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IMMUNOLOGY AND INFLAMMATION (W GAUSE AND L COVEY, SECTION EDITORS)

What We Can Learn from Current Inflammatory Bowel Disease (IBD) Biological Therapy—Dose Regimen and Others

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Abstract

Purpose of Review Inflammatory bowel disease (IBD), such as Crohn's disease (CD) and ulcerative colitis (UC), is an unmet need as indicated by less than ideal remission rates with current treatments. Understanding the clinical development of approved IBD biological therapy, particularly dose selection, may help improve future biologic development.

Recent Findings Seven biologics have been approved for CD and/or UC in the last two decades (as of January 2019), including anti-tumor necrosis factors (anti-TNFs) (infliximab, adalimumab, certolizumab, and golimumab), anti-integrins (natalizumab and vedolizumab), and anti-interleukin (IL)-12/IL-23 (ustekinumab). These agents demonstrate effectiveness in inducing sustained clinical remission despite the high and variable "placebo" response. Side effects such as infections and malignancies can occur for biologics partly due to the long-term immunosuppression. IBD biologics typically employ an intensive induction followed by maintenance therapy. Approved dose regimen (especially induction) tends to be the same or close to the highest doses that have been evaluated in clinical development, indicating a limited dose range tested. Biologics approved for CD and UC use the same dose regimen though a given drug may not work equally effectively for both indications.

Summary Lessons learned from current IBD biological therapy may help enhance the clinical development efficiency of future biologics, e.g., test a wide dose range; characterize full dose-response for desirable and untoward effects; understand influencing factors to the treatment (and placebo) effect; and leverage dose-ranging learning between CD and UC.

Keywords Inflammatory bowel disease · Biologics · Dose selection · Efficacy · Safety

Introduction

Inflammatory bowel disease (IBD) refers to a group of chronic inflammatory diseases of the gastrointestinal tract that results from the complex interplay of several factors, including dysregulated immune system, abnormal genetic factors, environmental triggers, and gut microbiome disturbances [1, 2]. IBD is comprised of two major clinical entities, Crohn's disease (CD) and ulcerative colitis (UC), which have some similarities and unique differences [3]. The inflammation of CD is transmural and discontinuous, affecting the entire gastrointestinal tract from the mouth to the anus, whereas UC is characterized by superficial colonic-restricted inflammation that progresses in a continuous manner proximally from the rectum [4]. The recent molecular profiling and genome-wide association study findings point to more similarities in dys-regulated sub-networks and biology of these two indications [5].

In clinical practice, the severity of CD and UC is typically measured as composite endpoints. For example, Crohn's Disease Activity Index (CDAI), which is used to determine the severity of CD, considers the following factors: the number of liquid stools, abdominal pain, sense of well-being, extra-intestinal complications, whether the patient is taking anti-diarrheal drugs, abdominal mass, hematocrit, and the deviation from standard weight. The severity of UC is usually measured

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using the Mayo Index, including stool frequency, rectal bleeding, mucosal healing, and the physician's global assessment. Disease remission for CD and UC is generally considered as a CDAI score of less than 150 [6] and a Mayo Score of ≤ 2 with no individual sub-score greater than 1 [7], respectively. In addition to these indices, inflammation markers such as serum C-reactive protein (CRP), fecal calprotectin, and fecal lactoferrin can be used to differentiate IBD from similar diseases such as irritable bowel syndrome (IBS).

The incidence of both CD and UC increased substantially during the twentieth century, associated with morbidity, mortality, and substantial costs to the health care system. A recent systemic review indicates that the prevalence of IBD has risen to more than 0.3% of the population in North America, Australia, and many countries in Europe [8]. The introduction and the widespread use of biologic agents over the last 2 decades have revolutionized the treatment paradigm in the clinical management of patients with IBD [9]. Currently, all approved biologic agents in IBD are monoclonal antibodies (or fragments thereof), and these agents induce sustained clinical remission, avoid the chronic needs for steroids, reduce hospitalizations, and prevent interventions for complications. This is a dramatic improvement over the conventional small molecular pharmacologic treatments for IBD such as aminosalicylates, corticosteroids, immunomodulators, and antibiotics, which are now commonly used as concomitant medications along with the biologics [10••, 11].

Despite the many advances in the therapeutic landscape for IBD, a significant portion of patients either fail to respond (i.e., primary non-response) or lose their initial response (i.e., secondary non-response) to treatment, highlighting the unmet medical need for more effective therapies, especially over the longer term [12, 13••]. This paper will review the therapeutic biologics currently approved for the treatment of IBD (excluding biosimilars), with a special focus on the dose and regimen selection in their clinical IBD development programs. Induction and maintenance dosing paradigm of IBD therapy and the leveraging of dose-ranging learning across CD and UC will also be discussed. Other topics that are briefly mentioned are mechanisms of action and clinical effectiveness and safety of these agents. From this review, we intend to highlight a few practical considerations that may help in the future clinical development of IBD biologics. Notably, the information described hereby is based on the original "innovator" products and for adult indications only, with most information coming from US package insert (USPI) until otherwise noted.

Mechanisms of Action of Current IBD Biological Therapy

As of January 2019, there are seven biologic agents (excluding biosimilars) approved for the treatment of CD and/or UC within three mechanisms of action: anti-tumor necrosis factor alpha (TNFα), anti-integrin, and anti-interleukin (IL)-12/IL-23. These biologics suppress the overactive immune system that plays a key role in IBD pathology, thereby reducing inflammation. Table 1 provides an overview of these IBD biologics; drugs are grouped according to their mechanisms of action and listed chronologically by the approval date when having the same mechanism of action.

TNF antagonists work by neutralizing TNFα, a pro-inflammatory cytokine with a central role in the inflammatory processes, including IBD. Four anti-TNF agents have been approved for the treatment of CD and/or UC, including infliximab (approved for CD in 1998 and UC in 2005 [Remicade® USPI]) [16], adalimumab (approved for CD in 2007 and UC in 2012 [Humira® USPI]) [17], certolizumab pegol (approved for CD in 2008 [Cimzia® USPI]) [18], and golimumab (approved for UC in 2013 [Simponi® USPI]) [19]. Infliximab was the first therapeutic protein approved for IBD. It is a chimeric IgG1 monoclonal antibody containing ~25% mouse sequence and ~75% human sequence, with a terminal elimination half-life of ~7–9 days. Certolizumab pegol is a humanized antigen-binding (F_{ab}') fragment of a monoclonal antibody linked to polyethylene glycol that enhances solubility and prolongs elimination half-life (~2 weeks). Adalimumab and golimumab are both human IgG1 antibodies (terminal half-life of ~2 weeks), which appear to have a lower incidence of immunogenicity compared to infliximab.

Anti-integrin agents work by blocking leukocyte migration from the blood vessels to sites of inflammation via inhibiting cell adhesion molecules. Cell adhesion molecules are transmembrane proteins expressed on endothelial cells and leukocytes and are critical for the migration of memory T lymphocytes across the endothelium into the inflamed gastrointestinal parenchymal tissue. Two anti-integrin humanized IgG monoclonal antibodies have been approved for the treatment of IBD, including natalizumab (approved for CD in 2008 [Tysabri® USPI]) [20] and vedolizumab (approved for CD and UC in 2014 [Entyvio® USPI]) [21]. Natalizumab binds to the α4-subunit of α4β1 and α4β7 integrins expressed on the surface of all leukocytes except neutrophils and inhibits the α4-mediated adhesion of leukocytes to their counter-receptor(s), whereas vedolizumab specifically targets α4β7 integrin and blocks the interaction of α4β7 integrin with mucosal addressin cell adhesion molecule-1 (MAdCAM-1). Vedolizumab does not bind to or inhibit the function of the α4β1 and αEβ7 integrins and does not antagonize the interaction of α4 integrins with vascular cell adhesion molecule-1 (VCAM-1).

Anti-IL-12/IL-23 agents work by neutralizing IL-12 and IL-23, two cytokines that have been implicated as important contributors to the chronic inflammation that is a hallmark of CD and UC. Ustekinumab is a fully human IgG1κ

monoclonal antibody directed against the common p40 subunit of IL-12 and IL23. It is the only anti-IL-12/IL-23 agent approved for IBD therapy (approved for CD in 2016 [Stelara® USPI] [22] and currently in development for UC [23]).

Effectiveness and Safety of Current IBD Biological Therapy

Clinical Effectiveness

The clinical effectiveness of the seven biologic agents approved for CD and/or UC have been extensively reviewed elsewhere [12, 13••, 24, 25]. For the convenience of the readers, we briefly summarized the clinical efficacy profiles of these agents in Table 1, with a focus on clinical remission following the induction and maintenance treatment at the approved dose regimen (based on USPI). As the study design, assessment period and the definition of remission are not identical across trials and biologics, remission rates listed hereby may not be directly comparable. Please refer to the systematic review and meta-analysis reports from Cochrane Library (https://www.cochranelibrary.com/cdsr/about-cdsr) for the comparison of clinical effectiveness across compounds for the management of IBD, including biologics.

Overall, effectiveness in inducing and maintaining remission in patients with CD and/or UC have been shown for the approved biologics: greater proportions of patients treated with these biologic agents achieved remission compared to placebos in the phase 3 pivotal induction and maintenance trials (Table 1). Of note, the "placebo" response seems to be high and variable across trials. Understanding the magnitude and time course of placebo response as well as the influencing factors would help design an efficient IBD trial to detect the true treatment effects. An analysis has been conducted to examine the placebo effect in CD induction treatment, where placebo remission rates through week 12 from 43 randomized placebo-controlled trials in patients with CD were pooled and analyzed [26]. Results suggest that the median placebo remission rates gradually increased over time and reached a plateau by weeks 8–12 (~ 20–23%); however, the placebo remission rate varied greatly for each individual trial. It was found that the placebo remission rates tended to be higher in anti-TNF-naive patients who had lower disease burden (i.e., lower baseline CDAI score). Additional work is needed to investigate the placebo effects in UC induction therapy. For maintenance therapy, placebo response may not represent the "true" placebo effect. Many of the maintenance trials are randomized withdrawal trials (or enriched trials), where induction responders to biologic agents are (re)randomized to biological maintenance therapy or placebo. Due to the carry-over effect, maintenance "placebo" rates from trials with re-randomization tend to be higher than those in trials with the treat-through design. In certolizumab CD maintenance trials, placebo remission rates were 18% in the treat-through trial versus 29% in the trial with re-randomization (Cimzia® USPI) [18]. Therefore, trial design, among many other factors, should be considered when examining the placebo effect over maintenance therapy.

As shown in Table 1, remission rates following IBD biological therapy tend to be low in anti-TNF-experienced versus anti-TNF-naïve populations. Most anti-TNF-experienced patients are patients who had failed TNF antagonist due to intolerance, inefficacy, or loss of efficacy (patients with adequate disease control with anti-TNFs are less likely to enter trials testing new agents). The insufficient disease control could be a primary non-response to the mechanism of action or a secondary loss of response due to inadequate drug levels and/or antibody formation to the drug [27]. In either case, these patients generally represent a difficult-to-treat population who are considered to have an increased risk to fail another biologic. Factors that could have negatively influenced the clinical outcome for a patient who failed prior anti-TNF therapy might apply to the same patient when receiving a new biologic agent. Patients with high body weights tend to have lower drug concentrations in blood and likely lower exposure in gut tissue (i.e., site of action for IBD) [28] and thus reduced clinical response at a fixed dose regimen (i.e., not body weight-based regimen). Patients who previously developed antibodies against an anti-TNF agent were reported to be more likely to develop anti-drug antibodies to subsequent anti-TNF agents (although none were cross-reactive) [27], and this would negatively impact the drug concentration. In addition to the subtherapeutic drug levels, suboptimal response to biological therapy has also been observed in patients with certain disease characteristics and biomarkers. Patients with heavier disease burden, as manifested by high baseline CDAI or Mayo score/sub-score, and high serum CRP level, may be more difficult to treat [24, 29, 30]. In ustekinumab CD maintenance trial, a greater proportion of ustekinumab-treated patients who had CDAI score < 75 at maintenance baseline achieved remission at week 44, compared to patients with CDAI score ≥ 150 at maintenance baseline [31]. Among the golimumab induction responders in UC maintenance trial, the proportion of patients in clinical response through week 54 was higher in patients who had a lower serum CRP (< 8 mg/L) than those with a higher CRP (≥ 8 mg/L) [32]. Nevertheless, despite the many potential influencing factors for IBD treatment, none of these seems to have a clinically significant impact on the dose-response (efficacy/safety) of approved IBD biologics, where covariate-based dose adjustment is not recommended.

Clinical Safety

Despite some safety-related observations, a large number of clinical trials have demonstrated that the benefits outweigh the risks for biologics approved for treatment of CD and/or UC. Biologics are generally considered to have a relatively wider

Table 1 Summary of Therapeutic Biologics Approved for the Treatment of IBD

Compound	Type/ Target/ Terminal half-life	Indication[a] (Approval Date)	Recommended Dose Regimen[a]	Clinical Remission Rate[a]	Major Side Effects[a,b]
Anti-TNFα					
Infliximab	*Type* Chimeric IgG1κ mAb *Target* TNFα *Half-live* ~7.7-9.5 days	*CD* (August 24, 1998) *UC* (September 15, 2005)	*CD and UC:* 5 mg/kg IV initially and at W2 and W6, followed by 5 mg/kg IV q8w thereafter. Some CD patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response. *Induction/maintenance dose ratio:* A total of 10 mg/kg IV over 1st 6 weeks/5 mg/kg IV q8w = **2.7-fold**	CD *Induction:* W4 (anti-TNF naïve): [Single dose at W0][e] Placebo= 4% Active= 48% *Maintenance:* W30 (anti-TNF naïve): [RWD, randomized at W2] Placebo= 25% Active= 39% UC *Induction:* W8 (anti-TNF naïve): [TT] Placebo= 15% Active= 39% *Maintenance:* W54 (anti-TNF naïve): [TT] Placebo= 17% Active= 35%	• **Serious infections** • **Malignancies** • **Fatal Hepatosplenic T-cell Lymphoma** • Hypersensitivity reactions • Hepatotoxicity • Hepatitis B virus reactivation • Neurologic reactions: new onset or exacerbation of demyelinating disease • Hematological reactions: cytopenia • Cardiovascular or cerebrovascular reactions • Autoimmunity: lupus-like syndrome
Adalimumab	*Type* Human IgG1κ mAb *Target* TNFα *Half-live* ~ 2-weeks	*CD* (February 27, 2007) *UC* (September 28, 2012)	*CD and UC:* 160 mg SC initially, followed by 80 mg SC at W2 and then 40 mg SC q2w. *Induction/maintenance dose ratio:* A total of 240 mg SC over 1st 4 weeks/40 mg SC q2w = **3-fold**	CD *Induction:* W4 (anti-TNF naïve): [TT] Placebo= 12% Active= 36% W4 (anti-TNF experienced): [TT] Placebo= 7% Active= 21% *Maintenance:* W56 (anti-TNF mixed)[d]: [RWD, re-randomized at W4[f]] Placebo= 12% Active= 36%	• **Serious infections** • **Malignancies** • Hypersensitivity reactions • Neurologic reactions: new onset or exacerbation of CNS/peripheral demyelinating disease • Hematological reactions: cytopenia • Worsening heart failure • Autoimmunity: lupus-like syndrome

Table 1 (continued)

Compound	Type/ Target/ Terminal half-life	Indication[a] (Approval Date)	Recommended Dose Regimen[a]	Clinical Remission Rate[a]	Major Side Effects[a,b]
				UC *Induction:* W8 (anti-TNF naïve): [TT] Placebo= 9.2% Active= 18.5% W8 (anti-TNF experienced): [TT] Placebo= 7% Active= 9% *Maintenance:* W52 (anti-TNF mixed)[d]: [TT] Placebo= 8.5% Active= 17.3% W52 (anti-TNF experienced)[d]: [TT] Placebo= 3% Active= 10%	
Certolizumab pegol	*Type* Humanized antibody Fab' fragment, conjugated to an approximately 40-kDa PEG *Target* TNFα *Half-live* ~ 2-weeks	*CD* (April 22, 2008)	400 mg SC initially and at W2 and W4, followed by 400 mg SC q4w thereafter. *Induction/maintenance dose ratio:* A total of 800 mg SC over 1st 4 weeks/400 mg SC q4w = **2-fold**	*Induction:* W6 (anti-TNF naïve) [53]: [TT] Placebo= 25% Active= 32% W6 (anti-TNF mixed)[d]: [TT] Placebo= 17% Active= 22% *Maintenance:* W26 (anti-TNF mixed)[d]: [TT] Placebo= 18% Active= 29% W26 (anti-TNF mixed)[d]: [RWD, re-randomized at W6[f]] Placebo= 29% Active= 48%	• **Serious infections** • **Malignancies** • Anaphylaxis or serious allergic reactions • Hepatitis B virus reactivation • Neurologic reactions: new onset or exacerbation of demyelinating disease • Hematological reactions: cytopenia • Worsening or onset heart failure • Autoimmunity: lupus-like syndrome

Table 1 (continued)

Compound	Type/ Target/ Terminal half-life	Indication[a] (Approval Date)	Recommended Dose Regimen[a]	Clinical Remission Rate[a]	Major Side Effects[a,b]
Golimumab	*Type* Human IgG1κ mAb *Target* TNFα *Half-live* ~ 2-weeks	*UC* (May 15, 2013)	200 mg SC initially, followed by 100 mg SC at W2 and then 100 mg SC q4w. *Induction/maintenance dose ratio:* A total of 300 mg SC over 1st 6 weeks/100 mg SC q4w = **2-fold**	*Induction:* W6 (anti-TNF naïve): [TT] Placebo= 6% Active= 18% *Maintenance:* W54 (anti-TNF naïve) [40]: [RWD, re-randomized at W6[f]] Placebo= 22% Active= 34%	• **Serious infections** • **Malignancies** • Hypersensitivity reactions • Hepatitis B virus reactivation • Neurologic reactions: new onset or exacerbation of demyelinating disease • Hematological reactions: cytopenia • Worsening or onset congestive heart failure • Autoimmunity: lupus-like syndrome
Anti-Integrin					
Natalizumab	*Type* Human IgG4κ mAb *Target* α4β1/α4β7 integrins (α4-subunit) *Half-live* ~ 10 days	*CD* (January 12, 2008)	300 mg IV q4w *Induction/maintenance dose ratio:* 1-**fold**	*Induction:* W12 (anti-TNF mixed)[d]: [TT] Placebo= 25% Active= 37% *Maintenance:* W36 (anti-TNF mixed)[d]: [RWD, re-randomized at W12[f]] Placebo= 26% Active= 45%	• **Increases risk of multifocal leukoencephalopathy (PML)** • Herpes infection • Hepatotoxicity • Hypersensitivity reactions Infections
Vedolizumab	*Type* Human IgG1κ mAb *Target* α4β1 integrin *Half-live* ~ 25 days at 300 mg IV dosage.	*CD* (May 20, 2014) *UC* (May 20, 2014)	300 mg IV initially and at W2 and W6, then q8w thereafter. *Induction/maintenance dose ratio:* A total of 600 mg IV over 1st 6 weeks/300 mg IV q8w = **2.7-fold**	CD *Induction:* W6 (anti-TNF mixed)[d]: [TT] Placebo= 7-12% Active= 15% *Maintenance:* W52 (anti-TNF mixed)[d]: [RWD, re-randomized at W6[f]] Placebo= 22% Active= 39% UC *Induction:* [TT] W6 (anti-TNF mixed)[d]: Placebo= 5% Active= 17%	• Progressive multifocal leukoencephalopathy (PML) • Hypersensitivity reactions including anaphylaxis Infections

Table 1 (continued)

Compound	Type/ Target/ Terminal half-life	Indication[a] (Approval Date)	Recommended Dose Regimen[a]	Clinical Remission Rate[a]	Major Side Effects[a,b]
				Maintenance: W52 (anti-TNF mixed)[d]: [RWD, re-randomized at W6[f]] Placebo= 16% Active= 42%	
Anti-IL-12/IL-23					
Ustekinumab	*Type* Human IgG1κ mAb *Target* IL-12/IL-23 (p40 subunit) *Half-live* ~19 days	*CD* *(*September 23, 2016)	~ 6 mg/kg IV (260 mg, 390 mg, and 520 mg for weight range of ≤ 55 kg, 55 – 85 kg and > 85 kg, respectively) at W0, followed by 90 mg SC at W8 and q8w thereafter. *Induction/maintenance dose ratio:* A total of 6 mg/kg IV over 1st 8 weeks/90 mg SC q8w = **5.8-fold**[c]	*Induction:* W8 (anti-TNF naïve): [TT] Placebo= 20% Active= 40% W8 (anti-TNF experienced): [TT] Placebo= 7% Active= 21% *Maintenance:* W44 (anti-TNF mixed)[d]: [RWD, re-randomized at W8[f]] Placebo= 36% Active= 53%	• Infections: Tuberculosis • Malignancies • Hypersensitivity reactions • Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

[a] From US Package Insert (USPI), unless otherwise indicated.

[b] Side effects bolded as listed as Black-box Waring in USPI.

[c] Assuming body weight of 70 kg and SC bioavailability of 75%.

[d] Trial conducted in a mixed anti-TNF naïve and anti-TNF experienced patient population.

[e] Data from a single dose trial, where patients received single 5 mg/kg infliximab IV or placebo at week 0.

[f] Patients who achieved clinical response with induction therapy were re-randomized.

Abbreviations: CD, Crohn's disease; IL, interleukin; IV, intravenous; IBD, inflammatory bowel disease; mAb, monoclonal antibody; kDa, kiloDalton; PEG, polyethylene glycol; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; qw, every week; SC, subcutaneous; RWD, randomized withdrawal study design; TNFα, tumor necrosis factor alpha; TT, treat-through study design; UC, ulcerative colitis; W0 (2,4,…), week 0 (2,4,…).

therapeutic window when compared to small molecule drugs, partly due to the high affinity and target specificity of biologics with less off-target effects. However, when the pharmacodynamic (PD) effects become exaggerated due to the potent and sustained suppression of the immune system, a range of adverse effects could be encountered with biological therapy, e.g., serious infection or malignancy, some of which have been fatal [33, 34]. In addition, administration of biologics carries the risk of immune reactions such as acute anaphylaxis, serum sickness, and generation of antibodies to drugs. Other notable adverse events associated with these complex therapeutic proteins include demyelinating disorders, liver enzyme elevation, autoimmune diseases (such as lupus), infusion/injection site reactions, and other hypersensitivity reactions. Table 1 lists the major side effects potentially associated with approved IBD biologics (based on USPI).

Certain side effects such as infections are the result of inhibition of the protective functions of the targeted cytokines and related immune cells. Serious infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens have been reported in patients with IBD who received anti-TNFs and other immunosuppressant therapeutic biologics. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with these therapeutic proteins, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to the initiation of therapy [34].

Malignancy, albeit rare, has been another important concern when using the immunosuppressant biologics. In controlled clinical trials of anti-TNFs, more cases of lymphoma and leukemia have been observed among patients receiving anti-TNF treatment compared to patients in the control groups; however, there are confounders when assessing the risk of malignancy associated with the use of these biologic agents in patients with chronic inflammatory diseases. Patients with chronic inflammatory diseases, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk (up to several folds) than the general population for the development of lymphoma and leukemia, even in the absence of anti-TNF therapy [35].

Some side effects of IBD biologics are considered to be mechanism related. For the anti-integrins, progressive multifocal leukoencephalopathy (PML), an opportunistic infection caused by the JC virus is a potential side effect. Between the two approved anti-integrin antibodies, natalizumab has a more restricted use with a requirement for patient registration due to its potential risk of PML. It has been hypothesized that preventing α4β1/α4β7 integrin binding to VCAM-1 may result in decreased immune surveillance within the central nervous system, in turn increasing the risk of developing PML. Unlike natalizumab, vedolizumab specifically targets α4β7 and does not inhibit binding at VCAM-1 [36]. Consistently, results from a meta-analysis suggest that the risk of PML with vedolizumab is lower than that with natalizumab [37] though continuous and careful monitoring of patients is needed. For TNF antagonists, lupus-like syndrome has been reported [38]. Most cases of anti-TNF-induced lupus were associated with infliximab and adalimumab (experience with golimumab is limited compared to infliximab or adalimumab in patients with IBD). The exact pathogenesis of anti-TNF lupus reaction is unclear, but proposed hypotheses include anti-TNF-induced cellular apoptosis releasing DNA and lupus auto-antigens, promotion of T-helper 2 immune response, and inhibition of cytotoxic T cells, leading to a reduction of the elimination of autoantibody-producing B cells. Most patients who develop anti-TNF-induced lupus may have a good prognosis, with normalization of autoantibodies and resolution of the symptoms within a few months after discontinuation of the causative agent [38].

Understanding the risks of side effects and complications of interventions is pivotal in drug development. As doses needed for the treatment of IBD are likely higher than those for other inflammatory diseases such as rheumatoid arthritis and psoriasis, patients receiving IBD biological therapy may have a higher risk for side effects. Unexpected serious adverse events that occur in the late-stage development or in the post-marketing setting may lead to delayed/denial of regulatory submission, and even post-marketing application withdrawal. Therefore, it is important to explore the dose-response relationships for safety (in addition to efficacy) prospectively and as thoroughly as possible, and consider whether certain adverse effects may arise during the acute or chronic period of treatment.

Dose and Regimen of Current IBD Biological Therapy

Induction and Maintenance Dosing Paradigm

The seven IBD biologic agents have different dosing regimens (Table 1). Infliximab, natalizumab, and vedolizumab are administered intravenously (IV); adalimumab, certolizumab, and golimumab are administered subcutaneously (SC); while ustekinumab uses a combined initial IV infusion followed by SC maintenance injection.

These biologics typically employ a short-term high-dose induction followed by a long-term low-dose maintenance treatment (except for natalizumab) for the treatment of IBD (Table 1). Intensive induction therapy is used to quickly achieve therapeutic drug exposure in order to obtain rapid control of the inflammatory disease burden. Once the inflammatory processes and the underlying disease pathophysiology have been adequately controlled, the drug

exposure or dose required to maintain efficacy is considered to be lower than what attained with initial induction dose. Therefore, the maintenance regimen typically represents a step down in dose intensity (lower dose and/or less frequent dosing) relative to the initial induction regimen. For example, the recommended dose of infliximab in CD and UC is 5 mg/kg IV at weeks 0, 2, and 6, followed by 5 mg/kg IV q8w thereafter. When normalized on a weekly basis, this represents a 2.7-fold lower in dose between the first 6-week induction period (1.67 mg/kg/week) and the follow-up maintenance treatment (0.625 mg/kg/week). Using a similar approach by normalizing dose on a weekly basis, the estimated induction relative to maintenance dose ratio ranged from 2-fold (certolizumab, golimumab) to 2.7-fold (infliximab, vedolizumab), 3-fold (adalimumab), and 5.8-fold (ustekinumab). In this regard, IV route of administration may be desirable for biologic agents, as the initial intensive IBD therapy would deliver a high dose of the agents in order to achieve rapid and sufficient disease control, whereas SC route of administration may be preferred for long-term maintenance therapy for patients' convenience.

Of note, the IBD induction treatment duration varies among the seven approved biologics. For the four anti-TNFs, the induction treatments are approximately 4–6 weeks; for the anti-integrins, the induction treatments are up to 12 weeks, while the anti-IL-12/23 ustekinumab uses an 8-week induction. Optimized induction treatment duration could be vital for the clinical management of patients with IBD—too long an induction treatment could result in unnecessarily high-drug exposure to the patients, which may lead to unacceptable toxicity, while too short an induction may reduce the chance of showing maximal efficacy. Vasudevan et al. [39•] reviewed the time-to-response for current IBD therapies, including biologics. It was found that anti-TNFs typically have a rapid time-to-response, working in most patients within the first 4–8 weeks; more rapid clinical remission has also been indicated for infliximab [40] and adalimumab [41] therapies when used with concomitant immunomodulators in patients with IBD. In phase 3 pivotal trials of ustekinumab, clinical response and remission were significant as early as week 3 in ustekinumab-treated patients and continued to improve through week 8 [22]. In contrast, anti-integrins have a slower onset of action, which could take months (at least 10–14 weeks) to achieve maximal efficacy. This may be related to anti-integrin's mechanism of action, with inhibition of lymphocyte gut migration taking more time to achieve therapeutic efficacy. For drugs with the same or similar mechanism of action, marked variations in time-to-response could also occur, which is further influenced by disease, patient-related factors, and concomitant therapies. One study reported that younger age, nonsmokers, absence of previous IBD surgery, and a lower disease activity score were associated with more rapid attainment of clinical remission when treating CD patients with certolizumab pegol [15]. Overall, these data suggest that it is important to understand the time to therapeutic response for drugs being developed for the treatment of IBD, to ascertain whether the dose regimen is optimal with respect to benefit to risk, in particular, if the drug is given an appropriate time frame to achieve maximal benefit in the induction treatment.

Dose and Regimen Selection in Clinical Development

Examination of the doses evaluated in the clinical development may provide valuable information about what has been done effectively in the past, and what could be improved in the future. Table 2 summarizes the doses and regimens tested for the seven approved IBD biologics in their clinical development of CD and/or UC. The following information has been collected: doses and the associated dose range tested in phase 2; doses tested in phase 3 and the dose ratios when compared to the top dose level tested in phase 2; and comparisons of the approved doses to those tested in phase 3 development. Post-marketing requirements (PMRs) [42] issued at the time of approval are also presented in Table 2 in order to demonstrate the changes in the regulatory requirement over the last two decades. From this in-depth review, several interesting trends are noticed and outlined below.

In a few cases, IBD biologics have an approved induction dose being the same or close to the highest dose tested in their IBD clinical development programs, including phase 2 dose-ranging and phase 3 dose confirmation. This has been shown for adalimumab, where the approved induction dose (i.e., 160 mg SC at week 0 and 80 mg SC at week 2) was the highest dose evaluated in its CD and UC clinical programs. Similarly, certolizumab pegol and ustekinumab both have an approved induction dose being the highest dose regimens tested in clinical development. In addition, doses selected for phase 3 development tend to be the top doses tested in phase 2 or even higher. For example, certolizumab pegol employed a more intensive induction regimen in patients with CD in phase 3 (400 mg SC at weeks 0, 2, and 4) when compared to phase 2 (400 mg SC at weeks 0, 4 [and 8]). This represented a 2-fold increase in the total dose level over the first 4 weeks of treatment (400 mg/4 weeks vs 800 mg/4 weeks). When there is no apparent safety concern, such a development approach (i.e., higher phase 3 dose regimen than what have been tested in phase 2) may be acceptable when supported by the totality of data. Likely, the phase 2 dose/exposure-response data indicated that a higher dose and/or more frequent dosing may yield better efficacy for certolizumab pegol. However, when there is consistently a need to choose the highest dose tested in phase 2 or even higher for phase 3, it implies that the dose range tested in phase 2 may not be wide enough. Across the seven approved IBD biologics, the overall dose ranges explored in

Table 2 Dose and Regimen Tested in Clinical Development for Approved IBD Biologics

Indication (Approval date)	Phase 2[a,b]		Phase 3[a,b]		Approved[a]		PMR[c]
	Dose Level	Dose Range	Dose level	vs Phase 2 Top Dose	Dose Level	vs Phase 3 Dose	
Anti-TNFα							
Infliximab							
CD (August 24, 1998)	1, 5, 10, 20 mg/kg sd (IV) 5, 10, 20 mg/kg sd (IV)	***20x (sd)***	*Induction*: 5 mg/kg at W0, W2 and W6 (IV) *Maintenance*: 5, 10 mg/kg q8w (IV)	***NA*** (only sd tested in P2)	5 mg/kg at W0, W2 and W6, and q8w thereafter (IV); May increase to 10 mg/kg IV if patient loses response	*Induction*: Same as P3 (one dose level tested in P3) *Maintenance*: P3 low dose, with escalation option to high dose	• Pediatric PMR • Identify genetic mutations and other biomarkers that predispose IBD patients to developing HSTCL
UC (September 15, 2005)	5, 10, 20 mg/kg sd (IV)	***4x (sd)***	*Induction*: 5 or 10 mg/kg at W0, W2 and W6 (IV) *Maintenance*: 5 or 10 mg/kg q8w (IV)	***NA*** (only sd tested in P2)	5 mg/kg at W0, W2 and W6, q8w (IV)	*Induction*: P3 low dose *Maintenance*: P3 low dose	• Pediatric PMR
Adalimumab							
CD (February 27, 2007)	*Induction:* 40/20 mg, 80/40 mg, or 160/80 mg at W0/W2 (SC) *Maintenance*: 40 mg qw or q2w (SC)	*Induction:* ***4x*** *Maintenance:* ***2x***	*Induction:* 40/20 mg, 80/40 mg, or 160/80 mg at W0/W2 (SC) *Maintenance*: 40 mg qw or q2w (SC)	***NA*** (Combined P2/3 trial)	160 mg at W0, 80 mg at W2 and 40 mg q2w thereafter (SC)	*Induction*: P2/3 high dose *Maintenance*: P2/3 low dose	• A study in IBD patients treated with Humira identify genetic mutations and other biomarkers that predispose these patients to developing HSTCL. • Pediatric PMR
UC (September 28, 2012)	*Induction:* 80/40 mg or 160/80 mg at W0/W2 (SC) *Maintenance*: 40 mg q2w (SC)	*Induction:* ***2x*** *Maintenance:* ***1x***	*Induction:* 80/40 mg or 160/80 mg at W0/W2 (SC) *Maintenance*: 40 mg q2w (SC)	***NA*** (Combined P2/3 trial)	160 mg at W0, 80 mg at W2 and 40 mg q2w thereafter (SC)	*Induction*: P2/3 high dose *Maintenance*: Same as P2/3 (one maintenance dose tested in P2/3)	• Pediatric PMRs • Assess the long-term safety • Evaluate the safety of induction regimens of adalimumab at doses higher than 160/80 mg • Evaluate trough concentrations of adalimumab and antibody levels at the time of loss of clinical remission.
Certolizumab							
CD (April 22, 2008)	1.25, 5, 10, or 20 mg/kg sd (IV)	***16x* (sd)**	*Induction:* 400 mg at W0, W2, and W4	***2x*** (over the first 4-weeks)	400 mg at W0, W2, and W4, and q4w thereafter (SC)	*Induction:* Same as P3 (one dose level tested in P3)	• Pediatric PMR • A long-term study that will include approximately 2000 active treated CD

Table 2 (continued)

Indication (Approval date)	Phase 2[a,b]		Phase 3[a,b]		Approved[a]		PMR[c]
	Dose Level	Dose Range	Dose level	vs Phase 2 Top Dose	Dose Level	vs Phase 3 Dose	
	100 mg, 200 mg, or 400 mg at W0, W4, and W8 (SC)	***4x***	(SC) *Maintenance*: 400 mg q4w (SC)	***NA*** (maintenance treatment not assessed in P2)		*Maintenance:* Same as P3 (one dose level tested in P3)	patients and 2000 matched controls receiving other treatments for CD
Golimumab *UC* (May 15, 2013)	100/50 mg, 200/100 mg, or 400/200 mg at W0/W2 (SC) 1, 2, or 4 mg/kg at W0 (IV)	***4x***	*Induction:* 200/100 mg, or 400/200 mg at W0/W2 (SC) *Maintenance:* 50 mg or 100 mg q4w (SC)	***0.5x/1x*** (2 higher dose tested in P2) ***NA*** (maintenance treatment not assessed in P2)	200/100 mg at W0/W2, and 100 mg q4w thereafter (SC)	*Induction*: P3 low dose *Maintenance*: P3 high dose	• Pediatric PMR • Identify genetic mutations and other biomarkers that may predispose them to developing HSTCL • A study to assess the long-term safety
Anti- integrins *Natalizumab* *CD* (January 12, 2008)	3 mg/kg sd (IV) 3 mg/kg at W0 and Placebo at W4; 3 or 6 mg/kg at W0 and W4 (IV)	***4x***	*Induction:* 300 mg at W0, W4 and W8 (IV) *Maintenance:* 00 mg q4w (IV)	***~0.7x*** (mg/kg regimen in P2 and flat dose regimen in P3) ***NA*** (maintenance treatment not assessed in P2)	300 mg q4w (IV)	Same as P3 (one dose level tested in P3)	• Pediatric PMR • Conduct a study in at least 2000 subjects with CD who are receiving *natalizumab*, with each subject followed for at least 5 years
Vedolizumab *CD* (May 20, 2014)	0.5 or 2 mg/kg at W0 and W4 (IV)	***4x***	*Induction:* 300 mg at W0 and W2 (IV) *Maintenance*: 300 mg q8w or q4w (IV)	**~0.7x** ***NA*** (maintenance treatment not assessed in P2) Note: mg/kg regimen in P2 and flat dose regimen in P3	300 mg at W0, W2 and W6, and q8w thereafter (IV)	*Induction*: Same as P3 (one dose level tested in P3) *Maintenance:* P3 low dose	• Pediatric PMR. • Pregnancy PMR • A study of vedolizumab versus other agents for IBD. The study's primary outcome is serious infections. • A study to reanalyze banked immunogenicity serum samples to determine the presence of ADA. • Drug-drug interaction trial for CYP substrate drugs

Table 2 (continued)

Indication (Approval date)	Phase 2[a,b]		Phase 3[a,b]		Approved[a]		PMR[c]
	Dose Level	Dose Range	Dose level	vs Phase 2 Top Dose	Dose Level	vs Phase 3 Dose	
UC (May 20, 2014)	0.5 or 2 mg/kg at W0 and W4 (IV)	***4x***	*Induction:* 300 mg at W0 and W2 (IV)	**~0.4x**	300 mg at W0, W2 and W6, and q8w thereafter (IV)	*Induction*: Same as P3 (one dose level tested in P3)	
	2, 6, or 10 mg/kg at W0, W2, W4, and W12 (IV)	***5x***	*Maintenance*: 300 mg q8w or q4w (IV)	**~0.25x/0.5x** Note: mg/kg regimen in P2 and flat dose regimen in P3		*Maintenance:* P3 low dose	
Anti-IL-12/IL-23 *Ustekinumab* *CD* (September 23, 2016)	4.5 mg/kg sd (IV)		*Induction:* 130 mg or ~6 mg/kg at W0 (IV)	**~0.3x/1x**	~ 6 mg/kg at W0 (IV); 90 mg q8w starting at W8 (SC)	*Induction*: P3 high dose	• Pediatric PMR • Pregnancy PMR • Provide data analyses regarding the occurrence of adverse events with exposure to ustekinumab • Assess the long-term safety • Drug-drug interaction trial for CYP substrate drugs
	90 mg at W0, W1, W2, and W3 (SC)					*Maintenance:* P3 high dose	
	1, 3, or 6 mg/kg at W0 (IV); 90 mg at W8 and W16 (SC)	*Induction:* ***6x*** *Maintenance:* ***1x***	*Maintenance:* 90 mg q8w or q12w starting at W8 (SC)	**~0.67x/1x**			

[a] From US Package Insert (USPI) unless otherwise indicated.

[b] Available from Clinical pharmacology review package in Drugs@FDA (https://www.accessdata.fda.gov/scripts/cder/daf/ Accessed January 9, 2019)

[c] Available from Postmarket Requirements and Commitments (https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm Accessed January 9, 2019).

Abbreviations: CD, Crohn's disease; CYP, cytochrome protein 450; HSTCL, hepatosplenic T-cell lymphoma; IBD, inflammatory bowel disease; IL, interleukin; IV intravenous; mg/kg, milligram per kilogram of body weight; P2, phase 2; P2/3, Phase 2/3; P3, phase 3; PMR, post-marketing requirement; q12w, every 12weeks; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; qw, every week; SC, subcutaneous; TNFα, tumor necrosis factor alpha; sd, single dose; UC, ulcerative colitis; W0 (2,4,…), week 0 (2,4,…).

phase 2 were up to 6-fold for induction at the multiple-dose setting (Table 2). For maintenance, phase 2 investigation is generally limited, with a short duration of 8–16 weeks and dose range up to 5-fold. Collectively, these observations suggest an inadequate characterization in dose/exposure–response relationships during the clinical development of IBD biologics, e.g. limited phase 2 dose-ranging and suboptimal phase 3 dose selection. The in terms of benefit/risk insufficient understanding of dose-response may become a hurdle for drug approval and may lead to PMR. For example, at the time of approval for UC, adalimumab was requested to evaluate the safety of induction doses higher than 160 mg SC at week 0 and 80 mg SC at week 2, the currently approved dose and the top dose tested in its clinical UC program. Given the moderate treatment effect of adalimumab in UC, adalimumab doses higher than what has been approved may have the potential for a higher therapeutic benefit, as its maximum response obtainable in UC is uncertain.

IBD pivotal clinical studies are typically designed to answer the questions of what the optimal induction dose is and then separately, what the optimal maintenance dose is to maintain the efficacy achieved with induction. Given a typical half-life of 2–3 weeks for monoclonal antibodies, drug exposure from induction doses (i.e., "carry-over" pharmacokinetic effect) should have been washed out during the long-term maintenance therapy. For maintenance efficacy or "carry-over" pharmacodynamic effect by induction therapy, results were mixed for approved biologics. For example, golimumab demonstrated a consistent maintenance treatment effect (e.g., proportion of patients in clinical response through week 54) among UC patients receiving the same 100 mg SC every 4 weeks (q4w) maintenance regimen, despite the 4-fold induction dose range (i.e., 100/50 mg, 200/100 mg or 400/200 mg SC at week 0/week 2) [32]. Among CD patients who received ustekinumab 90 mg SC every 8 week (q8w) maintenance regimen, there was a trend of lower maintenance treatment effect (e.g., proportion of patients in clinical remission at week 54) in patients who received the 130 mg IV induction treatment than the ~6 mg/kg IV induction treatment [31].

It should be mentioned that overall, the regulatory requirements for efficacy and safety assessment of IBD biologics have become more stringent since the first biologic approval in 1998. As the pioneer therapeutic protein developed for IBD, infliximab tested single doses in the phase 2 CD and UC development, although repeated dosing is needed to fully evaluate its clinical relevance for the treatment of IBD, a chronic inflammatory disease. This development strategy was acceptable 20 years ago, given the "breakthrough" nature of infliximab for IBD treatment at that time, where infliximab had indeed demonstrated substantial improvement over existing IBD therapies. Since then, biologic agent developed for IBD typically would have multiple-dose regimen investigated in phase 2 in order to provide sufficient clinical evidence for phase 3 development (single-dose regimen may also be tested in phase 2, usually before the multiple-dose studies). In terms of safety, every biologic approved for IBD has safety-related PMRs, in particular, long-term safety monitoring. Long-term safety is of concern for biologics, partly due to the fact that serious adverse effect is generally of low incidence and is not apparent in short-term biological therapy. In addition, there is a lack of predictive biomarker, preclinical screening tools, and animal models for the safety assessment of biologics [33]. Of note, class-specific side effects are typically required to be monitored for biologics with a same or similar mechanism of action. For example, the PMRs for anti-TNFs of infliximab, adalimumab, and golimumab asked for a study on hepatosplenic T cell lymphoma (HSTCL), a generally fatal disease [43]. Leveraging of safety data collected from drugs with similar mechanisms of action is highly encouraged and necessary in the clinical development of new drugs.

Another trend is that "new" types of PMRs are being requested for the more recently approved biologics, likely due to the emerging understanding of therapeutic protein and disease. For example, drug–drug interaction studies were requested for vedolizumab and ustekinumab, the two most recently approved biologics for IBD. These studies would assess the potential impact of biologics on small molecule drugs which are CYP substrates via drug–disease interaction, a hypothesis that has not been well understood until recently [44, 45]. Vedolizumab was also requested to reanalyze banked immunogenicity serum samples to determine the presence of antibodies to vedolizumab, given the improvement of drug-tolerant assays for the detection of anti-drug antibodies in the last few years [46].

Leveraging of Dose-Ranging Learning Across CD and UC

The three biologics (infliximab, adalimumab, and vedolizumab) approved for the treatment of CD and UC use the same dose regimen in both indications. This may imply a similar response to treatment between CD and UC, as these two diseases are known to have overlapped genetic loci [5], shared biology, and similar clinical features [3]. It may be intuitive to consider that similar dose regimen could be used for the treatment of UC once the optimal dose has been identified in CD or vice versa. However, dose extrapolation between CD and UC may not be as straightforward as it appears. As shown in Table 1, adalimumab is a very effective treatment for CD, but its efficacy in UC seems to be relatively modest. At the approved adalimumab dose in the anti-TNF-naïve population, 36% versus 12% of CD patients demonstrated remission following adalimumab induction versus placebo,

while 18.5% versus 9.2% of UC patients achieved remission following adalimumab induction versus placebo. This suggests that efficacy of the same drug may not share the same magnitude of clinical benefit across CD and UC.

Multiple factors could contribute to the response difference between CD and UC for a given drug. CD and UC are part of the similar spectrum of the disease but having distinctive characteristics [4]. Patients with UC may have a higher surface inflammatory burden, exemplified by its continuous gut lesions (versus the patchy lesions that are characteristic of CD). Therefore, drugs, such as adalimumab, may be less effective in UC taking into account the intensity and the overall surface or volume of inflamed mucosa [47]. It has also been hypothesized that patients with UC may have a "leakier" gut, meaning that the digestive lining is more damaged, allowing drug substances to pass through, leading to an increased clearance [48, 49]. Pharmacokinetic data from the three biologics approved for both CD and UC, however, may not support this hypothesis. Overall serum drug trough concentrations are comparable between patients with CD and UC (within 10–15%) at the same dose level. For example, the mean serum vedolizumab trough concentrations at steady state were approximately 14% lower in patients with UC (11.2 μg/mL) than patients with CD (13.0 μg/mL), following vedolizumab 300 mg IV every 8 weeks treatment (Entyvio® USPI) [21]. A population PK analysis has been conducted for vedolizumab using a pooled dataset from patients with CD and UC and the estimated linear clearance was 0.159 L/day for UC and 0.155 L/day for CD [50]. For adalimumab, the mean trough concentrations at the end of induction phase were slightly lower (within 10%) in patients with UC (11.7 μg/mL) versus CD (12.6 μg/mL) (Humira® USPI) [17]. The reported median trough concentrations of infliximab in the maintenance phase were, on the other hand, slightly higher in UC (2.4 μg/mL) [51] versus CD (2.2 μg/mL) [52]. Different response to treatment between CD and UC may also be mechanism related. It was reported that anti-trafficking agents, including vedolizumab, tend to work more successfully for the treatment of UC than CD [12]. The reason for this has not been well understood, but may reflect the difference in the intestinal compartments associated with diseases.

Collectively, these data suggest that the response to treatment between CD and UC are closely related. Therefore, when developing biologics for both CD and UC indications, dose range to be tested should each be carefully considered, taking into account the mechanism of action, dose-response shape, and the relevant elements in the study design of the prior indication. Leveraging of dose-ranging learning across CD and UC may be an efficient approach, which has been used successfully for a few IBD biologics. Historically, vedolizumab was approved at the same time for both CD and UC. Infliximab and adalimumab were approved for CD first and then UC; in both cases, a relatively limited dose range was tested in the follow-up UC indication versus the initially approved CD indication (Table 2). Infliximab was tested as a single IV dose from 1 to 20 mg/kg in CD (20-fold), while 5 mg/kg to 20 mg/kg (4-fold) in UC. Adalimumab had 3 SC induction doses (40/20 mg, 80/40 mg, or 160/80 mg at week 0/week 2, 4-fold range) and 2 maintenance doses (40 mg SC every 2 weeks or every week, 2-fold range) tested in CD, while 2 induction doses (80/40 mg or 160/80 mg at week 0/week 2, 2-fold range) and 1 maintenance dose (40 mg SC every 2 weeks) tested in UC. It is generally considered that data from earlier trials for one indication may form a basis for narrowing down the dose range to be tested for the next closely related indication.

Conclusion

There is still a significant unmet medical need for IBD therapy, as indicated by the less than ideal remission rates for current treatments and the potential safety concerns such as serious infection or malignancy. Seven biologics have been approved for the treatment of CD and/or UC, including four anti-TNFs (infliximab, adalimumab, certolizumab pegol, and golimumab), two anti-integrins (natalizumab and vedolizumab), and most recently the anti-IL-12/IL-23 ustekinumab. These biologic agents typically employ an intensive induction followed by maintenance therapy and demonstrate effectiveness in both inducing and subsequently sustaining clinical remission. Side effects such as serious infections and malignancies can occur for biologics partly due to the long-term immunosuppression. Lessons learned from the current IBD biological therapy may be helpful to expedite clinical development of the next generation of biologics. A wide dose range would be needed in phase 2 dose-finding to fully characterize the dose-response and/or exposure-response relationships of efficacy and safety. It is important to optimize the induction duration, taking into account time-to-response which could be mechanism related. There should be a balance between more complex and potentially more expensive study design, and the more informative 'smart-dsigned' study with greater confidence in choosing the right dose to ensure success in later clinical development. Given the complexity and heterogeneity of IBD, understanding how individual biological components interact with each other may help in the identification of influencing factors to the treatment (and the placebo) effect to guide clinical study design. Carefully leveraging of dose-ranging learnings across CD and UC, the two closely related IBD indications may be an efficient approach for dose optimization. Moving forward, it is likely that multiple therapies may be needed for improved therapeutic benefit in the treatment of IBD, such as a biologic agent with a

small molecule or on top of another biologic [53]. Lessons learned from IBD biologic monotherapy would be generally applicable to the combination therapy, though the PK and PD properties of drugs may change when used in combination, and such PK/PD changes may influence their efficacy and safety, and ultimately in optimal dose selection.

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Compliance with Ethical Standards

Conflict of Interest Aditi Sharma was an intern of Janssen Research & Development, LLC at the time of the study; all other authors are employees of Janssen Research & Development, LLC.

Disclaimer The opinions expressed in this publication are those of the authors and not necessarily those of the company that employs them.

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