Anti-TNF Biologic Therapies Other than Infliximab

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Calen A. Steiner, Emily P. Whitfield, Jeremy Adler, and Peter D.R. Higgins

Introduction

This chapter will review the use of anti-TNF targeted biologic therapies other than infliximab for the treatment of ulcerative colitis and Crohn's disease, with an emphasis on the use of these agents in pediatric patients. This review will focus on evidence of efficacy, safety, and relative efficacy in trials in children and adults with inflammatory bowel disease. When needed, data from clinical trials of these agents in children with psoriasis or rheumatologic diseases, or data from trials in adults with IBD will be included to provide additional information on the use of these agents in children.

The anti-TNF-α agents approved for use in inflammatory bowel disease other than infliximab include adalimumab, certolizumab, and golimumab.

Adalimumab in Children

After infliximab, adalimumab is perhaps the best studied anti-TNF therapeutic for inflammatory bowel disease. It is a fully human monoclonal IgG1 antibody against TNF-α that has been reported to have higher affinity for TNF-α than infliximab (Fig. 33.1a) [1]. Adalimumab is administered subcutaneously and has a half-life of 10–20 days and bioavailability of 64% [2]. It reduces inflammation through a complex and incompletely understood interplay of actions including direct inhibition of the interaction of TNF-α with p55 and p75 TNF receptors on cell surfaces, down-regulation of IL-10 and IL-12, and induction of monocyte apoptosis in a caspase dependent manner [1, 3, 4].

Efficacy of adalimumab in pediatric inflammatory bowel disease (IBD) was first described in the Retrospective Evaluation of the Safety and Effect of Adalimumab Therapy (RESEAT) study, a multicenter, retrospective chart review of patients with pediatric Crohn's disease [5]. This retrospective uncontrolled chart review was conducted at 12 sites that were part of the Pediatric Inflammatory Bowel Disease Collaborative Research Group and included a total of 115 pediatric patients with moderate to severe Crohn's disease (54% female), who had received at least one dose of adalimumab. Indication for adalimumab, concomitant medications, and clinical outcomes at 3, 6, and 12 months were recorded using the physician global assessment (PGA) and pediatric Crohn's disease activity index (PCDAI) [6]. Ninety-five percent of patients had previous treatment with infliximab, and the reason for switch to adalimumab was identified as loss of response (47%), infusion reaction, anti-drug antibodies (45%), or preference for subcutaneous injection (9%). They found the most common induction dosing strategy to be induction with 160 mg followed by 80 mg (160/80 mg) (19%), 80/40 mg (44%), and 40/40 mg (15%) with 40 mg every other week for maintenance dosing in 88%. Clinical response measured by PGA at 3, 6, and 12 months was 65, 71, and 70%, respectively, with steroid-free remission in 22, 33, and 42%. Adverse events were also recorded and no malignancies, serious infections, or deaths occurred in the subjects. Based on these results, the authors concluded that adalimumab was a well-tolerated and effective therapy, with steroid-sparing effect, for moderate to severe Crohn's disease in children [5].

Efficacy was further demonstrated in the IMAgINE 1 trial, a prospective double-blind dosing study of adalimumab (ADA) for 192 pediatric patients (6–17 years old) with

C.A. Steiner (✉)
Department of Internal Medicine, University of Michigan Health System, Ann Arbor, MI, USA

E.P. Whitfield • J. Adler, MD, MSc
Department of Pediatrics and Communicable Diseases, Pediatric Inflammatory Bowel Disease Program, C.S. Mott Children's Hospital, University of Michigan Health System, Ann Arbor, MI, USA
e-mail: ewhitfield@nwpedsgi.com; jeradler@med.umich.edu

P.D.R. Higgins
Department of Internal Medicine,
Inflammatory Bowel Disease Program, University of Michigan Health System, Ann Arbor, MI, USA
e-mail: phiggins@med.umich.edu

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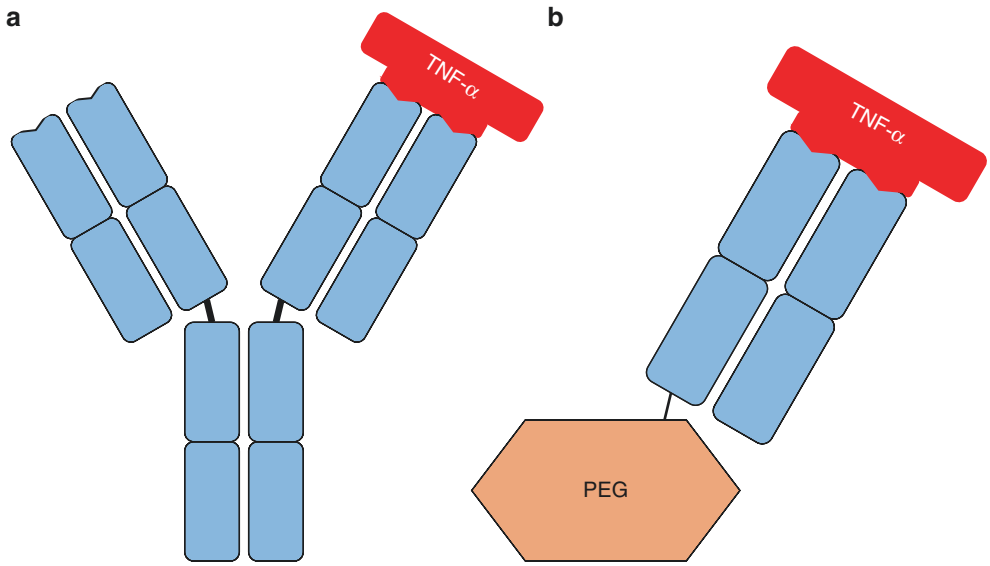


Fig. 33.1 (**a**) Adalimumab and golimumab are fully human IgG1 monoclonal antibodies. (**b**) Certolizumab pegol is a human FAB region conjugated to polyethylene glycol

Crohn's disease who had failed conventional therapy (PCDAI >30 despite treatment with oral corticosteroid for at least 2 weeks and/or an immunomodulator for at least 8 weeks, prior to baseline). Patients previously on infliximab were permitted if they had received at least two infusions and initially responded but stopped due to infusion reaction or loss of response due to antibodies. The last dose of infliximab had to be at least 8 weeks prior to baseline. Patients were ineligible if they had received an anti-TNF other than infliximab. Patients received open-label induction therapy with adalimumab at week 0 and 2 (160 mg and 80 mg or 80 mg and 40 mg, for ≥40 kg or <40 kg, respectively), and then at week 4188, patients were randomly assigned to high-dose (40 or 20 mg every other week) or low-dose (20 or 10 mg every other week) double-blind maintenance therapy for 48 weeks, grouped according to 4-week responder status and prior exposure to infliximab.

At the 12-week study visit, patients with disease flare or non-response were switched from blinded every other week dosing to blinded weekly dosing, continuing with the same dose. After 8 more weeks, those with a disease flare or non-response could switch to open-label weekly rescue with high-dose ADA (40 or 20 mg weekly). If patients had another flare or were persistent non-responders, they could be discontinued at the investigator's discretion. One hundred and twenty-four patients completed the study. The study found that adalimumab (low dose and high dose) induced and maintained clinical response in 28–39% of patients at week 26 and 23–33% at week 52. Patients with lower CRP at baseline had higher rates of remission in both dose groups. Of note, treatment with adalimumab was associated with significant improvements in height velocity. The safety profile was found to be comparable to adult studies with infections being the most common adverse event noted, with eight serious infections [7].

The safety and efficacy of weekly dosing was described in a sub-analysis of IMAgINE 1, which analyzed the data of patients who had been escalated to weekly therapy [7]. This analysis found that escalation to weekly dosing occurred in 50.5% on low-dose and 37.6% of those on high-dose treatment, and clinical remission rates at 52 weeks were 18.8% and 31.4% for low dose and high dose, respectively. Adverse events rates were similar to those on every other week therapy [8].

A recent study evaluated the pharmacokinetics of adalimumab in children with moderate to severe Crohn's disease in a phase 3 randomized, double-blind, 52-week trial [9]. There was a 4-week open-label induction phase followed by a 48-week double-blind maintenance phase, with a standard and low-dose arm, of ADA given every other week. Trough serum adalimumab levels and antibodies were collected at baseline and then weeks 16, 26, and 52. Disease activity was analyzed at the same time points using the PCDAI. Higher body weight, higher baseline CRP, and lower baseline albumin level were associated with greater clearance of adalimumab. Additionally, an exposure (serum concentration)-efficacy relationship was observed with higher serum level associated with a higher rate of remission [9].

Adalimumab has been demonstrated to be efficacious in pediatric Crohn's disease patients after failure of infliximab therapy. Cozijnsen et al. conducted a nationwide retrospective assessment of pediatric patients in the Netherlands who were treated with adalimumab after prior treatment with infliximab [10]. Among 53 patients identified, 6% were switched to adalimumab after primary non-response to infliximab, 64% after loss of response to infliximab, 21% after allergic reaction to infliximab, and 9% after adverse reactions to infliximab. Among those started on adalimumab, dosage was based on "body weight (20–40 mg for patients <40 kg, 40–80 mg for patients >40 kg)." Seventy-four

percent started with double-dosage induction sequence followed by maintenance dosing, while the remainder went straight to maintenance dosing. They found that 64% of patients reached remission within 3 months of starting adalimumab and 50% maintained remission for 2 years. Patients who had primary non-response to infliximab were more likely to fail to respond to adalimumab than those who had lost response to infliximab. Those who developed antibodies to infliximab were more likely to respond to subsequent adalimumab therapy.

The RESEAT trial found similar response rate to adalimumab after prior infliximab therapy. In that study, only six patients (5%) were treated with adalimumab as their first anti-TNF-α agent, and the authors did not comment on the efficacy of adalimumab in these small number of TNF-α-naïve patients.

Growth and Bone Health

Children who clinically respond to adalimumab therapy appear to have improved linear growth similar to that seen with infliximab. Malik et al. conducted a retrospective physician survey through the British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) in which they collected information on anthropometry and treatment information. Of the 70 patients included in the survey, 36 had been treated with adalimumab and had sufficient growth data at 3 points in time to assess growth. Of these patients, 34 (94%) had prior treatment with infliximab. Despite prior medical therapy, the authors demonstrated improved linear growth comparing growth 6 months prior to initiation of adalimumab to the first 6 months on adalimumab therapy. Of the 17 children who were Tanner stage 1–3 at the start of adalimumab, there was a significant increase in the height Z score after 6 months of adalimumab.

Veerappan et al. prospectively assessed markers of bone formation and resorption in children with Crohn's disease treated with adalimumab and compared their findings to those in control children without IBD. All of these children had previously been treated with immune suppressive therapy, most of whom had had prior treatment with infliximab. They found an increase in bone formation markers (osteocalcin and procollagen type 1 N-terminal propeptide) at 1 and 3 months after starting adalimumab. They also found increased osteoblast differentiation after 6 months, which the authors suggested was likely related to new bone formation.

Pain

In addition to efficacy and safety, pain with adalimumab injection is important to address, since this can impact patient adherence. Pain at the adalimumab injection site has been reported in both pediatric and adult studies. Hirai et al. conducted a survey of patient satisfaction with adalimumab self-injection [11]. They surveyed 124 patients (age 13–70 years) who were currently receiving adalimumab therapy. The majority of patients (88%) reported pain at the injection site, 28% of whom had "strong pain" at the injection site. Strategies that patients reported to help alleviate pain included "slow injection" and "warming the drug solution with their palms."

There was one report of mixing lidocaine into adalimumab prior to injection to minimize pain at the injection site. Ayala and colleagues presented findings of a study in which they recruited pediatric and adult patients treated with adalimumab who experienced pain and anxiety or were younger [12]. They added 0.2 ml of 1% lidocaine directly into the prefilled syringes of 0.8 ml adalimumab. They tested this in 15 patients who reported decreased pain at the injection site.

Adalimumab in Adults

Adalimumab has demonstrated efficacy in controlled trials in multiple disease states and received FDA approval for rheumatoid arthritis in adults in 2002, psoriatic arthritis in 2005, ankylosing spondylitis in 2006, plaque psoriasis in 2008, and juvenile idiopathic arthritis in 2008 [13–22]. Adalimumab achieved FDA approval for Crohn's disease in adults in 2007 and for ulcerative colitis in 2012. The efficacy in Crohn's disease in adults was established by four placebo-controlled trials demonstrating efficacy for induction as well as maintenance of remission [23–26]. Since these studies were published, additional randomized controlled trials have demonstrated efficacy of adalimumab in induction and maintenance of mucosal healing in adults with Crohn's disease [27] and in patients who recently underwent intestinal resection surgery [28]. Four-year maintenance data has also recently been published [29]. The efficacy of adalimumab in ulcerative colitis has been established primarily by two randomized controlled trials [30, 31], with recent 4-year maintenance data now available [32].

CLASSIC I

The CLASSIC I and CLASSIC II trials investigated the efficacy of adalimumab in patients who were anti-TNF therapy naïve with moderate to severe Crohn's disease [24, 25]. CLASSIC I first evaluated adalimumab as an induction therapy. This multicenter, randomized, double-blind, placebo-controlled trial enrolled 299 patients receiving loading doses of adalimumab in three different dose groups vs. placebo, with the primary endpoint being differences in rates of

remission (defined by Crohn's Disease Activity Index [CDAI] [33] scores of < 150) at week 4 [24]. Patients were randomized to receive loading dose regimens at weeks 0 and 2 of placebo, adalimumab 40 mg/20 mg, 80 mg/ 40 mg, or 160 mg/ 80 mg. Based on pharmacokinetic data obtained in trials for rheumatoid arthritis, the investigators anticipated a target dose of 40 mg every other week for efficacy in Crohn's disease. A dose group above and below that target was selected (20 mg every other week and 40 mg weekly or 80 mg every other week), and the loading doses were selected based on early dosing pharmacokinetic data. At week 4, rates of remission were 18% in the 40 mg/20 mg group ($p = 0.36$), 24% in the 80 mg/40 mg group ($p = 0.06$), 36% in the 160 mg/80 mg group ($p = 0.001$), and 12% in the placebo group. Differences in response when compared with placebo achieved significance as early as week 1 in the 80 mg/40 mg group. This study demonstrated that induction therapy with adalimumab is more effective than placebo, with the best tested loading dose being 160 mg/80 mg at weeks 0 and 2. Additionally, adalimumab was well tolerated, with similar rates of adverse events across groups, except for injection site reactions, which occurred more frequently in the ADA groups.

CLASSIC II

The CLASSIC II trial evaluated adalimumab for maintenance therapy in moderate to severe Crohn's disease in patients who were naïve to anti-TNF therapy and then responded to ADA, for a total of 56 weeks [25]. This trial was a continuation of CLASSIC I and enrolled 276 of the 299 patients from CLASSIC I. All patients who entered CLASSIC II from CLASSIC I received 40 mg ADA at week 0 (week 4 of CLASSIC 1) and week 2. At week 4, the 55 patients who had achieved remission at weeks 0 and 4 were re-randomized to receive placebo, adalimumab 40 mg every other week, or adalimumab 40 mg weekly. The primary endpoint was again defined as a CDAI score <150. At week 56, 79% of patients in the 40 mg every other week and 83% of patients in the 40 mg weekly were in remission vs. 44% of the placebo group ($p < 0.05$). At week 4, 204 patients who had not achieved remission at week 0 and week 4 entered a separate open-label arm and received 40 mg every other week. Patients in this arm could escalate to 40 mg weekly for a flare or non-response. In this arm, 71 continued on 40 mg every other week, while 60 had dose escalation to 40 mg weekly. At the end of 56 weeks, 46% of patients in this arm were in remission. Additionally, 65% had a 100-point clinical response, and 72% had a 70-point clinical response. The rates of patients achieving 70-point clinical response were not significantly affected by concomitant use of immunosuppressant therapy. Thus adalimumab is more effective than placebo as maintenance therapy in adults with Crohn's disease.

CHARM

The CHARM trial was a randomized, double-blind, multicenter placebo-controlled trial that studied adalimumab for the maintenance of remission in patients who had responded to induction therapy with adalimumab [23]. This study permitted concomitant use of a stable dose of immunosuppressant therapy, 5-ASA therapy, Crohn's disease-related antibiotics, and steroids and included adults with moderate to severe Crohn's disease. This study also included patients who had previously been on a TNF antagonist, so long as it was more than 12 weeks prior to screening, and excluding those with primary non-response. Eight hundred and fifty-four patients enrolled and received open-label adalimumab loading doses of 80 mg and 40 mg at week 0 and week 2, respectively. Patients were then assessed and stratified at week 4 based on response (decrease in CDAI score of 70 or greater), and 58% of patients were randomized to placebo, adalimumab 40 mg every other week, or adalimumab 40 mg weekly up to 56 weeks. Patients who experienced a flare or non-response were allowed to switch to 40 mg every other week after week 12. Two primary endpoints were evaluated as percentages of the randomized responder arms achieving remission at weeks 26 and 56 (defined as CDAI score <150). At week 26 the rates of remission were 17, 40, and 47% in the placebo, adalimumab 40 mg every other week, and adalimumab 40 mg weekly groups, respectively. At week 56, these rates were 12, 36, and 41%, respectively. This demonstrated that each adalimumab group achieved significantly greater rates of remission when compared pairwise with placebo ($p < 0.001$). Differences between the two adalimumab treatment groups did not achieve significance ($P = 0.22$ at week 26 and $p = 0.34$ at week 56). Differences in the rates of remission between treatment and placebo groups were seen as early as week 6, and most patients (81%) in the treatment groups who achieved remission at week 26 remained in remission at week 56, compared to 48% in the placebo group. Adalimumab achieved superiority to placebo regardless of concomitant use of immunosuppressive therapy or prior use of TNF-antagonists. Adalimumab was also demonstrated to be steroid sparing, with both treatment groups having a greater percentage of patients achieving steroid-free remission at 26 weeks ($p < 0.001$ for each treatment group vs. placebo) and 56 weeks ($p < 0.001$ for the 40 mg every other week group vs. placebo, $p = 0.008$ for adalimumab 40 mg weekly vs. placebo). This study demonstrated that treatment with adalimumab 40 mg every other week or 40 mg weekly is an effective therapy for maintenance of remission in adults with Crohn's disease. Recently, data regarding remission rates at 4 years has been released using data from the CHARM trial and its open-label extension, ADHERE [23, 29, 34]. These studies demonstrated good durability of response, with 54% of patients who achieved remission at 1 year still in remission at 4 years [29].

GAIN

The GAIN trial was a 4-week, randomized, double-blind, placebo-controlled trial designed to ascertain adalimumab efficacy in inducing remission in Crohn's disease patients with symptoms despite infliximab therapy or an inability to take infliximab secondary to adverse events [26]. In this study 325 adults with moderate to severe Crohn's disease who were either intolerant to infliximab or had initially responded but then lost response to infliximab were randomly assigned to receive placebo or adalimumab 160 mg at week 0 and 80 mg at week 2. Patients who did not ever respond to infliximab were excluded. At week 4, 21% of adalimumab-treated patients vs. 7% of placebo-treated patients achieved remission defined as CDAI<150 ($p < 0.001$). Rates of 70-point response in adalimumab vs. placebo at weeks 1, 2, and 4 were 35% vs. 21%, 52% vs. 33%, and 52% vs. 34%, respectively, with statistically significant response seen at week 1. Total CDAI scores were also significantly lower in the adalimumab group vs. placebo at weeks 1, 2, and 4. Subgroup analysis revealed that adalimumab demonstrated efficacy regardless of concomitant immunosuppressive therapy, previous intolerance to infliximab, previous loss of response to infliximab, previous intolerance of and loss of response to infliximab, or presence of antibodies to infliximab. Based on this study, adalimumab is safe and effective for use in patients with Crohn's disease who had previously responded and discontinued infliximab due to adverse events or a loss of response, but no conclusions can be drawn about infliximab primary non-responders.

EXTEND Trial in Mucosal Healing in CD

The EXTEND trial is the first randomized, double-blind, multicenter placebo-controlled trial investigating the efficacy of adalimumab in the induction and maintenance of mucosal healing in adults with moderate to severe ileocolonic Crohn's disease [27]. One hundred and thirty-five patients received open-label adalimumab 160 mg at week 0 and 80 mg at week 2. At week 4, 129 patients who remained in the study were randomized to receive maintenance therapy with adalimumab 40 mg every other week or placebo. Patients who experienced flares or non-response could receive open-label adalimumab 40 mg every other week, with the potential to increase dosage to 40 mg weekly. Absence of mucosal ulceration at week 12 was defined as the primary endpoint. Mucosal ulceration was defined as a score of least two on the ulcerated surface subscore of the Simple Endoscopic Score for Crohn's Disease (SES-CD) [35] in at least one of five ileocolonic segments. Secondary endpoints assessed included mucosal healing at week 52, Crohn's Disease Endoscopic Index of Severity (CDEIS) [36] remission (defined as a score of 4 or less) at week 12 and week 52, and CDAI remission (score<150) and response (100-point reduction and 70-point reduction in CDAI score) at week 12 and week 52. The primary endpoint of mucosal healing at week 12 was achieved in 27% of the continuous adalimumab group compared to 13% of the induction/placebo group ($p = 0.056$). This p-value improved to 0.046 when applying a prespecified per-protocol analysis which excluded some patients for major protocol deviations. Secondary endpoint analysis at 52 weeks revealed that 24% of the adalimumab-continuous arm and none of the induction/placebo arm achieved mucosal healing ($p < 0.001$). Similarly, all secondary endpoints achieved statistically significant superiority of continuous adalimumab compared to induction/placebo at week 52. At week 12, CDEIS remission rates and CDAI remission rates of the continuous adalimumab group achieved statistical superiority over the induction/placebo group, but not for CDEIS 75% responders nor CDAI score reductions of > 100 or >70. Ultimately this study demonstrated superiority of adalimumab maintenance therapy in mucosal healing of adults with moderate to severe Crohn's disease at 52 weeks, but not at 12 weeks post-induction. Despite the lack of statistical superiority of adalimumab on mucosal healing at week 12, this could be due to the lingering efficacy of the induction therapy that all participants received or that mucosal healing in patients with severe disease takes longer than 12 weeks. Overall this study demonstrates that adalimumab is efficacious in mucosal healing in addition to its established efficacy in clinical response and remission in Crohn's disease.

ADA in Postoperative CD

An additional randomized controlled trial (POCER) has evaluated the efficacy of adalimumab in preventing disease recurrence in patients with Crohn's disease who have undergone intestinal resection surgery [28]. This study was a randomized, prospective, open-label trial that included 51 patients with ileal or ileocolonic Crohn's disease who underwent an intestinal resection. Patients were randomized to receive adalimumab, azathioprine, or mesalamine following surgery for a period of 2 years. For the adalimumab arm, subcutaneous injections were administered as a loading dose of 160 mg/80 mg at weeks 0 and 2, respectively, followed by maintenance dosing of 40 mg every 2 weeks. The azathioprine arm received 2 mg/kg daily, while the mesalamine group received 3 g daily, divided in three doses. The primary outcome of this study was the proportion of patients with clinical and endoscopic remission at 2 years post-surgery using multiple previously developed scales, with a secondary outcome being a quality of life assessment via the previously validated IBDQ [28, 37]. After the 2-year study period, 1 of 16 patients treated with adalimumab (6.3%), 11 of 17 patients

treated with azathioprine (64.7%), and 15 of 18 patients treated with mesalamine (83.3%) experienced endoscopic recurrence. These values represent an OR = 0.036 for adalimumab compared to azathioprine and OR = 0.013 for adalimumab compared to mesalamine. Perhaps due to small sample size, there was no significant difference in endoscopic recurrence between azathioprine and mesalamine, with an OR = 0.367. With regard to clinical recurrence, using the scale proposed by Hanauer et al. [38], 2 of 16 adalimumab-treated patients (12.5%) had clinical recurrence, while 11 of 17 in the azathioprine arm and 9 of 18 in the mesalamine arm had clinical recurrence for odds ratios of 0.078 and 0.143, respectively [28]. These results were also reflected by using a CDAI >200, which results in clinical recurrence of 6.3% vs. 70.6% for OR = 0.028 and 6.3% vs. 50% for an OR = 0.067. Again, there was no significant difference in azathioprine vs. mesalamine when using these scales to measure clinical recurrence. Remission, defined as CDAI score <150, occurred in 15/16 of the adalimumab group compared with 4/17 in the azathioprine group (OR = 0.021) and 6/18 in the mesalamine group (OR = 0.033), with no difference between the azathioprine and mesalamine groups. Very similar outcomes were obtained when analyzing the secondary endpoint of quality of life using the IBDQ. Thus, adalimumab was shown to be superior to azathioprine and mesalamine in the prevention of disease recurrence in adults with Crohn's disease who underwent intestinal resection.

ULTRA/UC Data

The efficacy of adalimumab in ulcerative colitis was established primarily through two different phase-three clinical trials, ULTRA-1 (Ulcerative Colitis Long-Term Remission and maintenance with Adalimumab) and ULTRA-2 [30, 31]. ULTRA-1 was a multicenter, randomized, double-blind, placebo-controlled trial that lasted 8 weeks [30]. This enrolled adult patients with moderate to severe ulcerative colitis who had been treated with immunosuppressant therapy and/or corticosteroids but still had Mayo score [39] ≥6 and endoscopic subscore ≥2. All patients were naïve to anti-TNF agents. This study initially included 186 patients randomized to receive either placebo or induction therapy with adalimumab 160 mg at week 0 and 80 mg at week 4, followed by 40 mg maintenance dosing at week 4 and week 6. The protocol was amended to include a second treatment group with a regimen of 80 mg adalimumab at week 0, followed by 40 mg at weeks 2, 4, and 6 at the behest of European regulatory authorities. Ultimately, the primary endpoint of this study was assessed in 390 patients randomized to adalimumab 160 mg/80 mg/40 mg/40 mg, 80 mg/40 mg/40 mg/40 mg, or placebo. The primary endpoint was defined as clinical remission at week 8 as defined as Mayo score ≤2 with no individual subscore >1. At week 8, 18.5% of the 160 mg/80 mg group, 10.0% of the 80 mg/40 mg group, and 9.2% of the placebo group achieved remission (p = 0.031 for 160 mg/80 mg vs. placebo, p = 0.833 for 80 mg/40 mg vs. placebo). Serious adverse events occurred in 4.0% of the adalimumab 160 mg/80 mg group, 3.8% of the adalimumab 80 mg/40 mg group, and 7.6% of the placebo group. Evaluation of the primary endpoint leads to the conclusion that adalimumab 160 mg/80 mg induction dose followed by 40 mg every other week for 2 weeks is a safe and effective induction regimen for ulcerative colitis in adults when compared to placebo. Additionally, this study leads to the conclusion that loading doses of 80 mg/40 mg are not effective for induction of remission in ulcerative colitis.

ULTRA-2 was a randomized, double-blind, multicenter, placebo-controlled trial that included 494 patients with moderate to severe ulcerative colitis that were on immunosuppressant therapy and/or oral corticosteroids [31]. This study included both patients who had prior exposure to TNF-antagonists and those who had not. Patients were randomized to receive either placebo or adalimumab 160 mg at week 0, 80 mg at week 2, followed by 40 mg every other week. Remission in this study was also defined as Mayo score ≤2 with no individual subscore >1, with primary endpoints being remission at week 8 and week 52. The rate of clinical remission at week 8 was 16.5% of the treatment group vs. 9.3% of the placebo group, p = 0.019. At 52 weeks, the rates of clinical remission were 17.3% and 8.5% in the treatment and placebo groups, respectively, p = 0.004. Secondary analysis revealed that clinical response was achieved in 50.4% of the treatment group vs. 34.6% of the placebo group at week 8 and 30.2% of the treatment group vs. 18.3% of the placebo group at week 52, for p values of p < 0.001 at week 8 and p = 0.002 at week 52. In patients who were anti-TNF naïve, 21.3% of the treatment group and 11% of the placebo group achieved remission at week 8 and 22% vs. 12.4% at week 52 for p values of 0.017 and 0.039, respectively. For patients who had received prior anti-TNF therapy, rates of remission at week 8 were 9.2% in the treatment group vs. 6.9% in the placebo group and 10.2% in the treatment arm vs. 3% in the placebo arm at week 52, for p values of 0.559 and 0.039, respectively. This study demonstrated that adalimumab is superior to placebo for the induction and maintenance of remission in adults with ulcerative colitis, with markedly better efficacy in patients who are anti-TNF naïve compared to those with prior anti-TNF exposure. Recently, long-term data from adalimumab-treated patients in ULTRA-1, ULTRA-2, and the open-label extension ULTRA-3 has been published [32]. This study demonstrated that 199 of 600 patients randomized to receive adalimumab in the intent-to-treat analysis of ULTRA-1 and ULTRA-2 remained on adalimumab and demonstrated a rate of remission of 24.7% by partial Mayo score at week 208.

Levels and Antibodies

Approximately 18% of adult and pediatric Crohn's disease patients who are primary responders will lose response to adalimumab, with an annual risk of over 20% per patient-year, and 37% will require dose intensification, with an annual risk of nearly 25% [40]. The importance of drug levels has been emphasized in several studies evaluating endpoints such as mucosal healing, and endoscopic and clinical indicators of disease [41–48]. Typically drug levels are evaluated with either HMSA or ELISA, which have been found to be roughly equivalent [49]. Several groups have proposed different drug level thresholds to achieve mucosal healing, with levels as low as 4.9 μg/mL (via ELISA) [44] and as high as 8.14 μg/mL (HMSA) [43] being proposed. One study proposes levels as high as 8–12 μg/mL [45]. Anti-adalimumab antibodies are thought to be primarily responsible for the observed loss of response [50, 51], with rates of anti-adalimumab antibody formation reported to range from 3% in the CLASSIC II trial [25] to as high as 21% [50]. Further, anti-adalimumab antibodies have been shown to be inversely associated with adalimumab drug levels and achievement of good clinical outcomes [42, 49]. More studies are needed to cement our understanding of the relationship between adalimumab levels, anti-adalimumab antibodies, and response, as not all studies have demonstrated such a clear relationship. One large cross-sectional study demonstrated no difference between mucosal healing rates in patients with anti-adalimumab antibodies and those without [45]. However, that comparison was made in patients who had adequate adalimumab drug levels, and the lack of separation could have been due to individuals overcoming the anti-adalimumab antibodies effect via other means. In addition to increasing drug levels, research has been done to investigate the effect of immunomodulators on the rate of formation of anti-drug antibodies [2]; however this data is limited to patients being treated with infliximab. Another proposed mechanism for loss of response is tissue inflammation itself acting to reduce levels of anti-TNF agents [47], although this is less well studied. Despite the importance of adequate drug levels in achieving remission in IBD, recent studies (TAXIT, TAILORX) using infliximab and adalimumab have demonstrated that there is no significant value in prospective drug monitoring during successful maintenance therapy and suggest that therapeutic drug monitoring should be used largely during induction or upon loss of response [52].

Certolizumab in Children

There are no completed pediatric studies of certolizumab pegol use in IBD. There was one phase 2 open-label prospective study called "The Use of Certolizumab Pegol for Treatment of Active Crohn's Disease in Children and Adolescents (NURTURE)." This study was terminated due to "higher than projected discontinuation rate during the Maintenance Phase" [53]. However some preliminary data were presented in abstract form at Digestive Disease Week 2011 [54]. This abstract presented pharmacokinetic findings in children 6–17 years of age, after 6 weeks of certolizumab therapy. Patients received an induction sequence of certolizumab subcutaneously every 2 weeks for 3 doses (weeks 0, 2, 4). The dosing was 400 mg for patients ≥40 kg and 200 mg for patients 20–40 kg. In their first 14 pediatric patients with active Crohn's disease, they found that plasma concentrations of certolizumab during the 6 weeks of induction period were similar to those observed in adult patients, though younger children (6–11 years) had slightly higher serum concentrations than older patients (12–17 years).

Despite the lack of pediatric studies of certolizumab for IBD, there are studies in juvenile idiopathic arthritis (JIA). Tzaribachev et al. reported outcomes of 22 pediatric patients with JIA who were treated with certolizumab, most of whom had previously been treated with two prior anti-TNF-α agents (5 had 1 prior and 18 had 2 prior anti-TNF-α agents) [55]. By weeks 24–36, most (68%) had no active joint inflammation. There were no serious adverse reactions, but one child developed a transient skin reaction.

Certolizumab in Adults

Certolizumab is an antibody Fab' fragment that is humanized and conjugated to polyethylene glycol (Fig. 33.1b). Certolizumab binds and inhibits TNF-α, both soluble and membrane bound. It lacks an Fc region, and as such does not fix complement nor cause cell-mediated cytotoxicity. It is administered subcutaneously, with bioavailability of approximately 80%. Certolizumab has an indication for adults with moderate to severe Crohn's disease who have not had an adequate response to conventional therapy, as well as adult indications in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis [33]. The efficacy of certolizumab in Crohn's disease has been assessed in multiple phase II and phase III trials including the PEGylated Antibody Fragment Evaluation in Crohn's Disease Safety and Efficacy (PRECiSE) trials [56–59], and more recently the Mucosal Healing Study in Crohn's Disease (MUSIC) trial [60, 61]. Certolizumab has also been assessed for efficacy in patients who failed infliximab after previous clinical response in the WELCOME trial [62, 63].

Initial Phase 2 Trials

Two small phase 2 studies initially assessing certolizumab demonstrated that it is well tolerated and efficacious, but

these studies failed to achieve their primary endpoint [64, 65]. Both were randomized, double-blind, placebo-controlled multicenter studies. One study evaluated the safety and efficacy of certolizumab in 92 adults with Crohn's disease, who received certolizumab at doses of 1.25 mg/kg, 5 mg/kg, 10 mg/kg, or 20 mg/kg or placebo [65], which was later adjusted. The 1.25 mg/kg arm was dropped based on efficacy results in a study of rheumatoid arthritis. The primary endpoint was clinical response (CDAI score reduction of at least 100 points) or remission (CDAI score ≤ 150) at 4 weeks. While the treatment groups and placebo groups all had similar percentages of patients achieving these endpoints at week 4 (47.8–60.0%), the 10 mg/kg group did demonstrate significant separation in remission at week 2 (47.1 vs. 16.0%, p = 0.041). The second phase 2 trial included 292 patients with moderate to severe Crohn's disease randomized to 100, 200, 300, or 400 mg subcutaneous certolizumab or placebo at weeks 0, 4, and 8 [64]. This study again assessed response and remission as defined in the prior study but evaluated the endpoints at week 12. All treatment groups achieved significant separation from placebo at week 2, but this significance was not maintained. The 400 mg treatment group (roughly 6 mg/kg) maintained the highest response rate at all time points, with the most robust separation at week 10 with 52.8% vs. 30.1% for placebo (p = 0.006). However, this separation was lost in all groups at the primary endpoint analysis at week 12. It is not clear why a 700 mg (or 10 mg/kg) arm was not evaluated in phase 2.

PRECISE Trials

The PRECiSE 1 trial was the first major randomized, double-blind, placebo-controlled phase III trial evaluating the efficacy of certolizumab in adults with moderate to severe Crohn's disease [57]. This trial included 662 patients who were first stratified based on CRP ≥ 10 mg/L or CRP<10 mg/L and then randomized to receive 400 mg subcutaneous certolizumab or placebo at weeks 0, 2, and 4 followed by every 4 weeks thereafter. The primary endpoint was a decrease in CDAI score of at least 100 points at week 6, and at both week 6 and week 26, in the group with baseline CRP ≥10 mg/L. At week 6, 37% of the treatment group achieved response compared to 26% in the placebo group (p = 0.04). At both weeks 6 and 26, response was achieved in 22% of the treatment group and 12% of the placebo group (p = 0.05). These results were consistent with those in the overall population, with response rates of 35% in the treatment group vs. 27% in the placebo group at week 6 and 23% treatment vs. 16% placebo at weeks 6 and 26 (p = 0.02 in both instances). Rates of remission did not achieve statistical significance in treatment vs. placebo. The use of concomitant glucocorticoids, previous infliximab treatment, smoking status, and immunosuppressive therapy was not associated with the magnitude of response.

PRECiSE 2 was a randomized, double-blind, placebo-controlled trial evaluating the efficacy of certolizumab for maintenance therapy in adults with moderate to severe Crohn's disease [59]. In this study 668 patients entered the open-label induction phase, in which 400 mg subcutaneous certolizumab was administered at weeks 0, 2, and 4. Of the 668 subjects entering the induction phase, 428 had a response at week 6 as defined by at least a 100-point reduction in CDAI. Those patients were then randomized to receive 400 mg certolizumab or placebo at weeks 8, 12, 16, and 20. Patients were again stratified based on CRP level as well as concurrent use of glucocorticoids and concurrent use of immunosuppressive therapy. The primary endpoint was defined as clinical response at week 26 in the CRP ≥10 mg/L group. Clinical response was achieved in this group at week 26 in 62% of the treatment arm compared to 34% of placebo ($p < 0.001$). When assessing the intention-to-treat population, the clinical response at 26 weeks was 63% in the treatment group vs. 36% in the placebo arm ($p < 0.001$). Remission (CDAI ≤150) was achieved in 48% of the treatment group vs. 29% in the placebo group ($p < 0.001$). Secondary analysis revealed that when the patients were stratified into those who had received prior infliximab and those who had not, both groups experienced a significant difference in response at week 26 in treatment vs. placebo.

PRECiSE 3 is an open-label extension of PRECiSE 2 in which patients who completed PRECiSE 2 were eligible to receive 400 mg certolizumab every 4 weeks long term, with data published at 54 weeks (week 80 of PRECiSE 2) [56]. This study utilized the Harvey Bradshaw Index [66] (HBI) to assess response and remission in patient groups that received uninterrupted certolizumab and interrupted certolizumab at 54 weeks (week 80 of PRECiSE 2). Of the patients responding at week 26 of PRECiSE 2, the rates of response in the continuous and interruption groups were 66.1 and 63.3%, respectively. In patients that achieved remission at week 26, rates of remission at week 80 in the continuous and interruption groups were 62.1 and 63.2%, respectively. These data suggest that certolizumab is efficacious in maintaining response and remission in certolizumab responders.

PRECiSE 4 is an open-label evaluation of patients in PRECiSE 2 who entered the randomization phase but who relapsed before week 26 [58]. In this study, patients who relapsed from the treatment group received a single extra dose of 400 mg certolizumab, and patients from the placebo group received reinduction with 400 mg certolizumab at weeks 0, 2, and 4, followed by 400 mg certolizumab every 4 weeks. This study again utilized the HBI to assess response

rates. At week 4, response was attained in 63% of the continuous therapy group and 65% of the drug interruption group. At week 52, this clinical response was maintained in 55% of the continuous treatment group and 59% of the certolizumab-interrupted group. Based on this study, rescue or reinduction therapy with certolizumab in patients with an initial response may be a viable treatment option.

Certolizumab in Loss of Response to Infliximab

While the PRECiSE trials did not exclude patients on prior infliximab and were able to perform subgroup analysis on these patients, an additional randomized controlled trial has been published assessing the efficacy of certolizumab specifically in patients with Crohn's disease who experienced non-primary treatment failure on infliximab due to hypersensitivity or loss of response [63]. Five hundred and thirty-nine adults with moderate to severe Crohn's disease and secondary failure to infliximab enrolled in this 26-week trial [63]. This study also contained an open-label induction period with subsequent randomization and blinding at week 6. Patients received open-label certolizumab 400 mg subcutaneously at weeks 0, 2, and 4 and were assessed for response (CDAI reduction of ≥100). This was the primary endpoint and was achieved in 62.0% of patients entering the trial. Three hundred and twenty-nine patients who responded were then enrolled in the randomized, double-blind maintenance therapy portion of the trial and received certolizumab either every 4 weeks or every 2 weeks. Ultimately, response was achieved in 38.3% of patients at week 26, with no significant difference in rates of the every 4-week vs. every 2-week dosing groups. This trial was not placebo controlled but did demonstrate that good response and remission rates can be produced with certolizumab therapy in adults with Crohn's disease and prior secondary failure of infliximab.

TNF-Naïve Patients

One randomized trial evaluated the efficacy of certolizumab in adults with moderate to severe Crohn's disease but excluded patients who had received prior infliximab [67]. In this randomized, double-blind, placebo-controlled trial, 439 patients were randomized to receive either placebo or 400 mg subcutaneous certolizumab at weeks 0, 2, and 4. The primary endpoint for this trial assessed clinical remission (CDAI ≤150) at week 6. This study failed to achieve significance of its primary endpoint, with 32% of the treatment arm vs. 25% of the placebo arm achieving remission at week 6 ($p = 0.174$). The following subgroups did achieve significance: Men, patients ≤40 years old, patients with CRP ≥10 mg/L, ileocolonic or colonic involvement, disease duration less than mean, CDAI ≥300, and patients with no prior intestinal resection. When these results are taken with the body of knowledge around TNF-α inhibitors, they seem to suggest that certolizumab is efficacious in the treatment of Crohn's disease but may be best utilized after failure of another anti-TNF such as infliximab.

MUSIC

A recent study has evaluated the efficacy of certolizumab to achieve endoscopic mucosal healing of intestinal lesions [61]. This study was open label, and patients received certolizumab 400 mg subcutaneous at weeks 0, 2, 4, and every 4 weeks thereafter up to week 52. This study demonstrated good rates of endoscopic response and remission at week 10 and week 54, with rates of endoscopic response, endoscopic remission, complete endoscopic remission, and complete mucosal healing at week 54 of 49%, 27%, 14%, and 8%, respectively. While assessment of mucosal healing is a valuable emerging measure of disease activity and subsequently efficacy, more investigation via a placebo-controlled trial would be useful.

Trough Certolizumab Levels and Anti-drug Antibodies

Antibodies to certolizumab developed in 8% of patients treated with certolizumab in the PRECiSE I trial, including 4% of patients treated with concomitant immunosuppressive therapy and 10% who were not treated with concomitant immunosuppressive therapy [57]. The importance of adequate drug levels has also been demonstrated in certolizumab through post hoc analysis of clinical trial data [60]. This study demonstrated that higher levels of certolizumab were significantly associated with response and remission at week 10 ($p = 0.0016$ and 0.0302 respectively) as well as remission ($p = 0.0206$) at week 54 of the MUSIC trial [60, 61]. Additionally, there was a significant inverse relationship between levels of certolizumab in plasma and body weight ($p = 0.0373$) and C-reactive protein ($p = 0.0014$) [60]. This publication did not speculate as to what an adequate trough level may be, but the range of plasma concentration of certolizumab at week 54 in the response and remission groups was 14.9–38.1 μg/mL [60]. It appears that certolizumab at 400 mg q4 weeks in adults (roughly 6 mg/kg) may be significantly underdosed, as the highest quartile of serum drug levels had the highest response, and no dose plateau has been reached. Given the best responses in phase 2 studies were at 10 mg/kg dosing, higher doses and higher serum trough levels may be needed to produce optimal responses to certolizumab.

Golimumab in Children

Golimumab is a fully human IgG antibody specific for TNF-α (Fig. 33.1a) that has approved indications in adults for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis. It is administered subcutaneously with bioavailability of approximately 53% [40]. Golimumab binds bioactive TNF-α, both membrane bound and soluble, and through inhibition of TNF-α reduces levels of several cytokines and inflammatory proteins such as IL-6 and C-reactive protein, with unclear contribution towards antibody, complement, and apoptotic cell lysis [68].

The Program of Ulcerative Colitis Research Study Utilizing an Investigational Treatment in Pediatrics Pharmacokinetics (PURSUIT-PEDS PK) Study Group presented abstracts at Advances in IBD in 2015 and DDW 2016 describing an open-label pharmacokinetic study of golimumab in pediatric patients with moderate to severe ulcerative colitis who had failed corticosteroids or immunomodulators but were anti-TNF-α naïve [69–71]. The induction dosing sequence was given at weeks 0, 2, and 6. Dosing was weight based and administered subcutaneously. Patients <45 kg were given 90 mg/m^2 for the initial dose, followed by 45 mg/m^2/dose thereafter, while those ≥45 kg were given 200 mg followed by 100 mg/dose. In this study, 35 patients achieved similar serum concentration to published adult data at weeks 2, 4, 6, and 14. By week 6 of induction, 60% had clinical response and 43% achieved clinical remission. By week 6, partial mucosal healing (Mayo endoscopy subscore 0 or 1) was achieved in 54% and complete healing (subscore 0) in 23%. Fifteen patients (43%) discontinued the drug prior to week 14, 12 of whom discontinued at week 6 for nonresponse. Severe adverse events were reported including exacerbation of disease ($n = 10$) and pancreatitis. Mild injection site reactions were reported in 6 (17%). There were no opportunistic infections. Three patients (9%) developed antibodies to golimumab by week 14.

A case series of golimumab therapy in six pediatric patients with Crohn's disease was recently published by Merras-Salmio et al. [72]. They describe six patients, all from one clinic in Helsinki, with moderate to severe Crohn's disease based on endoscopy 1–3 months prior to initiation of golimumab. All patients had previously been treated with infliximab or adalimumab, and five of the six had been initial responders to anti-TNF-α therapy. The interval between the last anti-TNF-α dose and the first golimumab dose ranged from 1 month to 4.5 years. Four of the six patients had undergone surgery (jejunal/ileal resection $n = 2$; colectomy $n = 2$). They noted that these patients were the most therapy-resistant cases of Crohn's disease in their clinic. All patients underwent the same induction with injections of 200 mg, 100 mg, and 50 mg given at 0, 2, and 6 weeks, respectively. All patients noted a subjective benefit within a few days after the first dose, which was also objectively seen in acute phase reactants and fecal calprotectin. However, the response did not last, and all six patients required therapy escalation within 2 to 6 months of initiation of golimumab therapy. Four of the patients discontinued therapy due to lack of response within 1 year, with length of therapy ranging from 4 to 12 months. Two patients remained on golimumab with continued response at the time of the report, with total therapy time of 18–19 months. One patient was on 100 mg every 3 weeks and the other was one 50 mg every 2 weeks. All patients tolerated the injections well, and no adverse effects related to golimumab were reported [72].

There are no published studies of golimumab in JIA. However Brunner et al. presented an abstract describing a three-part double-blind placebo-controlled trial of patients treated with golimumab and concomitant methotrexate therapy, and then they were randomized to golimumab vs. placebo while continuing methotrexate [73]. They enrolled 173 patients aged 2–17 years with polyarticular JIA. After 48 weeks, they described serious adverse events (SAE) in 13% and serious infections in 3%. The most common SAE was exacerbation of JIA. The rate of serious infections with golimumab was reported to be 3.0 per 100 person-years [74].

Golimumab in Adults

The efficacy of golimumab in ulcerative colitis was established in the Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment (PURSUIT) trials [75–77].

PURSUIT

The PURSUIT-SC and PURSUIT-IV were phase II/III randomized, double-blind, placebo-controlled, multicenter trials that assessed the efficacy of golimumab for induction therapy in patients with moderate to severe ulcerative colitis [75, 76]. The PURSUIT-IV trial study utilized intravenous golimumab in the treatment arm, while the PURSUIT-SC trial used subcutaneous golimumab. Patients enrolled in these studies had Mayo scores of 6–12, with an endoscopic subscore ≥2. Eligibility required that patients had failed therapy with one or more conventional therapies or were corticosteroid dependent and excluded patients who had previously been on anti-TNF therapy.

PURSUIT-IV, the intravenous dosing study, was ultimately assigned 291 patients randomized to receive one-time induction doses of 1 mg/kg, 2 mg/kg, or 4 mg/kg of golimumab intravenously or placebo [75]. Enrollment in the phase III portion was stopped due to lack of efficacy in the phase II

portion, with 44.0% and 41.6% of the 2 mg/kg and 4 mg/kg groups, respectively, achieving clinical response compared to 30.1% for placebo at week 6 ($p = 0.081$ and 0.145, respectively). Clinical response was defined as Mayo score decrease from baseline ≥ 30% and ≥3 points, with rectal bleeding subscore of 0 or 1, or a decrease from baseline rectal bleeding score of ≥1.

PURSUIT-SC utilized subcutaneous dosing to evaluate 1064 adults with ulcerative colitis [76]. Enrollment criteria were the same as described above for PURSUIT-IV. Clinical response was again defined as Mayo score decrease from baseline ≥ 30% and ≥3 points, with rectal bleeding subscore of 0, or 1, or a decrease from baseline rectal bleeding score of ≥ 1. Remission was defined as Mayo score ≤ 2 with no individual subscore >1. Mucosal healing was defined as having an endoscopy subscore of 0 or 1. Initially, 169 adults were randomized to receive induction dosing at week 0 and week 2 of golimumab with doses of 100 mg/50 mg, 200 mg/100 mg, or 400 mg/200 mg, respectively, or placebo. Of these, 164 were analyzed for efficacy and the information was used for dose finding. One hundred and twenty-two additional patients were randomized using the same dosages, and data from this group were included in safety reports and analysis of pharmacokinetics. The 200 mg/100 mg and 400 mg/200 mg doses were selected based on these results for phase III development. In the phase III studies, 774 patients were randomized to receive golimumab at doses of 200 mg/100 mg or 400 mg/200 mg or placebo as induction therapy at week 0 and week 2, respectively. Seven hundred and sixty-one subjects were analyzed in the primary efficacy analysis. At week 6, the proportion of patients achieving clinical response was 51.0% for the 200 mg/100 mg group, 54.9% for the 400 mg/200 mg, and 30.3% of the placebo group ($p < 0.0001$ for both groups vs. placebo). Both treatment groups also achieved statistical significance vs. placebo for proportion of patients achieving clinical remission, mucosal healing, and IBDQ improvement from baseline. Based on this study, golimumab at induction doses of both 200 mg/100 mg and 400 mg/200 mg at week 0 and week 2 was established as efficacious therapy for adults with moderate to severe ulcerative colitis.

PURSUIT-M was a study of golimumab for maintenance therapy [77]. In this randomized, double-blind trial, the 464 patients who responded to golimumab induction from the prior PURSUIT trial were then randomized to receive placebo or golimumab at doses of 50 mg or 100 mg every 4 weeks through 52 weeks. Primary endpoint analysis was performed in 456 of the original 464 patients, with the primary endpoint being continued maintenance of clinical response (as defined in PURSUIT-SC) through week 54. This was achieved in 49.7% of the 100 mg treatment group and 47.0% of the 50 mg treatment group compared to 31.2% of the placebo group ($p < 0.001$ and $p = 0.010$, respectively). Secondary endpoints in this trial were not unanimously significant for both treatment groups vs. placebo, but taken as a whole, this study indicates that golimumab is more effective than placebo for maintenance therapy in adults with ulcerative colitis who initially responded to induction therapy with golimumab.

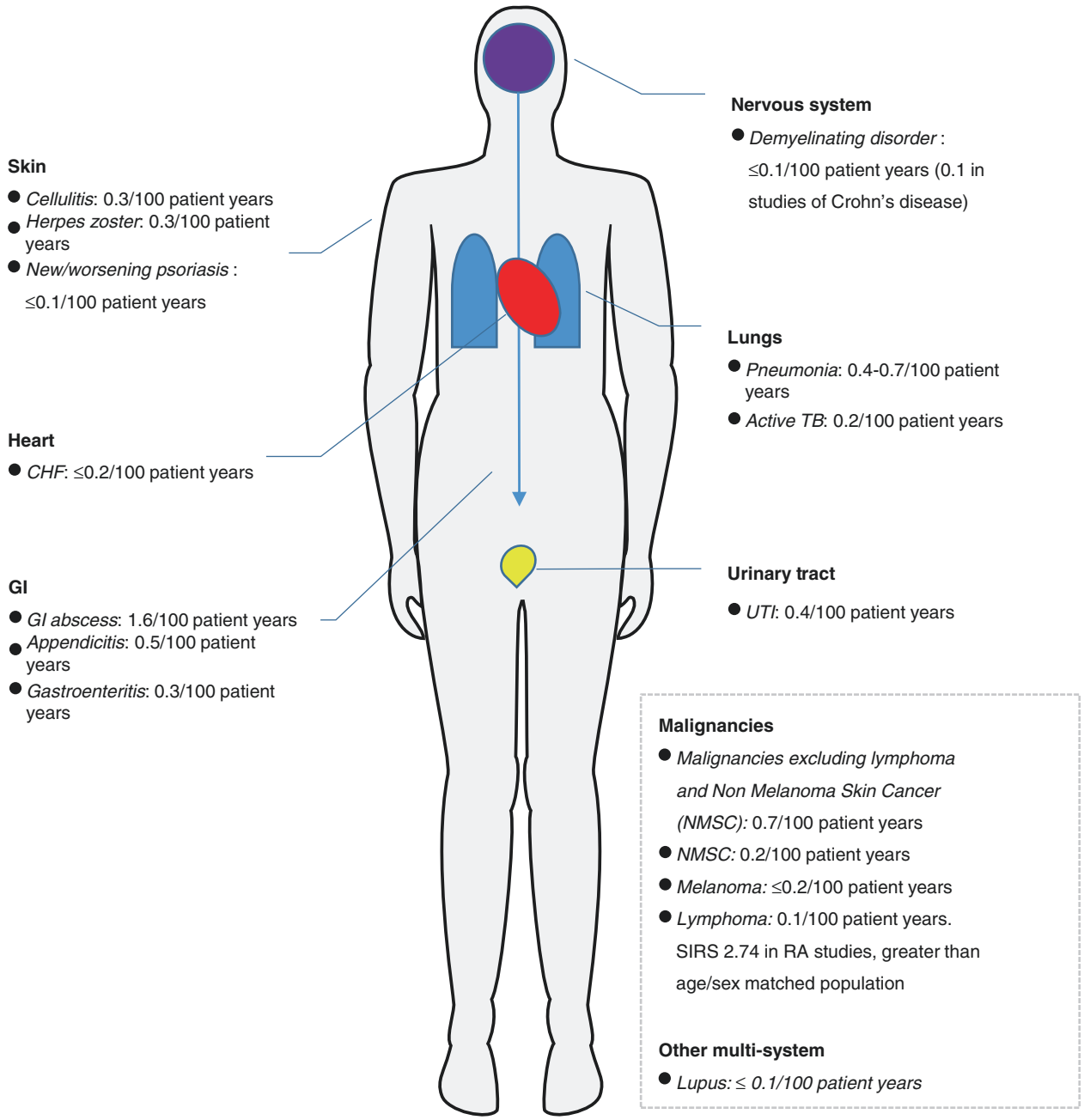
Little data on the effects of golimumab drug levels on clinical or mucosal response is available, but anti-drug antibody rates are low, as 0.4% of patients assessed for antibodies were found to have antibodies to golimumab [76].

Safety Data

There are extensive safety data in adult studies and post-marketing surveillance studies of adults with IBD treated with anti-TNF therapies. One of the largest studies of adverse events associated with adalimumab therapy in adults is a long-term safety analysis by Burmester et al., which is summarized in Fig. 33.2 [78]. Adverse events with other anti-TNF therapies in adults are similar in type and in rate per patient-year. Pediatric-specific data are limited.

As the most often cited concerns regarding anti-TNF risks are cancer and infection, Dulai et al. performed a systematic review of the literature to quantify the incidence of serious infection, lymphoma, and death with anti-TNF therapy in children with Crohn's disease and ulcerative colitis [79]. They searched MEDLINE, Embase, Cochran Library, and Web of Knowledge through March 22, 2013. Any case series with less than five patients were excluded. They included 65 studies, with a total of 5528 patients and 9516 patient-years of follow-up (PYF), in their final analyses. The majority of studies reported on fewer than 100 patients and had a follow-up period shorter than 2 years. Eighty-four percent of the patients had Crohn's disease, 11% ulcerative colitis, and 5% indeterminate colitis. Ten percent of the patients with Crohn's disease were on adalimumab, the remainder of Crohn's disease, UC, and indeterminate colitis patients were on infliximab. They reported that among prospective studies, 16 of 294 patients on adalimumab developed serious infection during 545 PYF. This rate was similar to that seen in patients on infliximab. They reported 2 patients who developed lymphoma, both of whom had been on infliximab, yielding a rate of 2.1 per 10,000 PYF. They reported on seven patient deaths, two of which were believed to be unrelated to anti-TNF-α therapy. The remaining 5 yielded an absolute rate of 5.3 per 10,000 PYF. Two of the five had been on adalimumab, and both died from central-line-related sepsis while receiving parenteral nutrition.

Another systematic review of the efficacy and safety of adalimumab in pediatric Crohn's disease by Dziechciarz et al. was recently published [80]. They searched MEDLINE, EMBASE, the Cochrane Library, and abstracts from the



[1] Adalimumab is the most studied of the three anti-TNFs covered in this chapter. The data shown is derived from a long term safety analysis of 23,458 patients (36,730.5 patient years) from clinical trials of adalimumab [Burmester, et. al]

[2] Adverse Event highlights [Burmester, et. al]:

- Most common serious AEs were infections
- Malignancies, excluding non-melanomatous skin cancer, were similar to that expected in the general population
- AE leading to death: ≤ 0.8/100 patient years
- Serious opportunistic infections: <0.1/100 patient years

[3] In a recent large meta-analysis, certolizumab was statistically more likely to cause a serious adverse event vs. placebo (OR 1.57), while adalumumab and golimumab were not [Singh et. al]

Fig. 33.2 Adverse events associated with anti-TNF biologics in adults based on long-term data with adalimumab and certolizumab[1–3]

main gastroenterology meetings from the past 5 years for randomized controlled trials (RCTs) or observational studies in children and adolescents with onset of Crohn's disease before the age of 18. Case series of less than five patients were not included. Eleven of the 14 articles included in the review reported on safety data, in 599 patients. Forty-nine percent of patients (n = 293/599) reported adverse effects, with infection (n = 162) and injection site reactions (n = 89) the most commonly cited. Other cited adverse events included arthralgia/myalgias (n = 7), xerosis (n = 6), abdominal pain (n = 5), headache (n = 5), nausea (n = 5), allergy (n = 4), depigmentation acne (n = 3), fever (n = 3), rash (n = 3), psoriasis (n = 2), tiredness (n = 2), tympanic membrane perforation (n = 1), dizziness (n = 1), hair loss (n = 1), dyspnea (n = 1), transient visual loss (n = 1), stomal bleeding (n = 1), itching (n = 1), and numbness (n = 1). Twelve percent (n = 69/599) reported serious adverse events, including death due to central-line sepsis (n = 2), medulloblastoma (n = 1), meningitis (n = 1), hematologic related AE (n = 24), allergic reactions (n = 10), hepatic related AE (n = 10), *C. difficile* infection (n = 2), perianal abscess (n = 2), anal abscess (n = 1), stomal abscess with fistula (n = 1), abdominal abscess (n = 3), colonic obstruction and abscess (n = 1), seton placement (n = 1), staphylococcus folliculitis (n = 1), scarlet fever (n = 1), disseminated histoplasmosis (n = 1), gastroenteritis (n = 1), H1N1 influenza (n = 1), viral infection (n = 1), and Yersinia infection (n = 1). One study cited a 35% (n = 64/182) withdrawal rate due to adverse events.

We found no additional studies reporting safety data for adalimumab in pediatric patients with inflammatory bowel disease that had not been included in either of these systematic reviews.

Comparative Effectiveness

Many authors have independently evaluated the efficacy of anti-TNF therapy in the treatment of inflammatory bowel disease [81–87]. In network meta-analyses (NMA) evaluating patients with Crohn's disease, infliximab, adalimumab, and certolizumab have all been found to be superior to placebo [82, 84]. These studies found trends toward superiority of infliximab relative to the other agents that did not reach significance [82, 84]. Additionally, one study found that when assessing the subcutaneous agents, adalimumab was superior to certolizumab for induction of remission [84].

Similarly, network meta-analysis of the anti-TNFs approved for ulcerative colitis have demonstrated that infliximab, adalimumab, and golimumab are all superior to placebo in measures of induction and maintenance of response and remission [81, 85, 86]. When taken as a whole, these studies also suggest that infliximab trends toward superiority to the other anti-TNF agents in the treatment of ulcerative colitis [81, 85, 86]. Similar to the network meta-analysis of Crohn's disease, this value determination is based on trends as opposed to statistically significant findings or superiority that is only statistically significant in a subset of measures. Of note, one NMA that specifically evaluated golimumab vs. infliximab vs. adalimumab for the treatment of ulcerative colitis found that golimumab and infliximab are comparable in efficacy, with golimumab being superior to adalimumab for sustained outcomes and infliximab being superior to adalimumab in the period following induction [87].

While these data support the use of the anti-TNF biologics discussed in this chapter for Crohn's disease and ulcerative colitis, an important additional consideration is choosing an initial anti-TNF agent in the biological therapy-naïve patient. One large systematic review specifically looked at biologic-naïve patients with Crohn's disease and concluded that infliximab is numerically the most efficacious anti-TNF agent to initiate therapy in Crohn's disease [83]. In this study both infliximab and adalimumab (but not certolizumab) were more likely to induce remission than placebo, and no significant direct differentiation between agents was able to be made [83]. Similarly, a network meta-analysis comparing infliximab to adalimumab in anti-TNF-naïve patients with ulcerative colitis found that both were superior to placebo and that infliximab trended toward superiority to adalimumab for induction of remission, mucosal healing, and response at 8 weeks, but not statistically significantly different in these measures at 52 weeks [86].

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