphoma risk may be primarily driven by prior or concurrent thiopurine exposure. Boxed warnings regarding malignancy as a potential adverse event have been required on the medication packaging [3–6]. Therefore, an index of suspicion for malignancy should be maintained when patients present with clinically relevant symptoms including unintended weight loss, "B" symptoms of night sweats and fevers, and dermatologic lesions. In general, age-appropriate cancer screening guidelines should be followed for all patients on biologic therapies.

For patients who are known carriers of HBV and require treatment with anti-TNF agents, close monitoring for clinical and laboratory signs of active HBV infection including viral load assessments periodically throughout therapy and for several months following termination of therapy should be performed. In patients who develop HBV reactivation, anti-TNF therapy should be stopped, and antiviral therapy with appropriate supportive treatment should be initiated [3–6].

In addition, inflammatory markers (sedimentation rate, CRP, fecal calprotectin), imaging, and colonoscopy should be periodically assessed for monitoring of disease activity and response to therapy.

Select Patient Populations: The Elderly

Approximately 15% of IBD cases are diagnosed after 65 years of age, and with the aging of the population, many patients are entering "the golden years" with an existing diagnosis of IBD [49]. Whether the efficacy and safety of biologic therapy among elderly IBD is similar to young patients has not been definitively established. There are only a few observational studies reporting anti-TNF response and remission across age groups; some studies show similar results in older and younger patients [50, 51], and others show that elderly patients treated with anti-TNF therapies have a lower rate of short-term clinical response and a higher rate of severe adverse events than younger patients receiving the same treatment [52]. Furthermore, elderly patients may have a higher likelihood for discontinuation of therapy [53].

When contemplating biologic therapy for elderly patients, age-specific concerns such as comorbidities, diminished physical and cognitive function, polypharmacy and its consequences, and costs should all be considered. The risk of adverse events may be significantly increased in elderly patients, especially serious infection and malignancy, suggesting the need for careful monitoring during therapy. This monitoring should include routine laboratory assessments for safety, inflammatory markers to monitor disease activity, screening for osteoporosis, and age-appropriate cancer screening for breast, colon, lung, prostate, and skin cancer [54]. In one study, over half of elderly patients had a significant comorbidity such as cardiovascular disease, chronic pulmonary disease, diabetes mellitus, smoking, or cancer histories. Caution is therefore required when considering relative and absolute contraindications (including class III–IV heart failure) and assessment for drug-drug interactions potentially induced by polypharmacy including supplements and over-the-counter medications [55].

Considerations Upon Discontinuation of Biologic Therapies

There are no clear recommendations or sufficient data to guide broadly relevant clear recommendations for the question of if and when to discontinue biologic therapy. These decisions are influenced by treatment efficacy, disease state and phenotype, risk of future complication, patient preference, tolerability, and external patient factors. Some suggest that discontinuation can be considered among patients in remission for at least 1 year on biologic therapy, with careful considerations of the benefits of continuing therapy weighed against the risks of discontinuation. Withdrawal of therapy may be more appropriate in patients with CD who have both complete mucosal healing and no biological evidence of inflammation [16]. A systematic review of studies looking at rates of relapse after discontinuation showed that approximately one-third of patients with IBD flare within/after 12 months of withdrawal of anti-TNF therapy after having achieved a sustained remission, and this proportion increased to 50% and higher in the longer term [56, 57]. A decision

to discontinue biologic therapy should therefore be individualized, taking into account disease phenotypes, preceding disease course, and potential consequences of disease relapse [56]. Critical to any discussion about biologic discontinuation should be a plan for disease activity monitoring over time, in order to potentially identify subclinical evidence of relapse and potentially allow for intervention before significant disease recurrence. Reassuringly, response to re-treatment with anti-TNF therapy is likely to be effective in patients who relapse after discontinuation, but immunogenicity may render re-treatment unpredictably less effective [57].

Follow-Up Assessments

Close follow-up is needed when biologic therapy is stopped, although the most appropriate way to optimally monitor these patients is not clear [58]. Monitoring of CRP and fecal calprotectin levels regularly (i.e., every 3 months) may be useful for predicting early clinical relapse, and a significant increase of these biomarker values may predict a relapse during the next few months [59, 60]. Colonoscopy and/or cross-sectional imaging may be appropriate at a prespecified interval after discontinuation, to assess disease activity (i.e., 1 year).

Overall, maximizing effectiveness and minimizing adverse effects of biologic therapies require attention to disease activity monitoring, assessment for adverse effects, and shared decision-making with patients. Careful, individualized patient assessment is necessary. Giving the right treatment to the right patient at the right time and in the right way has the inherent appeal of maximizing efficacy in those who are most likely to respond, while avoiding potentially costly and toxic therapy in patients who are less likely to benefit [61].

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