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REVIEW ARTICLE

Clinical Pharmacokinetics and Pharmacodynamics of Infliximab in the Treatment of Inflammatory Bowel Disease

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Abstract Infliximab was the first monoclonal antibody to be approved for the treatment of pediatric and adult patients with moderately to severely active Crohn's disease (CD) and ulcerative colitis (UC). It has been shown to induce and maintain both clinical remission and mucosal healing in pediatric and adult patients with inflammatory bowel disease (IBD) who are unresponsive or refractory to conventional therapies. The administration of infliximab is weight-based and the drug is administered intravenously. The volume of distribution of infliximab is low and at steady state ranges from 4.5 to 6 L. Therapeutic monoclonal antibodies, such as immunoglobulins, are cleared from the circulation primarily by catabolism. Median infliximab half-life is approximately 14 days. Infliximab concentration–time data in patients with CD and UC have been shown to be highly variable within an individual patient over time and between individuals by multiple population pharmacokinetic models. Covariates that have been identified to account for a part of the observed inter- and intra-individual variability in clearance are the presence of antidrug antibodies, use of concomitant immunomodulators, degree of systemic inflammation, serum albumin concentration, and body weight, which can affect the pharmacodynamic response. This article provides a comprehensive review of the clinical pharmacokinetics and pharmacodynamics of infliximab, as well as the role of therapeutic drug monitoring in the treatment of IBD.

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Key points

Infliximab is a chimeric immunoglobulin G1 monoclonal antibody that targets both soluble and transmembrane tumor necrosis factor (TNF)-α, a potent proinflammatory cytokine that plays a role in dysregulation of the mucosal immune response in inflammatory bowel disease (IBD).

Infliximab has an immediate central distribution with 100% bioavailability due to intravenous administration. Its concentration–time profile is biphasic, with a distribution and an elimination phase. Its distribution is restricted to the blood stream and extracellular spaces because of its high molecular weight and hydrophilicity. Catabolism may be dependent on rates of extracellular degradation via proteolysis and rates of recycling through interaction with the Brambell or neonatal Fc receptor (FcRn).

The presence of immunogenicity against infliximab accelerates clearance (CL) through the reticuloendothelial system, and/or impairs its efficacy by blocking the binding to the antigen. However, antidrug antibodies (ADAs) may be transient and not all ADAs appear to have the same impact on the pharmacokinetics of infliximab.

There is large interindividual variability in the pharmacokinetics of infliximab. Low serum albumin, high body weight, and the degree of systemic inflammation are associated with high infliximab CL, whereas the use of concomitant immunosuppressants is associated with lower CL.

Emerging evidence suggests an apparent association between sustained therapeutic infliximab levels and favorable clinical, biochemical, and endoscopic outcomes. Low infliximab exposure, as measured by infliximab trough concentrations, is associated with impaired response or loss of response to therapy. The clinical guidelines from the American Gastroenterological Association suggest performing therapeutic drug monitoring (TDM) to guide treatment changes for patients with active IBD treated with TNFα antagonists. There is also evidence to support performing proactive TDM, but evidence is lacking on how frequently to obtain infliximab concentrations.

1 Introduction

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory disorders of the gastrointestinal tract. The pathogenesis of IBD is multifactorial and involves an individual's genetic make-up, surrounding environment, gut microbiota, and intestinal mucosal immune response [1]. IBD is a result of a dysregulated mucosal immune response to intestinal microflora in a genetically predisposed host [2]. In the US, over 1.4 million people suffer from IBD [3]. Estimates of the prevalence of CD and UC in the US are 201 and 238 per 100,000 adults, respectively. In children younger than 20 years of age, estimates of the prevalence of CD and UC are 43 and 28 per 100,000, respectively [4]. As there is no unified surveillance system for IBD in the US, children and minorities may be underrepresented in epidemiologic studies [3]. Features of CD include discontinuous, transmural inflammation involving any area of the gastrointestinal tract from the mouth to the anus. CD can be classified as inflammatory, penetrating, structuring, or a combination phenotype. Features of UC include diffuse and continuous mucosal inflammation extending proximally from the rectum. CD involving the colon is more common in children than adults and the term IBD unspecified is reserved for patients who cannot be classified as CD or UC [5]. 25–30% of all patients with CD and 20% of those with UC present before 20 years of age [6]. The presentation can be variable, and symptoms include fever, abdominal pain, diarrhea, rectal bleeding, weight loss, growth failure, anemia, mouth ulcers, and perianal disease, including perianal fistulae, skin tags, or recurrent perianal abscesses. Extraintestinal manifestations in IBD are reported, with frequencies ranging from 6 to 47% [7], and may include ocular, dermatologic, musculoskeletal, hepatobiliary, renal, pancreatic, or hematologic manifestations.

The ultimate goal of IBD treatment is to restore a patient's quality of life by achieving clinical/patient-reported outcome remission and endoscopic remission [8]. Additionally, in pediatric IBD, important goals of treatment are to restore normal growth and eliminate complications [2]. Monoclonal antibodies have revolutionized the treatment of IBD. Infliximab, a chimeric immunoglobulin (Ig) G1, was approved by the US FDA in 1998 as a treatment for CD [9]. It is now approved to treat moderately to severely active CD and UC in pediatric and adult patients as well as other chronic inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis [10]. Infliximab has been shown to induce and maintain both clinical remission and mucosal healing in pediatric and adult patients with IBD

who are unresponsive or refractory to conventional therapies. Additionally, it has been shown to be efficacious in the treatment of perianal fistulas in adult [11–13] and pediatric patients with CD [14–17]. In pediatric CD, infliximab was shown to improve quality of life and height *Z*-scores, defined as the measure of the deviation of a patient's height from the expected height of an age- and sex-matched population [17–19].

The structure of infliximab consists of a murine variable region grafted into a human IgG1 κ scaffold [20]. Infliximab targets both soluble and transmembrane tumor necrosis factor (TNF)-α, a potent proinflammatory cytokine that plays a role in dysregulation of the mucosal immune response. Standard dosing is weight-based at 5 mg/kg administered intravenously according to a regimen that includes an induction phase with an intravenous infusion administered at weeks 0, 2, and 6, followed by maintenance treatment with an intravenous infusion administered every 8 weeks.

Although administering infliximab according to the standard dosing regimen was shown to be efficacious, response to therapy is highly variable among individuals. According to a recent systematic review with meta-analysis in adult CD, estimates of the incidence of loss of response to anti-TNF therapy ranged from 8 to 71%; specifically for infliximab, the effect estimate was 33% [21]. In pediatric patients, it is estimated that 20–50% of patients with IBD who initially respond to infliximab induction therapy lose response by approximately 1 year [22]. Loss of response to anti-TNF therapy is a challenging problem, particularly in children because of limited therapeutic options. Loss of response may be partly attributed to suboptimal drug exposure, which in turn may be caused by the formation of antidrug antibodies (ADAs). ADAs can impact the pharmacokinetics of therapeutic proteins in diverse ways. They may be directed against the biologically active site, preventing therapeutic target recognition (anti-idiotypic or neutralizing antibodies), or bind to other parts of the molecule (non-neutralizing antibodies). Both neutralizing and non-neutralizing antibodies can influence therapeutic exposure by accelerating clearance (CL) of the drug and decreasing its circulating half-life. ADAs against infliximab are predominantly neutralizing antibodies [23]. In adult patients receiving infliximab for the treatment of IBD, there is an approximately 20% incidence of ADAs [24]; less data are available on the prevalence of ADAs in pediatric patients. In a cross-sectional study assessing infliximab levels and the prevalence of ADAs in pediatric patients currently receiving infliximab for the treatment of IBD, 20% had detectable ADAs [25]. Acute infusion reactions, defined as any adverse event occurring within 1–2 h of an infusion, have been reported in 5–23% of IBD patients. The rate of infusion reactions in children receiving infliximab is similar to that in adults [18, 26–28]. Patients receiving infliximab therapy who develop ADAs have a twofold higher increased risk of acute infusion reactions and a sixfold higher risk of serious infusion reactions, defined as those determined to be life-threatening or resulting in significant disability or hospitalization, compared with those who do not develop ADAs [24].

In this article, we review the current literature on the pharmacokinetics and pharmacodynamics of infliximab in the treatment of adult and pediatric IBD, and synthesize the evidence for therapeutic drug monitoring (TDM) and dose optimization.

2 Pharmacokinetics

Population pharmacokinetic models have been developed for infliximab for pediatric and adult CD and UC patients, using two-compartment models with zero-order infusion and first-order elimination (Table 1) [29–31]. Monoclonal antibodies are large molecules with insufficient resistance against the hostile proteolytic gastrointestinal milieu and very limited permeation through the lipophilic intestinal wall [32]. Therefore, monoclonal antibodies are administered intravenously or subcutaneously. Infliximab is administered intravenously, which allows for administration of a larger volume of drug and immediate central distribution with 100% bioavailability, and eliminates variability in drug absorption between subjects [33]. The concentration–time profile of infliximab is characterized by high peak-to-trough ratios because of the relatively large intravenous dose and long infusion interval [30, 31].

The distribution of monoclonal antibodies is restricted to the blood stream and extracellular spaces because of their high molecular weight and hydrophilicity. Monoclonal antibodies have very limited penetration to the brain and cerebrospinal fluid [32]. The volume of distribution at steady state of infliximab is low and ranges from 3 to 6 L [34].

Due to their large size, renal CL of monoclonal antibodies is almost non-existent. Monoclonal antibodies are cleared from the circulation primarily by catabolism. Catabolism may be dependent on rates of extracellular degradation via proteolysis and rates of recycling through interaction with the Brambell or neonatal Fc receptor (FcRn) [35]. Catabolism is upregulated in a high inflammatory state, as shown by the association of C-reactive protein (CRP), albumin concentration (both indirect markers of inflammation and high concentration of TNF present in gut mucosa), and infliximab CL [31]. Proteolytic catabolism occurs after internalization of the antibody by phagocytic cells of the reticuloendothelial system, which is mediated by Fc gamma receptors (FcγRs) [33]. Antibody

Table 1 Overview of published parameter estimates of population pharmacokinetic models and identified covariates that impact the pharmacokinetics of infliximab

Study/reference	Population	Parameter estimates	Relationship of covariate to pharmacokinetic parameter
Fasanmade et al. [30]	Pediatric CD	CL 0.23 L/day	ALB on CL [−]
	(age range 6–17 years)	V_1 2.28 L	WT on CL [−]
	$n = 112$	V_2 1.23 L	WT on V_1 [−]
		Q 0.15 L/day	WT on V_2 [−]
		Half-life 13 days	
Fasanmade et al. [30]	Adult CD	CL 0.37 L/day	ALB on CL [−]
	$n = 580$	V_1 3.58 L	ADA on CL [+]
		V_2 1.29 L	IMM on CL [−]
		Q 0.15 L/day	WT on CL [−]
		Half-life 12 days	WT on V_1 [−]
			WT on V_2 [−]
Fasanmade et al. [31]	Adult UC	CL 0.407 L/day	ALB on CL [–]
	$n = 482$	V_1 3.29 L	ADA on CL [+]
		V_2 4.13 L	Sex (female) on CL [−]
		Q 7.14 L/day	Sex (female) on V_1 [−]
		Half-life 14 days	WT on V_1 [+]
Ternant et al. [29]	Adult CD/UC	CLc 0.288 L/day	ADA on CLc [+]
	$n = 33$	CLp 0.130 L/day	Sex (female) on V_1 [−]
	CD: $n = 30$	V_1 4.0 L	WT on V_1 [+]
	UC: $n = 3$	V_2 1.9 L	
		Half-life 19 days	
Dotan et al. [38]	Adult CD/UC	CL 0.381 L/day	ADA on CL [+]
	$n = 54$	V_1 2.37 L	WT on CL [+]
	CD: $n = 25$	V_2 1.37 L	ALB on CL [−]
	UC: $n = 25$	Q 0.122 L/day	WT on V_1 [+]
	Unspecified: $n = 4$	Half-life 11 days	WT on V_2 [+]
			WT on Q [+]

CD Crohn's disease, *UC* ulcerative colitis, *ALB* albumin, *IMM* immunodulators, *WT* weight, *ADA* antidrug antibody, *CL* clearance, *CLc* systemic clearance, *CLp* distribution clearance, V_1 volume of distribution in the central compartment, V_2 volume of distribution in the peripheral compartment, *Q* intercompartmental clearance, [+] indicates a positive correlation, [−] indicates a negative correlation

salvage and recirculation is medicated by FcRn. Antibodies bind tightly to FcRn with pH-dependent affinity inside the acidic environment of endosomes, and are protected from proteolysis. When the IgG–FcRn complex is returned to the cell surface, the antibody is released back into circulation at physiologic pH [33].

A single nucleotide polymorphism (SNP) in the gene encoding the FcγR has been associated with increased biological response to infliximab in CD, as defined by a decrease or normalization of CRP concentrations [36]. The investigators found that the FcγRIIIa-158 valine allotype had a higher affinity for IgG1 than the FcγRIIIa-158 phenylalanine allotype. Furthermore, CD patients with the homozygous valine nucleotides had a better biological response to infliximab. It is possible that *FCGR3A*, the gene coding for FcγRIIIa, may be functionally significant in impacting infliximab efficacy through antibody-dependent cell-mediated cytotoxicity [36]. It is unclear whether FcγR polymorphisms have an impact on response through an effect on pharmacokinetics. In a recent retrospective, single-center study, a variable number of tandem repeat (VNTR) polymorphisms in the FcRn were found to influence anti-TNF concentrations in patients with IBD. The VNTR2/3 genotype in the FcRn gene was associated with a 14% lower infliximab area under the curve compared with the VNTR3/3 genotype [37].

In the first study to describe the pharmacokinetics of infliximab using a two-compartment model in CD and UC in 33 adults (age range 19–53 years) with a median weight of 67 kg, systemic CL was 0.288 L/day without the presence of ADAs and 0.768 L/day in the presence of ADAs. Most patients received concomitant immunosuppressive treatment: thiopurines (6-mercaptopurine/azathioprine, 25 patients) methotrexate (4 patients), azathioprine then

methotrexate (1 patient), and tacrolimus (1 patient). The estimated volume of distribution in the central compartment (V_1) was 4.0 L and the volume of distribution in the peripheral compartment (V_2) was 1.9 L. The mean elimination half-life was 19 days [29].

In the REACH (A Randomized, Multicenter, Open-Label Study to Evaluate the Safety and Efficacy of Anti-TNF-α Chimeric Monoclonal Antibody in Pediatric Subjects with Moderate-to-Severe Crohn's Disease) and ACCENT I (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New, Long-term Treatment Regimen) clinical studies, a population pharmacokinetic model was developed separately for children, adults, and a combination of both using serum infliximab concentration–time data. Final model parameter estimates for a typical child (age range 6–17 years) with a median weight of 42 kg who had a baseline serum albumin concentration of 3.8 mg/dL, had not developed antibodies to infliximab, and was receiving infliximab and an immunomodulator were as follows: CL, 0.23 L/day; V_1, 2.28 L; V_2, 1.23 L; and intercompartmental CL (Q), 0.15 L/day. Infliximab pharmacokinetic properties appeared to be comparable between pediatric and adult patients with CD. Corresponding parameter estimates for a typical adult (age range 18–76 years) based on a median weight of 68 kg and serum albumin concentration of 4.1 mg/dL were as follows: CL, 0.37 L/day; V_1, 3.58 L; V_2, 1.29 L; and Q, 0.15 L/day. The estimated interindividual variability in serum infliximab concentrations from pediatric and adult populations for CL, V_1, and V_2 were 36.6, 14.7, and 59.1%, respectively, and median infliximab half-lives obtained from post hoc analyses were 13.2 days and 12.4 days in pediatric and adult patients, respectively [30].

ACT 1 and 2 (Active Ulcerative Colitis Trials) were two randomized, double-blinded, placebo-controlled trials including patients with moderately to severely active UC despite concurrent treatment with corticosteroids alone or in combination with azathioprine or 6-mercaptopurine (ACT 1 and 2) or medications containing 5-aminosalicylates (ACT 2 only). Population pharmacokinetic parameter estimates for the ACT 1 and ACT 2 studies were as follows: CL, 0.407 L/day; V_1, 3.29 L; V_2, 4.13 L; Q, 7.14 L/day. Baseline patient characteristics were age 41.2 ± 13.9 years (range 18–81 years), body weight 78.8 ± 18.4 kg, CRP level 1.4 ± 2.2 mg/dL, and albumin level 4.1 ± 0.4 g/dL. Infliximab exhibited interindividual variability for CL and V_1 of 37.7% and 22.1%, respectively. Infliximab steady-state volume of distribution (V_{ss}) was estimated to be 7.7 L, which is slightly higher than the volume of the vascular system. The median half-life was approximately 14 days, with an interquartile range of 10.4–17.8 days [31].

Dotan et al. investigated patient-related factors affecting infliximab pharmacokinetic variability in IBD [38]. Baseline patient characteristics for the 54 recruited patients were age 35.6 ± 12 years (range 20–70 years), body weight 68.5 ± 14.8 kg, body mass index 23.4 ± 4.5 kg/m^2, CRP level $1.52 \pm 1.6.9$ mg/dL, and albumin level 4 ± 0.5 g/dL. The concomitant medications included thiopurines (6-mercaptopurine/azathioprine, 32 patients) methotrexate (7 patients), and corticosteroids (19 patients). Disease location for patients with CD was 33.3, 14.8 and 51.9% for ileal, colonic, and ileocolonic disease, respectively, while disease location for patients with UC was 50% for left-sided colitis and 50% for pancolitis. Population pharmacokinetic parameter estimates for a typical patient who is ADA negative were as follows: CL, 0.381 L/day; V_1, 2.37 L; V_2, 1.37 L; Q, 0.122 L/day. Between-patient variability for CL, V_1, V_2, and Q were 13.45, 42.07, 32.40, and 85.15%, respectively, and the median half-life was 11.23 days. Patient factors significantly associated with high infliximab CL were low albumin, high body weight, and the presence of ADAs.

In summary, these pharmacokinetic studies demonstrate that the concentration–time profile of infliximab is best described by a two-compartment model with zero-order elimination. CL of infliximab ranges between 0.230 and 0.407 L/day, resulting in a half-life of between 11 and 19 days, which was similar between adults and children. Interindividual variability in CL was substantial and ADA increases infliximab CL significantly.

3 Key Covariates Influencing the Pharmacokinetics of Infliximab

3.1 Patient Demographics

Patients with higher body weight have accelerated CL, yet the influence of weight on infliximab CL is not linear [30]. Therefore, linear dosing based on weight may not result in adequate exposure levels in all patients. Conversely, patients with a low body weight are at risk for underexposure and may require higher-than-standard doses. For example, pediatric patients who receive a 5 mg/kg dose have substantially (25–40%) lower exposure than adults [38]. Gender has been found to have a modest effect on infliximab CL but may not be significant after accounting for weight [38].

Both weight and gender were also found to influence V_1 [29–31, 38]. V_1/kg decreased as total weight increased in pediatric and adult populations. The influence of gender on V_1 may occur because, for a given body weight, plasma volume is lower in women than in men [29]. Body-size parameters such as body mass index, lean body weight, or body surface area may be more precise than body weight in pharmacokinetic studies [31, 38].

3.2 Antidrug Antibodies

Immunogenicity is the potential for an antigen to induce an immune response after it has been recognized by a pre-existing T- or B cell receptor. Infliximab is structurally comprised of 75% human and 25% murine sequences [39]. Murine peptide sequences are generally more immunogenic than sequences of human origin [40]. Murine antibodies have a short half-life of approximately 1–2 days, chimeric antibodies have a half-life of approximately 10–14 days, and humanized and fully human antibodies have a longer half-life of approximately 10–20 days [41]. Modifications to protein structure by glycosylation may also protect monoclonal antibodies from proteolytic breakdown and immunologic recognition [33]. However, even fully humanized monoclonal antibodies (adalimumab) and pegylated humanized monoclonal antibodies (certolizumab pegol) may be immunogenic because multiple drug-related factors and intrinsic patient factors determine immunogenicity towards a therapeutic antibody [40]. Multiple treatment strategies to prevent ADA formation are utilized, including regular scheduled dosing, use of concomitant immunomodulators, and maintenance of a stable therapeutic trough drug concentration.

The reported incidence of ADAs to infliximab in the IBD literature ranges widely from 6.1 to 73%; this wide range may be explained by varying degrees of sensitization and differences in assay methodology [40]. A prospective observational study found that 75% of patients developed ADAs to infliximab by week 22 and 90% of patients developed ADAs to infliximab within the first 12 months of therapy [42]. Brandse et al. demonstrated that insufficient exposure to infliximab, reflected by the time during which infliximab concentrations fell below a trough level of 3 μg/mL during a dose interval, was the most predictive factor of developing ADAs [43].

The formation of ADAs is associated with accelerated drug CL, loss of response, and increased risk for an infusion reaction. The presence of immunogenicity against infliximab may reduce its exposure through formation of immune complexes that accelerate CL through the reticuloendothelial system and/or impair its efficacy by blocking the binding to the antigen [44]. ADA formation is associated with an average 2.5-fold increase in infliximab CL [38], which correlates with a shorter duration of response owing to lower infliximab concentrations. In a study on the influence of immunogenicity on the efficacy of infliximab in CD, the presence of ADA concentrations of ≥ 8.0 μg/mL before an infusion predicted a shorter duration of response (35 days, compared with 71 days among patients with ADA concentrations of < 8.0 μg/mL). The presence of ADAs has also been associated with infusion reactions in 6.9–19% of patients [45].

The type of detection assay affects the reported incidence of ADAs. Drug-sensitive assays are typically used to detect ADAs but may underestimate ADAs because of drug interference. In a post hoc analysis of the TAXIT (Trough concentration Adapted infliXImab Treatment) trial, serum samples of patients with an infliximab trough concentration < 3 μg/mL at screening undergoing dose intensification were reanalyzed using a drug-tolerant assay [46]. The impact of ADAs on the cumulative infliximab dose that was required to achieve and maintain infliximab trough concentrations within a target interval was evaluated. The drug-tolerant assay identified 63% of patients with ADAs at screening, an increase in the ADA detection rate of 42% compared with the drug-sensitive assay. After drug optimization, ADAs were not cleared immediately but remained 'hidden' for drug-sensitive assays for a prolonged period. Although the immunogenicity detection rate increased when using a drug-tolerant assay, patients had similar rates of clinical, biological, and endoscopic remission after 1 year of infliximab dose optimization based on TDM, regardless of ADA status. Indeed, drug-tolerant assays may increase ADA detection rates, but not all ADAs have an impact on pharmacokinetics and/or are clinically relevant [38]. In several cohorts, it was shown that the antibody response to infliximab and its impact on pharmacokinetics may be transient [42, 47]. Patients with transient ADAs were less likely to discontinue infliximab, whereas patients with sustained ADAs had significantly higher ADA levels compared with patients with transient ADAs, and a fivefold higher relative risk for infliximab discontinuation because of sustained loss of response or intolerance [47]. Current data do not define universal ADA cut-offs for low-titer versus high-titer antibodies.

3.3 Concomitant Immunosuppressive Therapy

In a retrospective analysis of serum infliximab concentration data from 692 patients from the REACH and ACCENT I studies, concurrent immunomodulator use was found to have a modest effect, with a decrease in infliximab CL of 14% [30].

The Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease (SONIC) was a randomized, double-blind trial that evaluated the efficacy of 5 mg/kg of infliximab monotherapy (with oral placebo) on the standard schedule, 2.5 mg/kg of azathioprine monotherapy (with intravenous placebo), and combination therapy with infliximab and azathioprine in 508 adults with moderate-to-severe CD who had not undergone previous immunosuppressive or biologic therapy. The primary endpoint was corticosteroid-free clinical remission at week 26, which was achieved in 75 of 169 patients (44.4%) receiving infliximab alone, 51 of 170 patients (30.0%) receiving

azathioprine alone, and 96 of 169 (56.8%) receiving combination therapy. Median trough concentrations of serum infliximab at week 30 were 1.6 μg/mL for patients in the infliximab group and 3.5 μg/mL for those in the combination-therapy group. Additionally, there was a lower incidence of ADAs to infliximab detected in patients receiving combination therapy compared with monotherapy (0.9 versus 14.6%) [48].

Drobne et al. retrospectively analyzed trough levels of infliximab and levels of ADAs throughout co-treatment with an immunomodulator, at immunomodulator withdrawal, and after withdrawal of 223 patients over a period of 34 months [49]. Patients receiving co-treatment had a 1.44-fold higher trough level of infliximab than those receiving infliximab monotherapy. Twenty-two percent of patients receiving co-treatment developed ADAs compared with 38% of patients receiving infliximab monotherapy. Infliximab trough levels and CRP at the time of immunomodulator withdrawal were predictors for long-term outcome. Patients with intermediate infliximab trough levels (detectable but <5 μg/mL) had a 20% risk for loss of response to infliximab. None of the patients with infliximab trough levels >5 μg/mL at the time of immunomodulator withdrawal lost response to infliximab. CRP >5 mg/L at the time of immunomodulator withdrawal was associated with an increased risk for dose escalation, IBD surgery, and discontinuation of infliximab because of loss of response, compared with patients who had a normal CRP at the time of immunomodulatory withdrawal. De novo formation of ADAs after immunomodulator withdrawal was a rare event and was only observed in 4% of patients.

3.4 High Baseline Tumor Necrosis Factor

Olsen et al. reported an inverse independent association between pretreatment TNFα gene expression and both clinical and endoscopic response to infliximab in patients with UC. Infliximab treatment was found to be less effective in patients with very high colorectal levels of TNFα messenger RNA (mRNA). In the low, medium, and high TNFα-level groups the percentages of patients with healed mucosa after infliximab treatment were 82, 64 and 42%, respectively [50]. Patients with a higher degree of systemic inflammation may require a greater amount of drug to neutralize excess TNFα, which could result in lower infliximab serum concentrations, less functional available drug, and treatment failure or loss of response [33].

3.5 High C-Reactive Protein Levels

Systemic inflammation upregulates protein catabolism in the reticuloendothelial system. An increased serum concentration of CRP has been associated with increased drug CL [31]. In UC patients receiving infliximab induction therapy, high baseline CRP levels had a strong negative impact on serum infliximab concentrations. The area under the serum infliximab concentration–time curve was significantly smaller in patients with a baseline serum CRP >50 mg/L than in patients with CRP below 50 mg/L (587 vs. 1361 mg/L/day) [51]. This association has also been observed for infliximab treatment in patients with rheumatoid arthritis as pretreatment CRP was found to negatively correlate with serum infliximab concentrations [52] and systemic CL increased by 20% with pretreatment CRP concentration [53].

CRP is also a useful biomarker in assessing inflammatory activity and response to infliximab therapy. Jürgens et al. found that early normalization of CRP levels correlated with sustained long-term response and that CRP levels remained significantly higher among patients who lost their response to infliximab. At the time of loss of response, CRP levels were significantly increased and did not return to baseline levels [54]. A post hoc analysis of the ACCENT 1 trial confirmed that serum infliximab trough concentrations ≥ 3.5 μg/mL at week 14, and a $\geq 60\%$ CRP decrease from baseline to week 14, were significantly associated with durable sustained response [55].

3.6 Low Albumin

By including serum albumin in a population pharmacokinetic model, the interindividual variability on infliximab CL was able to be reduced by 28.6% [43]. The common elimination and rescue pathways for both albumin and IgG are likely responsible for the relationship between serum albumin and serum infliximab concentrations. Additionally, severe inflammation of the mucosa and intestinal barrier function damage induces luminal protein loss and hypoalbuminemia, called protein-losing enteropathy, in which loss of protein through the gastrointestinal tract can be as high as 60% of the total albumin pool, resulting in a severe catabolic state. The serum proteins most often affected by this leakage are those with long half-lives, such as albumin and many immunoglobulins [56].

Patients with severe colitis often require higher-than-standard doses of anti-TNF antibodies to achieve clinical improvement. Brandse et al. reported that intestinal loss of therapeutic anti-TNF antibodies is associated with treatment failure in patients with moderate to severely active UC [57]. The authors demonstrated that therapeutic antibody can be found at detectable levels in feces and the greatest loss of infliximab occurs when serum drug concentrations are the highest and when the mucosa is most severely inflamed or 'leaky'. Patients with low serum albumin concentrations at baseline had higher fecal infliximab concentration at day 1 and lower serum

infliximab concentrations at week 2. The cohort only included patients with UC, but measurable fecal infliximab levels were also detected in an additional pilot study including CD patients with colonic disease and isolated small bowel disease.

Fasanmade et al. analyzed data from patients with UC from two clinical trials to evaluate trends between the pharmacokinetics of infliximab and serum albumin [58]. Patients in the highest serum albumin quartile had several-fold greater trough infliximab concentrations when compared with those in the lowest quartile, while patients with serum albumin concentrations lower than the normal laboratory reference range had much lower median serum infliximab concentrations and lower response rates compared with patients within normal serum albumin concentrations.

4 Pharmacodynamics and Exposure–Response Relationship

The proposed mechanisms of action of infliximab generally fall into two categories: blockade of TNF receptor-mediated mechanisms and induction of transmembrane TNF-mediated mechanisms, which is elegantly reviewed elsewhere [59]. The contribution of each of these mechanisms remains an open question, yet it is likely that a combination of these mechanisms attributes to the drug's efficacy. For example, it has been shown that infliximab is able to bind to peripheral blood lymphocytes and lamina propria T cells, and subsequently induce apoptosis of activated lymphocytes [60]. Furthermore, in patients treated with infliximab, an inverse correlation between the acute phase CRP and infliximab serum concentrations has been observed in CD and UC patients [31, 61].

There is an apparent association between infliximab drug exposure during induction and maintenance therapy in CD and UC and clinical and endoscopic outcomes (Fig. 1) [61, 62]. Patients with a detectable serum infliximab concentration compared with those in whom the trough serum infliximab was undetectable had higher rates of clinical remission, endoscopic improvement, and endoscopic remission, and a lower rate of colectomy [61, 63]. Achieving infliximab trough concentrations > 3.5 μg/mL at week 14 has been associated with sustained response to therapy in CD [55]. Infliximab concentrations ≥ 15 μg/mL at week 6 and ≥ 2.1 μg/mL at week 14 were independent factors associated with mucosal healing in patients with UC, which is a predictor of long-term outcome [64]. Post-induction infliximab trough concentrations > 2.5 μg/mL have also been associated with a lower risk for relapse or colectomy in patients with UC [65]. A positive relationship was noted between the serum infliximab concentration and

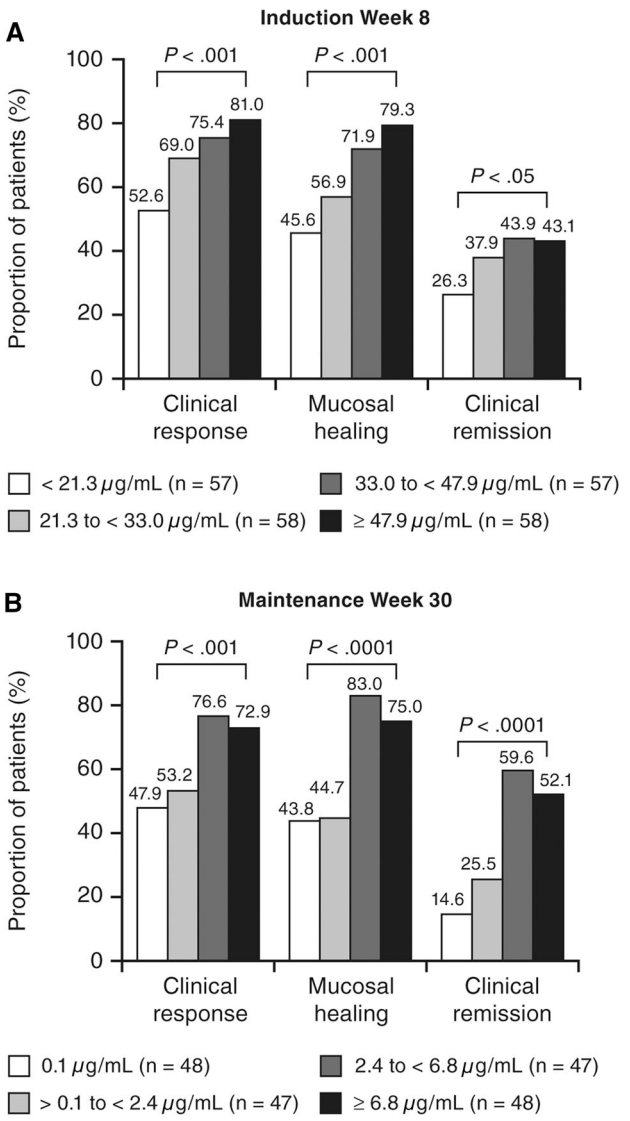

Fig. 1 Exposure–response relationship for infliximab in patients with ulcerative colitis included in the ACT-1 and ACT-2 trials for the 5 mg/kg treatment group, as demonstrated by the proportion of patients achieving efficacy outcomes per infliximab concentration quartile at **a** induction week 8 and **b** maintenance week 30. The trend of the proportion of patients achieving efficacy outcomes across the quartiles was evaluated using the one-sided Cochran–Armitage trend test (reproduced from Adedokun et al. [62], with permission)

clinical effect in pediatric IBD following induction therapy, similar to adults. In pediatric IBD, infliximab cut-points of > 3, > 4, and > 7 μg/mL at week 14 had positive predictive values of 64, 76 and 100%, respectively, for predicting persistent remission, defined as clinical remission without infliximab dose intensification [66]. In pediatric UC, higher serum infliximab concentrations (≥ 41.1 μg/mL) at week 8 were associated with greater proportions of patients achieving efficacy endpoints (clinical response, 92.9%; mucosal healing, 92.9%; and clinical remission,

64.3%) [67]. Conversely, not achieving these thresholds may result in non-response and/or non-remission.

Primary non-response is defined as the lack of improvement of clinical signs and symptoms with induction therapy [68]. Hypotheses for primary non-response include genetic predisposition, non-TNF-driven disease, or an early immunogenic effect. However, it is important to note that some patients may appear to have primary non-response because an induction dose of infliximab was too low relative to the disease state of the patient [69]. For example, patients with acute severe UC may develop protein-losing enteropathy in addition to an upregulated catabolic state, resulting in accelerated drug CL and making it difficult or impossible to achieve adequate drug exposure with standard dosing [57].

Secondary loss of response is defined as a loss of clinical benefit after initially responding [68] and is due to the development of ADAs, subtherapeutic drug concentrations, or dominance of inflammatory processes independent of TNFα [70, 71]. Although one contributing factor is the development of antibodies to infliximab, Maser et al. reported that 25% of patients exhibited an undetectable trough serum infliximab concentration without detectable antibodies [61]. Moreover, 16–39% of patients treated with scheduled infliximab have undetectable drug prior to the next infusion without antibody formation. In children with CD, standard infliximab maintenance dosing of 5 mg/kg every 8 weeks was predicted to frequently result in trough concentrations < 3 μg/mL [72]. A trough concentration > 3 μg/mL was predicted to be achieved in 32% of patients; however, to achieve a trough concentration > 3 μg/mL, a dosing interval less than or equal to every 6 weeks was predicted to be required in 29% of patients [73]. A high number of children diagnosed with IBD and treated with infliximab have been found to have subtherapeutic trough levels < 3 μg/mL [74, 75]. Through intensive blood sampling of infliximab levels and evaluation of patient and disease covariates, sources of between-patient variability in infliximab exposure can be identified. Covariates that have been demonstrated to influence the CL of infliximab are shown in Table 1.

5 Assays for Therapeutic Drug Monitoring

The most commonly used techniques for monitoring infliximab concentrations and ADAs are the enzyme-linked immunosorbent assay (ELISA), the high-pressure liquid chromatography-based homogeneous mobility shift assay (HMSA), and the electrochemiluminescence-based immunoassay (ECLIA). Marini et al. compared the commercial assays from KU Leuven, Sanquin, Dynacare, and LabCorp with Janssen's infliximab and ADA assay used in published pivotal infliximab clinical trials [71]. The infliximab assays were specific, accurate, and reproducible. Strong agreement was observed between Janssen's infliximab and ADA assays and the diagnostic service provider assays [73]. The detection of ADAs is strongly influenced by assay technique. Drug-sensitive ADA assays, such as the 'original' ELISA assay used in the published pivotal infliximab clinical trials, are not able to detect ADAs in the presence of drug, and underestimate ADA development [71]. Drug-tolerant assays have been developed and markedly increased the detection of ADAs. These assay formats are compatible with a sample pretreatment protocol including an acid dissociation step to allow for the detection of ADAs in the presence of drug [76–79]; however, current assays do not propose one universal cut-off that can be regarded as 'meaningful' ADAs. Misinterpretations and erroneous therapeutic decisions may be made if ADAs are positive but are not clinically significant.

6 Therapeutic Drug Monitoring

The American Gastroenterological Association recently reviewed the role of TDM in the management of IBD. Reactive TDM was defined as TDM performed in response to active IBD (ongoing active inflammation based on biochemical, endoscopic, or radiologic assessment, usually with symptoms) after a period of quiescent disease, or continued inflammation without achieving remission with index therapy [80]. Routine proactive TDM was defined as TDM performed in patients regardless of clinical status (generally in quiescent disease) periodically as part of routine clinical care.

The American Gastroenterological Association suggests reactive TDM to guide treatment changes. The panel suggests target trough concentrations of ≥ 5 μg/mL for infliximab to guide whether escalation of therapy may be beneficial (if the trough is below this threshold), compared with switching therapy (to be considered if the trough is above this threshold) to achieve clinical response in patients who are experiencing secondary loss of response on maintenance therapy [81]. Paul et al. performed the first prospective study investigating the association between TDM of infliximab following dose intensification, clinical remission, and mucosal healing. The study demonstrated that an increase of infliximab trough concentrations after infliximab dose intensification was strongly associated with mucosal healing in patients with IBD. The median delta infliximab concentration was higher in patients with IBD who achieved mucosal healing than those who did not achieve mucosal healing (2.2 vs. 0.2 μL, respectively) [82]. Furthermore, Steenholdt et al. investigated the cost

effectiveness of interventions based on serum infliximab and infliximab antibody concentrations using a proposed algorithm [83]. Their main finding was that interventions based on the algorithm achieved similar clinical, biological, and quality-of-life outcomes as empiric dose intensification, but at a 34% lower cost. Velayos et al. also found that a testing-based strategy is cost effective [84]. This strategy yielded similar quality-adjusted life-years gained compared with the empiric-based strategy but was less expensive (US$31,870 vs. US$37,266, respectively).

In patients with quiescent IBD treated with anti-TNF agents, the benefit of routine proactive TDM over no therapeutic monitoring is uncertain [80]. The TAXIT study was the first randomized controlled trial, in any immune-mediated disease in which TNF plays a central role, to evaluate the efficacy and cost effectiveness of dosing based on TNF antagonist drug exposure [85]. Patients were randomly assigned to standard care or prospective dose optimization based on TDM. Targeting infliximab trough concentrations to 3–7 μg/mL resulted in more efficient use of the drug. Dose escalation in CD patients with suboptimal trough concentrations led to a significant increase in clinical remission (88 vs. 65%) and a concomitant drop in CRP concentrations (3.2 vs. 4.3 mg/L), confirming the causality of the relationship between drug exposure and response. A dose reduction in CD and UC patients led to a 28% reduction in drug cost from before dose reduction, without affecting the proportion of patients in remission. In a pilot, retrospective, observational study, of the patients who underwent proactive TDM, 75% (36/48) achieved a trough concentration of 5 μg/mL or higher. In that subset of patients, none developed antibodies to infliximab or infusion reactions. Patients who had proactive TDM of infliximab had a greater probability of remaining on infliximab at 5 years (86 vs. 52%) [86]. However, in TAILORIX, a prospective, randomized, double-blinded, multicenter controlled trial in patients with active CD, proactive trough concentration-based dose intensification was not superior to dose intensification based on symptoms alone [87]. The application of TDM during induction and in dose reduction was not studied.

Because of the lack of prospective, randomized controlled trials on routine proactive TDM versus no TDM, the overall quality of evidence to the recommendation by the American Gastroenterological Association was rated as low. There may be some benefit of early optimization of therapy during induction through proactive TDM, but there is a lack of prospective interventional data [80]. Optimal target trough concentrations and timing of achieving maximal effectiveness of anti-TNF agents during induction therapy are unclear [81]. Additionally, proactive TDM may be inconvenient and expensive due to repeat testing, for which target thresholds are poorly defined to date [80].

Dotan et al. used a published pharmacokinetic model to conduct stochastic stimulations to explore the expected range of infliximab concentration–time profiles given different dose strategies. When dosing was based on body weight, albumin level, and ADA status, 38.3% of patients had troughs below 1 μg/mL. In contrast, when the pharmacokinetically guided dosing approach was implemented, including trough concentrations, most patients (96%) had a trough concentration above 1 μg/mL, suggesting that a combination of TDM and patient factors enables the least variability in concentrations and achieves the most reliable effective doses [38]. The large interpatient variability in exposure and the relationship between exposure and response in children are similar to those observed in adult patients [88]. In pediatric IBD, it is clear that infliximab dose intensification can optimize durability and overcome loss of response [22]. This is of utmost importance because infliximab and adalimumab are the only biopharmaceuticals approved for pediatric IBD. Additionally, personalized dosing regimens may lead to reduced school absences, reduced hospital length of stay, reduced injection/infusion schedules, and, ultimately, improved quality of life [88]. TDM has been proposed by several authors for pediatric IBD, but data regarding the application of TDM remains scarce [72–74, 89].

7 Biosimilars

Infliximab lost patent protection, which allowed for lower priced biosimilars to enter the market. In 2013, the biosimilar of infliximab, CT-P13, with the brand names Remsima™ and Inflectra™, was approved in Europe for pediatric and adult CD and UC, based on extrapolation of results from ankylosing spondylitis and rheumatoid arthritis. In 2016 and 2017, the US FDA approved Inflectra™ and Renflexis™, respectively, for pediatric CD and adult CD and UC, but not as an interchangeable product. Infliximab's pediatric UC indication is protected by orphan exclusivity through September 2018.

Pharmacokinetic evaluations on the use of biosimilars in patients with IBD are unavailable. Extrapolation across indications is difficult. In particular, the influence of the underlying disease influences the pharmacokinetics of infliximab. In IBD patients, the volume of distribution and CL were found to be 49–52 and 47–60% higher, respectively, than in ankylosing spondylitis. In addition, in rheumatoid arthritis, CL was found to be 49% higher than in ankylosing spondylitis [90]. Pharmacokinetic and pharmacodynamic studies with biosimilars in patients with IBD are warranted, in the presence and/or absence of immunomodulators. In addition, available assays should be validated to determine whether biosimilar concentrations

can be quantified with the same sensitivity and specificity as infliximab [91].

8 Conclusions

Although the use of infliximab in the treatment of IBD has led to improved disease outcomes, not all patients respond to treatment, and patients are at risk to lose response to the drug over time. There is large interindividual variability in the pharmacokinetics of infliximab, which may contribute to response to therapy. The pharmacokinetics of infliximab in pediatric and adult patients with CD and UC appeared to be affected by several covariates. ADA positivity, a higher inflammatory burden, a low serum albumin, and a higher body weight increase infliximab CL, while the use of concomitant immunomodulators decreases infliximab CL. The association between infliximab drug exposure and higher rates of clinical response, clinical remission, endoscopic improvement, and sustained response to therapy has been demonstrated. In adult patients, reactive TDM is recommended. Target infliximab trough concentrations of $\geq$5 μg/mL should be used to guide whether escalation of therapy may be beneficial compared with switching therapy. Challenges for the future will be to define the optimal target trough concentration at the time point that is most relevant during induction and maintenance therapy and to better define clinically relevant ADAs. Further data are needed to improve our understanding about the subpopulation of patients who show non-response to infliximab and benefit from modification or personalization of infliximab dosing, which may be safer, more effective, and more cost effective.

Compliance with Ethical Standards

Conflict of interest Amy Hemperly has no conflicts of interest to declare. Niels Vande Casteele has received consultancy fees from Boehringer Ingelheim, UCB Pharma, Pfizer, and Takeda outside of the submitted work.

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