Therapeutic Drug Monitoring of Tumor Necrosis Factor Antagonists in Crohn Disease: A Theoretical Construct to Apply Pharmacokinetics and Guidelines to Clinical Practice

Niels Vande Casteele, PharmD, PhD,*,† Brian G. Feagan, MD, FRCPC,‡ Douglas C. Wolf, MD,§ Anca Pop, MD,∥ Mohamed Yassine, MD,¶ Sara N. Horst, MD, MPH,¶ Timothy E. Ritter, MD,¶ and William J. Sandborn, MD*  

Therapeutic drug monitoring (TDM) is the measurement of drug and antidrug antibody concentrations in individuals to guide treatment decisions. In patients with Crohn disease (CD), TDM, used either reactively or proactively, is emerging as a valuable tool for optimization of tumor necrosis factor (TNF) antagonist therapy. Reactive TDM is carried out in response to treatment failure, whereas proactive TDM involves the periodic monitoring of patients responding to TNF antagonist therapy to allow treatment optimization. In patients with CD, most of the available data for TDM relate to the first-to-market TNF antagonist infliximab and, to a lesser extent, to adalimumab and certolizumab pegol. Several gastroenterology associations, including the American Gastroenterology Association, have endorsed the use of reactive TDM in patients with active CD. However, fewer recommendations currently exist for the use of proactive TDM, although several new prospective randomized controlled trials evaluating proactive TDM strategies have been published. In this review, the current evidence for reactive and proactive TDM is discussed, and a proactive treatment algorithm for certolizumab pegol based on previously published threshold concentrations is proposed.

Key Words: antidrug antibody, certolizumab pegol, proactive TDM, reactive TDM, therapeutic drug monitoring

INTRODUCTION

Treating patients who have Crohn disease (CD) with tumor necrosis factor (TNF) antagonist monoclonal antibodies is often complicated by high interpatient variability in clinical response, in part because of differences in pharmacokinetics.1–3 Furthermore, because these monoclonal antibodies are largemolecular-weight proteins, their absorption and excretion are often influenced by differences in the extent and rate of metabolic degradation.4,5 For this reason, some have advocated the use of TDM to allow for individualized dosing. However, until recently, the use of TDM with TNF antagonists was limited to infliximab, a TNF antagonist monoclonal antibody that can be administered only intravenously. Currently, there are several other therapeutic agents available for the treatment of CD, including systemic adalimumab, certolizumab pegol, and subcutaneous guselkumab, all of which are monoclonal antibodies that may be ideal candidates for TDM.6,7 For instance, unlike infliximab, adalimumab, certolizumab pegol, and guselkumab are not metabolized in the liver, allowing for measurement of drug concentrations in the serum. For these agents, TDM may be more beneficial, as the duration of drug exposure and drug effects may be prolonged, as compared with infliximab. However, differences in the pharmacokinetics and biodistribution of these agents may lead to interpatient variability in drug exposure and drug effects that are not readily apparent with routine monitoring of drug concentrations alone. Additionally, the dynamic nature of the metabolism of these agents and the potential for drug accumulation may lead to problematic drug interactions that are best monitored with TDM. Therefore, in a proactive approach, TDM may be useful to guide dosing and adjustment and, in a reactive approach, TDM may be helpful in identifying subtherapeutic or supratherapeutic drug concentrations, allowing for appropriate adjustment of dosing. However, before TDM can be considered for CD therapy, the clinical, pharmacokinetic, and pharmacodynamic benefits of proactive TDM need to be considered.
molecular-weight foreign proteins, they can elicit an immune response in a subgroup of patients with CD, resulting in the formation of antidrug antibodies (ADAbS). Negative consequences include reduced efficacy as a result of increased drug clearance, reduced binding to target, and increased likelihood of adverse reactions through several mechanisms.1

Therapeutic drug monitoring (TDM), in which serum drug and ADAb concentrations are measured in individual patients, is emerging as a valuable tool to optimize therapy with TNF antagonists. It can be performed reactively or proactively: Reactive TDM is carried out in response to treatment failure (secondary nonresponse), whereas proactive TDM is the periodic monitoring of patients responding to TNF antagonist therapy to allow optimization of treatment by dose adjustment to a target drug concentration. Because TNF antagonist treatment regimens consist of both an induction and a maintenance phase, there are a number of time points when proactive TDM is potentially useful. The aims of this review are to provide an overview of assays and guidelines on TDM and of clinical studies investigating TDM of TNF antagonists, in particular infliximab, adalimumab, and certolizumab pegol, for the treatment of CD, and to provide practical advice for clinicians on the use of both reactive and proactive TDM.

**TDM OF TNF ANTAGONISTS IN CD**

Most of the available data for TDM relate to the first-to-market TNF antagonist infliximab and, to a lesser extent, to adalimumab and certolizumab pegol.

**Assays for TDM**

Several assays and assay formats have been developed to measure TNF antagonist drug and ADAb concentrations in serum, some of which are commercially available, either as a kit or as a service provided by a specialized laboratory.4, 5 The most common assay formats are enzyme-linked immunosorbent assay (ELISA), radioimmunoassay, and the homogeneous mobility shift assay. Some first-generation assays (irrespective of their format) are drug-sensitive—i.e., they do not detect ADAbS in the presence of the drug (TNF antagonist) because free drug in the serum sample competes for ADAbS with the drug that is used to coat the assay plate. A second generation of ADAb assays is now available that is drug-resistant.6, 9

A comparative study indicated that 4 commercially available assays for infliximab were suitable for TDM, even in the presence of infliximab ADAbS or TNF in the serum sample.10 Similarly, a comparative study evaluating 2 commercially available assays for the assessment of adalimumab concentrations found that both methods were accurate and suitable for TDM.11 However, between assays, absolute concentrations of TNF antagonist drugs and ADAbS can differ: A comparison of the LISA-TRACKER (Theradiag) ELISA-based certolizumab pegol assay for the quantification of certolizumab pegol with a custom-made ELISA assay developed by UCB Pharma (validated in line with U.S. Food and Drug Administration/European Medicines Agency regulatory requirements for bioanalytical methods) showed that certolizumab pegol concentrations measured with the LISA-TRACKER certolizumab pegol assay were in good agreement with the ELISA assay developed by UCB Pharma, with a reported Bland-Altman mean ratio of 1.19 (95% confidence interval [CI], 1.13-1.25), suggesting a less than 20% variation in certolizumab pegol concentration between the 2 analytic methods.12 Overall, the good agreement between these two assays suggests that data measured with either assay can be extrapolated to clinical practice.12 Although the certolizumab pegol concentrations measured with the LISA-TRACKER certolizumab pegol assay were higher than those measured the UCB Pharma ELISA, the variability between these 2 assays is to be expected, given that the different format and reagents of these assays (see Fig. 1 for a comparison).12

Furthermore, although a comparison of commercially available homogenous mobility shift assay and ELISA to assess infliximab and adalimumab concentrations found good correlation between the assays for each biologic (infliximab: \( r = 0.861; \ P < 0.001; \) adalimumab: \( r = 0.935; \ P < 0.001 \)), agreement between the assays was weak (infliximab intraclass correlation coefficient = 0.356 [95% CI, −0.069 to 0.720]; \( P < 0.001 \); adalimumab intraclass correlation coefficient = 0.395 [95% CI, −0.073 to 0.759]; \( P < 0.001 \)).13 Therefore, if the aim is to establish whether a particular cutoff concentration of a TNF antagonist has been reached as part of a TDM approach, it is always recommended to select the assay that was initially used to establish the respective threshold.

Often the slow turnaround time of the ELISA-based assays (up to 8 hours) has constrained the immediate implementation of treatment decisions based on test results. This situation has led to the development of more rapid assays with a time-to-result of 20 minutes,14, 15 which will in time allow clinicians to make appropriate treatment decisions based on rapidly available test results at the point of care.

**Guidelines for Reactive and Proactive TDM in Inflammatory Bowel Disease**

Several American, Australian, Canadian, and European gastroenterology associations have issued recommendations regarding the use of TDM of biologics in a reactive and/or proactive setting.16-21

**Reactive TDM**

Guidelines from the American Gastroenterological Association (AGA) conditionally recommend the use of reactive TDM in patients with active inflammatory bowel disease receiving TNF antagonists.16, 22 Trough concentrations (i.e., the concentration of a drug in a patient just before the next dose) for reactive TDM in patients with active disease...
on maintenance TNF antagonist therapy, as suggested by the AGA, are ≥5 µg/mL, ≥7.5 µg/mL, and ≥20 µg/mL for infliximab, adalimumab, and certolizumab pegol, respectively. The AGA trough concentration thresholds have also been endorsed by the American College of Gastroenterology. A consensus statement funded by the Gastroenterological Society of Australia (GESA) endorsed the use of reactive TDM in patients with secondary nonresponse. Trough infliximab and adalimumab concentrations of 3.8 µg/mL and 5 to 12 µg/mL, respectively, were considered appropriate by the GESA panel to achieve clinical remission in luminal CD. Furthermore, the Toronto consensus statement by the Canadian Association of Gastroenterology recommended the use of TDM in patients who had lost response to anti-TNF therapy to help with clinical decision-making and dose optimization. A guideline/consensus paper by the European Crohn’s and Colitis Organization concurred that TDM can be beneficial in patients with difficult cases, notably in patients with primary or secondary treatment failure. An expert panel led by Melmed et al recommended testing for TNF antagonist and ADAb concentrations in patients with secondary loss of response (LOR) and primary nonresponse.

**Proactive TDM**

Guidelines that endorse a proactive TDM approach have been less prevalent than those endorsing a reactive approach. The AGA guidelines, for example, do not make any recommendations regarding the use of routine proactive TDM in patients with quiescent IBD receiving TNF antagonists. Those that do endorse a proactive approach do so very cautiously or only in certain clinical scenarios. For example, the GESA panel proposed that proactive TDM should be considered on a periodic basis only, when test results are likely to affect management decisions. Furthermore, an expert panel led by Melmed et al endorsed testing for TNF antagonist and ADAb concentrations both during the first year of maintenance therapy and after the initial dose after a drug holiday.

Current guidelines do not address the use of TDM during induction, although several studies have shown the association of early adequate drug exposure with long-term clinically
important outcomes. Furthermore, different phenotypes (eg, fistulizing CD) may require different therapeutic thresholds.

**TDM for Infliximab**

**Factors affecting infliximab exposure**

A subgroup of patients (6%-17%) treated with regularly scheduled infliximab (without dose interruption) develop ADAbs, resulting in drug–ADAAb complexes that are cleared from the body much more quickly than the uncomplexed drug. This development negatively impacts overall exposure to the drug and consequently lowers infliximab trough concentrations. Low trough concentrations are associated with poor clinical outcome, such as LOR. A meta-analysis based on 10 studies and 668 patients found an association between infliximab ADAbs and LOR. The relative risk of LOR to therapy in patients with infliximab ADAbs was 3-fold higher than in patients who did not develop ADAbs (relative risk = 3.2; 95% CI, 1.9-5.5; \( P < 0.0001 \)). In some patients, ADAAb formation is “transient”—ie, ADAAbs disappear over time and LOR is reversed, whereas in many other patients ADAAb formation is persistent and LOR is sustained. Monitoring infliximab and ADAAb concentrations in patients receiving infliximab therapy is important to help distinguish between these 2 patient subgroups based on ADAAb status, thus aiding clinical decision-making. In patients who test positive for ADAbs, combination therapy with immunomodulators (IMMs; eg, azathioprine) in addition to TNF antagonist use is recommended to suppress ADAbs formation and is suggested to reverse the enhanced clearance of the TNF antagonist.

Factors other than ADAbs have also been shown to correlate with increased infliximab drug clearance, including serum albumin and C-reactive protein (CRP) concentrations and body weight.

**Exposure–response relationship**

Considerable data support an association between exposure, as defined by blood drug concentrations, and clinically important outcomes in patients treated with infliximab, adalimumab, or certolizumab pegol, indicating that this association is a class effect. This finding holds out the possibility that greater efficacy could be obtained by individualizing drug dosing to ascertain optimal exposure in individual patients, consistent with the principle of proactive TDM. Posthoc analyses that have evaluated the exposure–response relationship of infliximab identified a trough concentration ≥3 \( \mu \text{g/mL} \) during maintenance as being predictive of lower disease activity or sustained remission in patients with CD. A posthoc analysis from the Active Ulcerative Colitis Trials indicated that the proportion of patients achieving clinical remission increased with increasing quartiles of serum infliximab concentrations, with similar trends observed for clinical response and mucosal healing. Specifically, infliximab serum concentrations ≥18.6 \( \mu \text{g/mL} \) at week 2, ≥10.6 \( \mu \text{g/mL} \) at week 6, and ≥34.9 \( \mu \text{g/mL} \) at week 8 (induction time points) were associated with a week 8 Mayo Clinic endoscopic subscore ≤1. Infliximab serum concentrations ≥5.1 \( \mu \text{g/mL} \) at week 14 and ≥2.3 \( \mu \text{g/mL} \) at week 30 (maintenance time points) were associated with a week 30 Mayo Clinic endoscopic subscore ≤1, whereas higher concentrations of ≥6.7 \( \mu \text{g/mL} \) and ≥3.8 \( \mu \text{g/mL} \), respectively, were associated with the more stringent outcome of a subscore of 0. A retrospective, single-center study identified an infliximab concentration ≥15 \( \mu \text{g/mL} \) at the end of the induction period (week 6; \( P = 0.025 \)) as an independent factor of mucosal healing. Although these studies were conducted in patients with ulcerative colitis (UC), they are still relevant to this review because similar associations have also been observed in CD: in a posthoc analysis of ACCENT 1, a multicenter, randomized, placebo-controlled study of patients with CD, serum infliximab trough concentrations of >3.5 \( \mu \text{g/mL} \) at week 14 were predictors of durable sustained response during infliximab maintenance therapy at 5 mg/kg.

**Reactive vs proactive TDM**

A number of studies have evaluated TDM of infliximab in a reactive setting. A prospective, 8-week cohort study evaluated TDM in patients with CD or UC who had received dose intensification after secondary failure to infliximab; an increase in infliximab trough concentration after dose intensification was associated with mucosal healing in both groups of patients (\( P = 0.001 \); Table 1). Furthermore, in a prospective, randomized, controlled cost-effectiveness study, patients with secondary infliximab treatment failure were randomized to either a conventional dose intensification (5 mg/kg every 4 weeks) or interventions using an algorithm based on combined infliximab and infliximab ADAAb measurements. The algorithm-based treatment approach achieved similar clinical, biological, and quality-of-life outcomes to conventional dose intensification but at significantly lower costs (ie, 34% at week 12; \( P < 0.001 \)). This cost reduction was maintained for up to 1 year (Table 1).

A number of studies have reported differences in clinical outcomes between patients who were proactively managed using TDM vs those who were conventionally managed. In the Trough Concentration Adapted Infliximab Treatment (TAXIT) randomized controlled trial, patients with CD (n = 178) or UC (n = 85) on maintenance infliximab therapy all underwent proactive TDM with dose optimization to achieve trough concentrations within the 3–7 \( \mu \text{g/mL} \) window. This intervention, in patients with subtherapeutic drug exposure, led to a significant increase in the proportion of patients in clinical and biochemical remission, whereas in patients with supratherapeutic drug exposure, significant cost reductions were achieved with attainment of response and remission status. After dose optimization, patients were randomized; those who were managed based on clinical...
| Study | Number of Patients | Study Design | Intervention Primary Endpoint | Results |
|-------|-------------------|--------------|------------------------------|---------|
| **Efficacy studies** | | | | |
| Vande Casteele, Ferrante, et al (TAXIT trial) | N = 263 patients with CD or UC | 1-y prospective randomized controlled trial | IFX Clinical and biochemical remission at 1 y after optimization phase | No differences in clinical, biological, and endoscopic remission between IFX TC-based dosing and clinically based dosing arms; however, TC-based dosing was associated with fewer flares requiring rescue therapy and more efficient use of drug. |
| D’Haens et al (TAILORIX trial) | N = 122 patients with CD randomized to 3 maintenance regimens: (1) dose intensification based on clinical symptoms, biomarker analysis, and serum TC IFX; (2) dose intensification of IFX to 5-10 mg/kg based on the same criteria; (3) IFX dose intensification to 10 mg/kg based on clinical symptoms alone | Prospective randomized double-blind controlled trial | IFX Sustained, steroid-free clinical remission from weeks 22-54 and absence of ulceration at 1 y based on endoscopy | Proactive IFX TC-based dose intensification was not superior to clinically based dose intensification. |
| Paul, Del Tedesco, et al | N = 52 patients with CD or UC with secondary failure to IFX | Prospective 8-wk cohort study | IFX n/a | An increase in IFX TC after dose optimization was associated with mucosal healing in patients with CD and with UC (P = 0.001). |
| Assa et al | N = 78 pediatric patients with CD naïve to treatment with TNF antagonists | Nonblinded randomized controlled trial | ADA Sustained corticosteroid-free clinical remission at all visits (wks 8-72) | Proactive TDM of ADA TCs resulted in significantly higher rates of corticosteroid-free clinical remission than did reactive TDM. |
| Chiu et al CLASSIC subanalysis | N = 275 patients with CD receiving ADA as induction therapy in CLASSIC I and II studies | Prospective study | ADA n/a | A positive correlation between serum ADA and remission was identified at several time points up to week 56. |
| Karmiris et al | N = 168 patients with CD after failure of IFX therapy | Prospective observational study | ADA n/a | ADA TCs were lower in patients who discontinued; patients with ADA ADAbs had lower median ADA TC throughout entire follow-up period (P < 0.0001) |
| Bodini, Giannini, Savarino, et al | N = 23 patients with CD | Prospective 72-week study | ADA n/a | ADA TCs were significantly higher (11.9 µg/mL) in patients with remission vs mild and moderate/severe disease (5.5 µg/mL; P = 0.0002). |
| Ward et al | N = 19 patients with CD on maintenance ADA regimen had ADA concentrations measured repeatedly to predefined schedule | Prospective observational study | ADA n/a | ADA concentrations >4.9 µg/mL obtained during the first 9 days predicted therapeutic ADA TCs with reasonable confidence. |
| Vande Casteele, Feagan, Vermeire, et al | N = 2157 patients with CD | CZP simulation study based on data from 9 clinical trials | CZP n/a | CZP concentrations of 36 µg/mL and 15 µg/mL at weeks 6 and 12 were associated with attaining a combined efficacy outcome of CDAI ≤150 and FCP ≤250 µg/g at week 26. |
| **Cost-effectiveness studies** | | | | |
| Steenholdt et al | N = 69 patients with secondary IFX failure were randomized to conventional dose intensification (5 mg/kg every 4 weeks) or interventions based on serum IFX and IFX ADAbs using an algorithm | Randomized controlled single-blind study | IFX Accumulated mean cost per patient for CD at week 12 in the algorithm group vs the group receiving conventional dose intensification | Algorithm-based treatment achieved similar clinical, biological, and quality of life outcomes to conventional dose intensification but at significantly lower costs; this cost reduction was maintained for up to 1 year. |

ADA indicates adalimumab; CDAI, Crohn’s Disease Activity Index; CZP, certolizumab pegol; IFX, infliximab; n/a, not available; TC, trough concentration.
factors had a greater need for rescue therapy compared with patients who were managed based on trough concentrations of infliximab. However, overall remission rates were similar between the 2 arms 1 year after proactive dose optimization in all participants (ie, the primary endpoint; Table 1). The limitations of the TAXIT trial are the design (ie, carryover effect of dose optimization in all patients before randomization) and the relatively short follow-up. A follow-up retrospective study of TAXIT evaluating longer-term outcomes showed that concentration-based dosing was associated with fewer infliximab discontinuations for all reasons than dosing based on clinical factors (P < 0.04).59

TAILORIX, a randomized controlled trial, evaluated 122 patients with CD who were randomized to 3 maintenance regimens: (1) infliximab dose intensification to 10 mg/kg based on clinical symptoms alone; (2) dose intensification in 2.5 mg/kg increments based on clinical symptoms, biomarker analysis, and serum trough concentrations of infliximab; and (3) dose intensification of infliximab to 5 to 10 mg/kg based on clinical symptoms, biomarker analysis, and serum trough concentrations of infliximab (Table 1).40 Infliximab trough concentration–based dose intensification was not superior to clinically based dose intensification with regard to achieving the primary endpoint of steroid-free clinical remission from weeks 22 to 54 and the absence of ulceration at 1 year based on endoscopy.49 However, note that only 14% of patients in TAILORIX actually underwent dose optimization based on infliximab trough concentrations in the combined intervention groups.

The concept that combination therapy with IMMs may not be necessary if adequate TNF antagonist concentrations are attained using proactive TDM is supported by a number of studies. In a pilot observational study, optimization of infliximab (“optimized monotherapy”) to a trough concentration of ≥5 µg/mL using TDM was reported as an alternative strategy to combination therapy with concomitant IMMs in a subset of patients.50 A retrospective study also showed that infliximab trough levels of >5 µg/mL had similar drug persistence after at least 6 months regardless of IMM therapy.51 Furthermore, in a posthoc analysis of the Study of Biologic and Immunomodulator-Naïve Patients in Crohn’s Disease trial, stratification of infliximab trough concentrations showed a similar outcome (corticosteroid-free remission at week 26) within each concentration quartile regardless of IMM therapy.52

In summary, considerable research supports an exposure–response relationship in patients treated with the approved dosing regimen of infliximab; however, the controlled studies performed to date do not provide strong evidence for proactive TDM. Conversely, reactive TDM has become well established in the management of patients with IBD and has some controlled data to support its use.

TDM for Adalimumab

Factors affecting adalimumab exposure

A comprehensive population pharmacokinetics (PK) analysis of adalimumab in patients with moderate-to-severe CD was recently published. Intense serum sampling enabled characterization of the absorption phase of this subcutaneously administered drug and revealed a 4-fold difference in the range of serum adalimumab concentrations 7 days after the first dose (160 mg). Substantial interindividual variability was also observed in clearance, and the presence of adalimumab ADAbs and higher lean body weight were found to be predictors of accelerated drug clearance.53

Exposure–response relationship

The relationship between trough adalimumab concentrations and clinical outcomes in the management of patients with CD is similar to that of infliximab, albeit less well described. Increased adalimumab trough serum concentrations have been reported as a key predictor of improved therapeutic outcome in CD.55–57 A prospective subanalysis study evaluating data from the Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn’s Disease I and II trials identified a positive association between serum adalimumab concentration and remission at several time points up to week 56 (Table 1).55 However, in this study it was not possible to identify cutoff concentrations indicative of clinical remission.55 In a prospective 72-week study, trough adalimumab concentrations were significantly higher (11.9 µg/mL) in patients with remission vs mild and moderate/severe disease (5.5 µg/mL; P = 0.0002; Table 1).56 In addition, in a cross-sectional study of 40 patients, median trough concentrations of adalimumab were higher in patients in clinical remission (6.0 µg/mL) than in those with active disease (3.2 µg/mL; P < 0.012).57 Finally, in a cross-sectional study evaluating 118 trough serum samples from adalimumab-treated patients, higher adalimumab trough serum concentrations were associated with remission (P < 0.001), with an adalimumab serum cutoff value of >5.85 µg/mL being identified as a positive predictor for attaining remission. High adalimumab ADAAb concentrations were positively associated with disease activity.56

Endpoints such as mucosal healing (ie, lack of endoscopic and histologic inflammation) may require even higher adalimumab concentrations (in the range of 13-14 µg/mL) than those required for clinical endpoints, as was reported in a cross-sectional study evaluating 66 patients with CD and UC.58 Furthermore, in a cross-sectional study of 40 patients, trough concentrations were higher in patients with mucosal healing (6.5 µg/mL) than in those without mucosal healing (4.2 µg/mL; P < 0.005). Trough concentrations and duration of adalimumab treatment were independently associated with mucosal healing. Absence of mucosal healing was associated with...
tough concentrations <4.9 µg/mL. Similar to what has been observed for infliximab, the presence of adalimumab ADAb concentrations was associated with a higher LOR to adalimumab. The recent Study to Evaluate the Safety and Efficacy of Two Drug Regimens in Subjects With Moderate to Severe Ulcerative Colitis trial compared higher adalimumab induction doses with the standard induction dosing regimen. After 8 weeks of treatment, standard adalimumab induction doses resulted in similar clinical and endoscopic efficacy compared with the high-induction doses. The similar efficacy was observed despite adalimumab trough concentrations being higher after the higher induction dosing regime vs the standard induction dosing regime (mean [standard deviation] = 19.3 [9.5] µg/mL vs 8.0 [4.9] µg/mL, respectively). These results indicate that not all patients may benefit from higher doses, but rather a selection of patients who are at risk of accelerated drug clearance.

**TDM for Certolizumab Pegol**

Factors affecting certolizumab pegol exposure

Similar to infliximab and adalimumab, a subgroup of patients receiving certolizumab pegol develop ADAb concentrations that may result in increased drug clearance from the body. A population PK model was developed that made it possible to describe the time-varying nature of covariates and certolizumab pegol ADAb concentrations and how this affects certolizumab pegol PK parameters, such as clearance. This model predicted that high certolizumab pegol ADAb concentrations are more likely to lead to certolizumab pegol exposure below therapeutic concentrations compared with lower certolizumab pegol ADAb concentrations. Whereas this population PK model identified time-varying body weight and CRP as additional factors that increase certolizumab pegol clearance, it identified albumin as a factor that decreases clearance.

**Exposure–response relationship**

An exposure–response relationship has been described for certolizumab pegol, similar to infliximab and adalimumab. Two studies have evaluated certolizumab pegol concentrations and certolizumab pegol ADAb concentrations and correlated these with clinical outcomes in patients with CD. A post hoc analysis by Colombel, Sandborn, Allez, et al reported that higher certolizumab pegol serum concentrations at week 8 (n = 80) were associated with endoscopic response (P = 0.0016; area under the receiver operating curve = 0.69) and clinical remission at week 10 (P = 0.0302, area under the receiver operating curve = 0.70) in patients with CD. At week 54 (n = 45), the rates of endoscopic remission correlated with certolizumab pegol plasma concentrations. Furthermore, there was an inverse relationship between certolizumab pegol plasma concentrations and body weight (P = 0.0373) and CRP concentrations (P = 0.0014) at baseline.

In a retrospective study using endoscopic and radiologic data to investigate certolizumab pegol treatment in patients with IBD, certolizumab pegol trough concentrations >27.5 µg/mL were associated with radiological healing, radiological response, and symptomatic response. No association was found between median certolizumab pegol trough concentrations and mucosal healing. Lower trough concentrations (<27.5 µg/mL) were significantly associated with changes in clinical management (including a decrease in dose interval, addition of an IMM, or certolizumab pegol discontinuation; P = 0.007).

A recent longitudinal report from the 7-year Pegylated Antibody Fragment Evaluation in Crohn’s Disease: Safety and Efficacy-3 study (N = 594) examined the impact of transient (defined as >2.4 U/mL with transient or no effect on certolizumab pegol plasma concentration >5 µg/mL) vs persistent (defined as >2.4 U/mL with continuous impact on certolizumab pegol plasma concentration) certolizumab pegol ADAb concentrations and markers of inflammation. There were 134 (22.6%) patients who were positive for ADAb at least once during the study. Of those, 40 were categorized as having transient ADAb and 94 were categorized as having persistent ADAb. In patients with persistent certolizumab pegol ADAb concentrations, median plasma concentrations of the inflammatory markers CRP and FCP were significantly higher (P < 0.05 at some visits) and plasma certolizumab pegol concentrations were significantly lower (P < 0.0001) compared with patients who were certolizumab pegol ADAb-negative. However, in patients with transient certolizumab pegol ADAb concentrations, plasma certolizumab pegol, CRP, and FCP concentrations
were similar to those in patients who were certolizumab pegol ADAb-negative, which may suggest that transient ADAs may not affect certolizumab pegol concentrations or the clinical response to certolizumab pegol.

When the above-mentioned population PK model was applied to pooled data from 9 clinical trials investigating certolizumab pegol in adult patients with CD, approximate certolizumab pegol concentrations of 36 µg/mL at week 6 and 15 µg/mL at week 12 were associated with attainment of a robust combined efficacy outcome (Crohn’s Disease Activity Index ≤ 150 and FCP ≤ 250 µg/g, respectively) at week 26 (Table 1). Knowledge of specific drug concentration thresholds that corresponded with efficacy outcomes, such as the week 6 certolizumab pegol concentrations of 36 µg/mL and 15 µg/mL at week 12 identified in this analysis, may inform TDM and guide decisions in clinical practice.

In summary, similar to infliximab and adalimumab, extensive research supports an exposure–response relationship in patients with CD receiving approved doses of certolizumab pegol. Concentration thresholds have been identified that correspond with efficacy outcomes.

A theoretical construct for proactive certolizumab pegol TDM

Although no controlled studies evaluating proactive TDM of certolizumab pegol have been conducted to date, we propose a theoretical construct for TDM of certolizumab pegol in patients in clinical remission based on previously published certolizumab pegol trough concentration thresholds, as illustrated in Fig. 2. In this treatment algorithm, certolizumab pegol trough concentrations are measured after induction and during maintenance therapy. Patients with subtherapeutic certolizumab pegol trough concentrations (<36 µg/mL at week 6 and/or <15 µg/mL at week 12, as described previously) are identified and evaluated further for ADAb status. Patients with negative ADAs are considered for the addition or optimization of IMM therapy and/or dose escalation. Patients with positive ADAs may need repeat TDM (perhaps after an intervention such as dose escalation and/or addition or optimization of IMM therapy at provider discretion) to differentiate between persistent vs transient ADAs. In patients with confirmed persistent ADAb status, switching to another TNF antagonist or to a different drug class should be considered.

LIMITATIONS OF CURRENT DATA AND KNOWLEDGE GAPS

Limitations of the data on which the proposed TDM treatment algorithm for certolizumab pegol is based include the absence of endoscopic outcomes, which were often not assessed in historic trials of CD. There is a need for studies evaluating clinical outcomes that support the long-term benefits of a proactive TDM strategy, with regard not only to steroid-free clinical remission but also to endoscopic and histologic healing. Furthermore, the causal relationship between certolizumab pegol exposure and clinical outcomes is not clearly established. A potential solution is a prospective, interventional clinical trial looking at early and optimized dosing of certolizumab pegol vs a reactive approach per standard of care.

CONCLUSIONS

There is substantial variability in pharmacokinetics and observed response rates between TNF antagonists in CD. We find that TDM offers the potential to optimize therapy in individual patients. Reactive TDM is supported by guidelines and is currently being widely adopted in clinical practice. Proactive TDM has current uncertainties, but data are emerging that indicate that it is an effective strategy for the improved retention of TNF antagonist therapy.

ACKNOWLEDGMENTS

The authors acknowledge Fionna Nitsche, PhD, CMPP and Richard Fay, PhD, CMPP of Evidence Scientific Solutions (London, UK and Philadelphia, PA) for writing and editorial assistance, which was funded by UCB Pharma. The authors also acknowledge Mylene Serna, PharmD (UCB Pharma, Smyrna, GA) for publication coordination.

REFERENCES

1. Lin K, Mahadevan U. Pharmacokinetics of biologics and the role of therapeutic monitoring. Gastroenterol Clin North Am. 2014;43:565–579.
2. Vande Casteele N, Gils A. Pharmacokinetics of anti-TNF monoclonal antibodies in inflammatory bowel disease: adding value to current practice. J Clin Pharmacol. 2015;55:S39–S50.
3. Vande Casteele N, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosage for patients with inflammatory bowel disease. Gastroenterology. 2015;148:1320–1329.e3.
Vande Casteele et al

4. Lab Corp. Certolizumab and anti-certolizumab antibody. DoseASSURE™ CTX. Accessed December 31, 2019. https://www.labcorp.com/test-menu/46121/certolizumab-and-anti-certolizumab-antibody-idose-tassure#E%288%A2ctx#

5. Mayo Clinic Laboratories. Test ID: FCERT-cetolizumab pegol and anti-cetolizumab antibodies. Accessed December 31, 2019. https://qa.mayocliniclabs.com/test/catalog/clinical+and+interpretative/75189.

6. van Schouwenburg PA, Bartelds GM, MH MH, et al. A novel method for the detection of antibodies to adalimumab in the presence of drug reveals “hidden” immunogenicity in rheumatoid arthritis patients. J Immunol Methods. 2010;362:82–88.

7. Wang SL, Ohmund L, Hauenstein S, et al. Development and validation of a homogeneous mobility assay for the measurement of infliximab and antibodies-to- infliximab levels in patient serum. J Immunol Methods. 2012;382:177–188.

8. Wang SL, Hauenstein S, Ohmund L, et al. Monitoring of adalimumab and antibodies-to-adalimumab levels in patient serum by the homogeneous mobility shift assay. J Pharm Biomed Anal. 2013;78:79–89.

9. Patton A, Mullenic MS, Swanson SJ, Koen E. An acid dissociation bridging ELISA for detection of antibodies directed against therapeutic proteins in the presence of antigen. J Immunol Methods. 2005;304:189–195.

10. Masaer E, Villois R, Silverberg MS, Greenberg GR. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn’s disease. Clin Gastroenterol Hepatol. 2006;4:1248–1254.

11. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn’s disease. N Engl J Med. 2004;350:876–885.

12. Vermeire S, Noman M, Van Assche G, et al. Effectiveness of concomitant immunosuppressive therapy in suppressing the formation of antibodies to infliximab in Crohn’s disease. Gut. 2007;56:1226–1231.

13. Nanda KS, Cheifetz AS, Moss IA. Impact of antibodies to infliximab on clinical outcomes and serum infliximab levels in patients with inflammatory bowel disease (IBD): a meta-analysis. Am J Gastroenterol. 2013;108:40–47.

14. Vande Casteele N, Gils A, Ballet V, et al. Randomized controlled trial of drug level versus clinically based dosing of infliximab maintenance therapy in IBD: final results of the TAKIT study [EUGW abstract EUG13-ABS-2468]. Presented at 21st United European Gastroenterology Week. Berlin, Germany.

15. Colombo BF, Sandborn WJ, Reich N, et al.; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn’s disease. N Engl J Med. 2010;362:1383–1395.

16. Sadamade AA, Aedoekun OJ, Blank M, et al. Pharmacokinetic properties of infliximab in children and adults with Crohn’s disease: a retrospective analysis of data from 2 phase III clinical trials. Clin Ther. 2011;33:946–964.

17. Fasanmade AA, Adeoekun OJ, Blunt M, et al. Serum albumin concentration: a predictive factor of infliximab pharmacokinetics and clinical response in patients with ulcerative colitis. Int J Clin Pract. 2010;64:297–301.

18. Vande Casteele N, Feagan BG, Gils A, et al. Therapeutic drug monitoring in the management of inflammatory bowel disease: current state and future perspectives. Curr Gastroenterol Rep. 2014;16:378.

19. Bouillot M, Duricova D, Malickova K, et al. Infliximab trough levels may predict sustained response to infliximab in patients with Crohn’s disease. J Crohns Colitis. 2016;10:736–743.

20. Fourneau F, Hanauer SB, Diamond RH, et al. Postinduction serum infliximab trough level and decrease of C-reactive protein level are associated with durable sustained response to infliximab: a retrospective analysis of the ACCENT I trial. Gut. 2016;65:1217–1221.

21. Vande Casteele N, Khrana R, Levesque BG, et al. The relationship between infliximab concentrations, antibodies to infliximab and disease activity in Crohn’s disease. Gut. 2015;64:1539–1545.

22. Reinsch W, Feagan BG, Rutgeerts P, et al. Infliximab concentration and clinical outcome in patients with ulcerative colitis. Gastroenterology. 2012;142:S114.

23. Vande Casteele N, Jeyarajah J, Jairath V, et al. Infliximab exposure-response relationship and thresholds associated with endoscopic healing in patients with ulcerative colitis. Curr Gastroenterol Rep. 2019;17:1814–1821.

24. Papamichael K, Van Stappen T, Vande Casteele N, et al. Infliximab concentration thresholds during induction therapy are associated with short-term mucosal healing in patients with ulcerative colitis. Curr Gastroenterol Rep. 2016;18:543–549.

25. Paul S, Del Tedesco E, Marotte H, et al. Therapeutic drug monitoring of infliximab and mucosal healing in inflammatory bowel disease: a prospective study. Inflamm Bowel Dis. 2013;19:2568–2576.

26. Steenholt C, Brynskov J, Thomsen OO, et al. Individualised therapy is more cost-effective than dose intensification in patients with Crohn’s disease who lose response to anti-TNF treatment: a randomised, controlled trial. Gut. 2016;63:919–927.

27. Vande Casteele N, Hauenstein S, Ohrmund L, et al. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn’s disease. N Engl J Med. 2006;354:1248–1254.

28. Vaughn BP, Martinez-Vazquez M, Patwardhan VR, et al. Detection of anti-infliximab antibodies with a drug-tolerant assay: post hoc analysis of the TAXIT study [UEGW abstract UEG13-ABS-2468]. Presented at 21st United European Gastroenterology Week. Berlin, Germany.

29. Pouillon L, Ferrante M, Van Assche G, et al. Mucosal healing and long-term outcomes of patients with inflammatory bowel diseases receiving clinical-vs trough concentration-based dosing of infliximab. Curr Gastroenterol Rep. 2018;20:135.60.2762–2770.

30. Poisson L, Ferrante M, Van Assche G, et al. Mucosal healing and long-term outcomes of patients with inflammatory bowel diseases receiving prednisolone vs trough concentration-based dosing of infliximab. Curr Gastroenterol Rep. 2018;20:135.60.2762–2770.

31. D’Haens G, Vermeire S, Lambrecht G, et al.; GETAID. Increasing infliximab drug concentrations during induction of anti-tumor necrosis factor therapy in inflammatory bowel disease. J Crohns Colitis. 2015;9:514–521 e4.
52. Colombel JF, Adedokun OJ, Gasink C, et al. Combination therapy with infliximab and azathioprine improves infliximab pharmacokinetic features and efficacy: a post hoc analysis. *Clin Gastroenterol Hepatol.* 2019;17:1525–1532.e1521.

53. Vande Casteele N, Baert F, Biau S, et al. Subcutaneous absorption contributes to observed interindividual variability in adalimumab serum concentrations in Crohn's disease: a prospective multicentre study. *J Crohns Colitis.* 2019;13:1248–1256.

54. Bodini G, Giannini EG, Savarino V, et al. Adalimumab trough serum levels and anti-adalimumab antibodies in the long-term clinical outcome of patients with Crohn's disease. *Scand J Gastroenterol.* 2016;51:1081–1086.

55. Chiu YL, Rubin DT, Vermeire S, et al. Serum adalimumab concentration and clinical remission in patients with Crohn's disease. *Inflamm Bowel Dis.* 2013;19:1112–1122.

56. Mazor Y, Almog R, Kopylov U, et al. Adalimumab drug and antibody levels as predictors of clinical and laboratory response in patients with Crohn's disease. *Aliment Pharmacol Ther.* 2014;40:620-628.

57. Robin X, Marotte H, Rmaudo M, et al. Association between pharmacokinetics of adalimumab and mucosal healing in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol.* 2014;12:80-84.e2.

58. Yarur AJ, Jain A, Hauenstein SI, et al. Higher adalimumab levels are associated with histologic and endoscopic remission in patients with Crohn's disease and ulcerative colitis. *Inflamm Bowel Dis.* 2016;22:409–415.

59. Baert F, Kondragunta V, Lockton S, et al. Antibodies to adalimumab are associated with future inflammation in Crohn's patients receiving maintenance adalimumab therapy: a post hoc analysis of the Karmiris trial. *Gut.* 2016;65:1126-31.

60. Karmiris K, Paintaud G, Noman M, et al. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease. *Gastroenterology.* 2009;137:1628–1640.

61. Paul S, Moreau AC, Del Tedesco E, et al. Pharmacokinetics of adalimumab in inflammatory bowel diseases: a systematic review and meta-analysis. *Inflamm Bowel Dis.* 2014;20:1288–1295.

62. Panès J, Colombel J-F, D’Huennes GR, et al. High versus standard adalimumab induction dosing regimens in patients with moderately to severely active ulcerative colitis: results from the SERENE-UC induction study. *United European Gastroenterol J.* 2019;7:118.

63. Assa A, Matar M, Turner D, et al. Proactive monitoring of adalimumab trough concentration associated with increased clinical remission in children with Crohn's disease compared with reactive monitoring. *Gastroenterology.* 2019;157:985–996.e982.

64. Ramos GP, Al-Bawardy B, Willrich MAV, et al. Certolizumab trough levels and antibodies in inflammatory bowel disease: a single-center experience. *Gastroenterology.* 2018;154:8826-8827.

65. Sandborn WJ, Feagan BG, Stoenov S, et al.; PRECISE 1 Study Investigators. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med.* 2007;357:228-238.

66. Schreiber S, Khaliq-Kareemi M, Lawrance IC, et al.; PRECISE 2 Study Investigators. Maintenance therapy with certolizumab pegol for Crohn's disease. *N Engl J Med.* 2007;357:239-250.

67. Vande Casteele N, Mould DR, Course J, et al. Accounting for pharmacokinetic variability of certolizumab pegol in patients with Crohn’s disease. *Clin Pharmacokinetics.* 2017;56:1513-1523.

68. Colombel JF, Sandborn WJ, Allez M, et al. Association between plasma concentrations of certolizumab pegol and endoscopic outcomes of patients with Crohn's disease. *Clin Gastroenterol Hepatol.* 2014;12:423-431.e421.

69. Sandborn WJ, Wolf DC, Kosutic G, et al. Effects of transient and persistent anti-drug antibodies to certolizumab pegol: longitudinal data from a 7-year study in Crohn's disease. *Inflamm Bowel Dis.* 2017;23:1047-1056.

70. Vande Casteele N, Feagan BG, Vermeire S, et al. Exposure-response relationship of certolizumab pegol induction and maintenance therapy in patients with Crohn's disease. *Aliment Pharmacol Ther.* 2018;47:229-237.

71. Ward MG, Thwaites PA, Beswick L, et al. Intra-patient variability in adalimumab drug levels within and between cycles in Crohn's disease. *Aliment Pharmacol Ther.* 2017;45:1135-1145.