SYMPOSIUM

IV CHALLENGES IN THERAPEUTIC DRUG MONITORING

OPTIMIZING TREATMENT IN IBD PATIENTS

May-June 2020
Webinar Sessions

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IN IBD PATIENTS

CONTENTS

Optimizing the treatment of inflammatory bowel disease through use of proactive therapeutic drug monitoring

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INTRODUCTION

Therapeutic drug monitoring (TDM) is a component of personalized medicine that involves measuring drug concentrations in a patient's blood at a designated timepoint to determine the dosage regimen required to maintain therapeutic concentrations. TDM has an important role for certain drugs including biologic therapies, and hence has application in several immune-mediated inflammatory disorders. This review describes the role of TDM with anti-tumor necrosis factor (TNF) biologics in inflammatory bowel diseases (IBD), and examines the potential benefits of proactive versus reactive TDM.

OPTIMIZING AND PERSONALIZING THE TREATMENT OF IBD

The objectives of personalizing care for patients with IBD are to:

- Treat smarter, i.e. predict which patients will have aggressive disease
- Treat earlier in the disease course with effective therapy. In the case of IBD, this involves treating while the disease is inflammatory to prevent the development of irreversible complications such as strictures and fistula
- Treat deeper to achieve endoscopic improvement given that better endoscopic appearance translates into superior long-term outcomes
- Treat to target to achieve the treatment goal agreed with the patient
- Treat more effectively by utilizing proactive TDM.

In IBD, it is important to optimize the initial drug selected for treatment as the first agent invariably works best. Anti-TNF-exposed patients do not respond as well as anti-TNF-naïve patients, regardless of the drug chosen for treatment. There are significant rates of primary nonresponse and secondary loss of response to drugs used to treat IBD, much of which may be due to underdosing which leads to subtherapeutic drug concentrations and antidrug antibody formation. Antidrug antibodies occur most commonly with anti-TNF therapies. As infliximab continues to be the most effective agent in severe IBD, particularly severe hospitalized ulcerative colitis (UC) and perianal Crohn's disease (CD), every attempt should be made to retain its use for as long as possible. TDM, especially proactive TDM, is a valuable technique to optimize drug concentrations and improve clinical outcomes with anti-TNF therapies.

REACTIVE VERSUS PROACTIVE THERAPEUTIC DRUG MONITORING

Reactive TDM can be defined as the measurement of trough concentration and antibody level in the setting of primary or, more commonly, secondary loss of response to a biologic agent. The aim of reactive TDM is to gather information about the reasons for lack of response or loss of response in order to inform therapeutic decisions about increasing the amount of drug,

adding an immunomodulator, or switching the drug in or out of class. Reactive TDM is currently the most common method of TDM performed by physicians.

Guideline and consensus statements for reactive TDM are summarized in **Table 1**. Apart from one equivocal set of recommendations [1], the groups are supportive of reactive TDM in patients with loss of response to anti-TNF therapy [2-8]. Compared with empiric dose escalation, reactive TDM better directs patient care as more drug is given to patients who would benefit, whereas switching drug is recommended for patients who would not benefit from receiving more drug (i.e. those with high-titer antidrug antibodies). Reactive TDM is also more cost effective than empiric dose escalation. However, reactive TDM carries the risk that, by the time the drug concentration is measured, the patient will already have high levels of antibodies and use of the drug will be lost. It is arguably counter-intuitive to wait until a patient is failing a medication to measure drug concentrations.

Proactive TDM is the measurement of trough concentration and antibody level with the goal of optimizing drug concentration (through dosing) to achieve a threshold drug concentration at specific timepoints (e.g. during induction, end of induction, during maintenance). The aim of proactive TDM is to improve response rates and prevent secondary loss of response and antibody development by targeting drug concentrations considered to be in the optimal therapeutic range.

Guideline and consensus statements for proactive TDM are summarized in **Table 2**. The American Gastroenterological Association suggests that evidence for proactive TDM is insufficient and that the benefits are uncertain [5]. Conversely, the Australian TDM consensus group and international Building Research in Inflammatory Bowel Disease Globally (BRIDGe) group are in favor of proactive TDM [6,7,9]. These latter groups recommend that, in responders to anti-TNF therapy, the anti-TNF drug concentration should be measured after induction and during maintenance therapy to ensure that it is adequate and to dose the drug appropriately [6,7,9].

The current BRIDGe group consensus statements [9] recommend that TDM is performed in the following situations:

- Anti-TNF agents
  - Responders
    - End of induction
    - At least once during maintenance therapy

    } Proactive TDM
  - Primary nonresponse (end of induction)
  - Secondary loss of response
- Vedolizumab and ustekinumab
  - Primary nonresponse (end of induction)
  - Secondary loss of response

For novel agents in IBD such as vedolizumab and ustekinumab, in the absence of evidence for proactive TDM, the BRIDGe group recommends performing reactive TDM [9]. However, at the Beth Israel Deaconess Medical Center, our approach is to use proactive TDM also for vedolizumab and ustekinumab in order to know and confirm that drug concentrations are not undetectable. Moreover, some data exist with regard to improved outcomes with higher threshold concentrations for both agents.

WHY PROACTIVE TDM?

Proactive TDM is not a new concept as it is commonly performed in other settings, for example,

Table 1. Consensus statements for reactive therapeutic drug monitoring.

Guideline/Consensus	Year	Recommendation
European Crohn's and Colitis Organisation (CD) [1]	2020	In CD patients who have lost response to an anti-TNF agent, there is currently insufficient evidence to recommend for or against the use of reactive TDM to improve clinical outcomes, but does suggest a cost savings benefit potentially justifying the use of such an approach where TDM is available. TDM can at least be used to guide dose optimization
British Society of Gastroenterology [2]	2019	Treatment options for failure of initial anti-TNF therapy (increase dose, shorten dosage interval, switch to alternative anti-TNF, or switch to different drug class) may be informed by the clinical context and by measurement of serum drug and antidrug antibodies concentrations. Patients with secondary loss of response to anti-TNF therapy may have serum drug and antidrug antibodies concentrations measured to inform appropriate changes in treatment
Canadian Association of Gastroenterology (CD) [3]	2019	Dose optimization informed by TDM is suggested for patients with CD who lose response to anti-TNF therapy
American College of Gastroenterology (UC) [4]	2019	In patients with moderately to severely active UC who are responders to anti-TNF therapy and are losing response, measuring serum drug levels and antibodies is suggested to assess the reason for loss of response
American Gastroenterological Association (TDM in IBD) [5]	2017	Reactive TDM may be of benefit over empirically escalating the dose or switching therapies to guide treatment changes
Australian TDM consensus [6]	2017	TDM is recommended in secondary loss of response to guide clinical decision-making. TDM can inform decision making in patients with primary nonresponse
BRIDGe group RAND appropriateness panel [7]	2016	Assessment of anti-TNF drug and antibody concentrations was rated appropriate at the end of induction therapy in primary and secondary nonresponders
Toronto Consensus (UC) [8]	2015	In cases of loss of response, use TDM for optimization and before switch and switch out of class for better decision process

BRIDGe, Building Research in IBD Globally; IBD, inflammatory bowel disease; TDM, therapeutic drug monitoring; TNF, tumor necrosis factor; UC, ulcerative colitis; CD: Crohn's disease

Table 2. Consensus statements for proactive therapeutic drug monitoring.

Guideline / Consensus	Year	Recommendation
BRIDGe group panel [9]	2019	TDM should be performed in patients responding to anti-TNF therapy at the end of induction and at least once during maintenance therapy
American Gastroenterological Association (TDM in IBD) [5]	2017	In patients with quiescent IBD treated with anti-TNF agents, the benefit of routine proactive TDM over no therapeutic monitoring is uncertain
Australian TDM consensus [6]	2017	TDM should be considered in patients in remission after induction and periodically in patients in clinical remission. Patients maintained in clinical remission in whom a drug holiday is contemplated are suggested to have TDM along with other investigations to help guide this decision
BRIDGe group RAND appropriateness panel [7]	2016	In patients responding to maintenance therapy, assessment of drug and antibody concentrations is appropriate at least once during the first year of maintenance therapy and following a drug holiday

BRIDGe, Building Research in IBD Globally; IBD, inflammatory bowel disease; TDM, therapeutic drug monitoring; TNF, tumor necrosis factor.

cyclosporine and tacrolimus in solid organ transplantation [10], and vancomycin and gentamycin in sepsis [11,12]. The concept of proactive TDM is that of a therapeutic window: with certain medications high drug concentrations are associated with increased toxicity, whereas low drug concentrations result in lack of efficacy. In the case of biologics, low concentrations are also associated with a greater risk of immunogenicity and potential loss of response.

The bulk of current evidence for proactive TDM in IBD patients relates to maintenance therapy and most is with use of infliximab. During maintenance therapy in treatment responders (to infliximab unless otherwise noted), proactive TDM has numerous benefits:

- Improves clinical scores and markers of inflammation (C-reactive protein; CRP) [13]
- Decreases the need for rescue therapy [13]
- Prolongs the duration of infliximab and adalimumab therapy with less discontinuations [14,15]
- Decreases IBD-related hospitalizations and surgeries, serious infusion reactions (SIR) and antibodies to infliximab compared with reactive TDM [14]
- Increases clinical remission in children with CD receiving adalimumab (compared with reactive monitoring) [16]
- Reduces IBD-related hospitalization and surgery and incidence of SIRs, and increases long-term durability of infliximab compared with empiric dosing [17]
- Improves clinical outcomes after reactive TDM [18]
- Is cost effective [19,20].

Evidence for each of these benefits is examined in more detail below.

EVIDENCE FOR PROACTIVE TDM

Drug concentrations of biologics correlate with outcomes

Many studies have shown that higher drug concentrations of biologics are associated with better outcomes. Although lower infliximab or adalimumab thresholds may be sufficient to produce a clinical response, increasingly higher thresholds are required to achieve clinical remission, biochemical improvement (reduced CRP levels), endoscopic improvement and, ultimately, histological improvement (**Figure 1**) [9]. Moreover, several studies have shown that undetectable or low infliximab concentrations are associated with loss of response, antibody formation and infusion reactions [9].

A few years ago, our group performed a retrospective, observational study comparing outcomes in patients with IBD who responded to infliximab induction, received maintenance therapy and had either proactive TDM (n = 48) or standard of care (defined as reactive TDM or empiric dose escalation; n = 78) [21]. At the time, the therapeutic window for infliximab in patients undergoing proactive TDM was a trough concentration of 5-10 mg/L: a trough concentration below 5 mg/L would trigger a dose increase, whereas a trough concentration above 10 mg/L on two or more occasions would trigger a dose decrease. Compared with standard of care, proactive TDM and dose optimization was associated with a greater probability of remaining on infliximab (hazard ratio [HR] 0.3; 95% confidence interval [CI] 0.1-0.6, p = 0.0006) and a lower rate of treatment discontinuation (10% *vs.* 31%; p = 0.009). Infliximab was escalated in about 25% of patients after the first proactive measurement, and was de-escalated in about 15% of patients during the observation period.

The Trough Concentration Adapted Infliximab Treatment (TAXIT) study from Belgium was the first prospective study of proactive TDM conducted in IBD [13]. The study enrolled 263 patients (178 with CD)

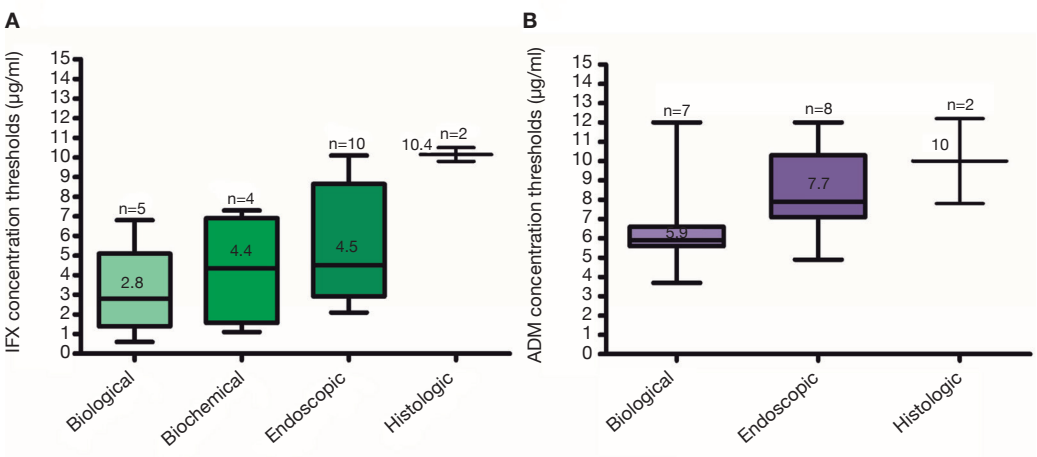

Figure 1. Infliximab (A) and adalimumab (B) concentration thresholds are associated with objective therapeutic outcomes in IBD. Box plots (5-95%) show median (solid line within box), interquartile range (upper and lower box boundaries) and standard deviation (whiskers). Reproduced with permission from [9]. ADM, adalimumab; IBD, inflammatory bowel disease; IFX, infliximab.

who had a stable clinical response (including remission) while receiving infliximab maintenance therapy. During an initial optimization phase, all patients had their infliximab doses escalated or reduced to a target trough concentration of 3-7 mg/L. Among 43 CD patients with infliximab trough concentrations < 3 mg/L, a one-time dose escalation resulted in better disease control. In this group, the remission rate increased from 65% to 88% (p = 0.02), and median CRP levels decreased from 4.3 to 3.2 mg/L (p = 0.001) after dose escalation. These same benefits were not observed among 28 UC patients with subtherapeutic trough concentrations, however, because most patients (90%) were already in remission at the time of enrollment. Following dose optimization and start of maintenance therapy, patients were randomized to receive continued concentration-based dosing to a therapeutic window of 3-7 mg/L (n = 128) or clinically-based dosing according to symptoms and CRP levels (n = 123). At 1 year, there were no differences in clinical or biological remission rates between the concentration-dosed and clinically-dosed groups (primary endpoint) which, on reflection, was not surprising given that all patients had started maintenance therapy from an optimized dose level. Other possible reasons for the lack of difference in outcomes were the short observation period (1-year follow-up) and potentially subtherapeutic therapeutic window for infliximab. Nevertheless, several secondary endpoints favored concentration-based dosing of infliximab to a trough level of 3-7 mg/L. Fewer proactive TDM patients than clinically-dosed patients required rescue therapy (7% *vs*. 17.3%; p = 0.004) or had undetectable trough concentrations (odds ratio [OR] 3.7; p < 0.001), and more proactive TDM patients remained in the target range (74% *vs*. 57%; p < 0.001). As 25% of patients in the proactive TDM group underwent dose de-escalation, the cost of concentration-based dosing and clinically-based dosing was similar.

More recently, our center in conjunction with a group from the University of Pennsylvania undertook a retrospective, observational study of 264 patients with IBD (167 with CD) who were infliximab responders and received maintenance therapy [14]. Patients received either proactive or reactive TDM based on their first measurements of infliximab concentration and antibodies to infliximab. Compared with the reactive TDM group, the proactive TDM group showed a markedly lower incidence of treatment failure extending up to 5 years after the start of infliximab therapy [HR 0.16, 95% CI 0.09-0.27; p < 0.001; **Figure 2**). Proactive TDM patients also had less IBD-related surgery (HR 0.30, 95% CI 0.11-0.80; p = 0.017), less IBD-related hospitalization (HR 0.16, 95% CI 0.07-0.33; p < 0.001), less antibody formation (HR 0.25, 95% CI 0.07-0.84; p = 0.025), and fewer SIRs (HR 0.17, 95% CI 0.04-0.78; p = 0.023). Significantly higher incidences of treatment failure (p < 0.001), IBD-related hospitalization (p = 0.020), antibodies to infliximab (p < 0.001) and SIRs (p = 0.007) among patients in the lowest quartile of trough infliximab levels (< 2.1 mg/L) highlighted the clear association between drug concentration and outcomes.

Furthermore, a modelling study showed that standard infliximab dosing is insufficient in the majority of pediatric patients with CD [22]. A Monte Carlo simulation analysis was constructed using a population pharmacokinetic model based on data from 112 children with moderate-to-severe CD who had participated in the REACH study [23]. Maintenance dosing strategies of infliximab 5, 7.5, and 10 mg/kg at dosing intervals of every 4, 6, and 8 weeks were modelled by varying the characteristics of age, weight, albumin level, and concomitant immunomodulator therapy. Among 1000 children simulated in the model, only 21% (albumin = 3 g/dL) and 41% (albumin = 4 g/dL) of those receiving standard dosing of 5 mg/kg every

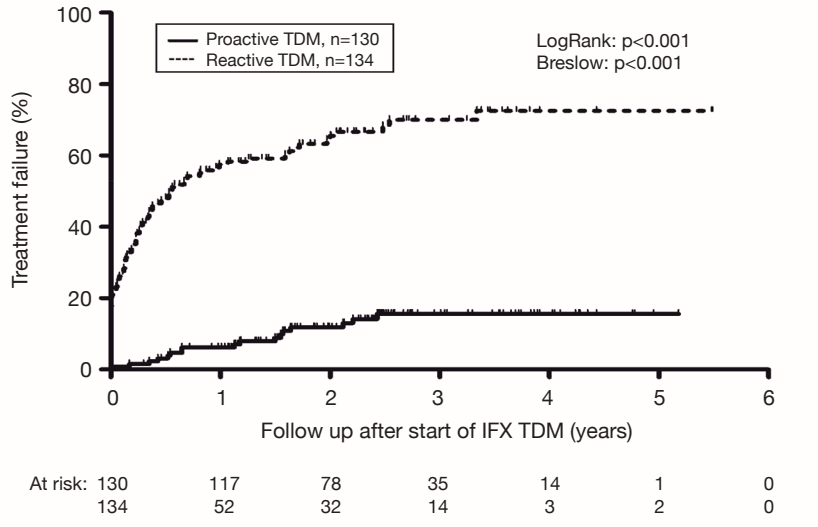

Figure 2. In patients with IBD who had responded to infliximab and received maintenance therapy, the cumulative probability of treatment failure up to 5 years after first TDM was significantly lower with proactive TDM versus reactive TDM. Reproduced with permission from [14]. IBD, inflammatory bowel disease; IFX, infliximab; TDM, therapeutic drug monitoring.

8 weeks achieved an infliximab trough level > 3 mg/L. Most children who were modelled to achieve an infliximab trough level > 3 mg/L required dosing of 5 mg/kg every 4 or 6 weeks or 10 mg/kg every 6 or 8 weeks.

Proactive TDM with adalimumab has also been investigated. In association with a group from Minnesota, our center performed a retrospective, observational study involving 382 patients with IBD (311 with CD) who had responded to adalimumab and received maintenance therapy [15]. Patients received at least one proactive TDM measurement (n = 53) or standard of care defined as empiric dose escalation (n = 279) or reactive TDM (n = 50). Median follow-up was 3.1 years. In multiple Cox regression analyses, at least one proactive TDM measurement was independently associated with reduced risk for treatment failure (HR 0.4, 95% CI 0.2-0.9; p = 0.022). This finding was confirmed by a group from Israel who conducted a nonblinded, controlled trial in 78 children with CD who were naïve to biologics and responding to adalimumab by week 4 of treatment [16]. Patients were randomized to receive proactive TDM (week 4, 8 and every 8 weeks) or reactive TDM. The treatment aim was an adalimumab trough concentration of > 5–10 mg/L. Proactive TDM markedly outperformed reactive TDM for all endpoints: sustained corticosteroid-free clinical remission at all visits (primary endpoint); sustained CRP < 0.5 mg/dL; sustained fecal calprotectin < 150 µg/g; and the composite endpoint of sustained corticosteroid-free remission and CRP < 0.5 mg/dL and fecal calprotectin < 150 µg/g. Dose optimization was undertaken in 87% of patients in the proactive TDM group versus 60% of patients in the reactive TDM group (p=0.001), highlighting the need to dose optimize the majority of CD patients receiving adalimumab.

Some of the most robust data on the importance of adequate drug concentrations early in the course of IBD treatment were reported in the Personalised

ANti-TNF Therapy in Crohn's diSease (PANTS) study, a prospective uncontrolled cohort study involving 1610 patients from 120 sites in the United Kingdom (UK) [24]. Study objectives were to investigate the clinical and pharmacokinetic factors that predict and mitigate anti-TNF treatment failure in patients with CD. Patients ≥ 6 years of age, receiving a first anti-TNF agent for the primary indication of active luminal CD, and with elevated CRP (> 3 mg/L) and/or calprotectin (> 50 µg/g) levels within 90 days of visit 1, were included. Patients received infliximab (n = 955) or adalimumab (n = 655) and were evaluated for 12 months or until drug withdrawal. At week 14, 23.8% of 1241 assessable patients had a primary nonresponse to treatment. At week 54, nonremission was present in 63.1% of 1211 assessable patients. For both biologics, low drug concentrations at week 14 were independently associated with primary nonresponse (infliximab: OR 0.35, 95% CI 0.20-0.62, p = 0.00038; adalimumab: OR 0.13, 95% CI 0.06-0.28, p < 0.0001) and with week 54 nonremission (infliximab: OR 0.29, 95% CI 0.16-0.52, p < 0.0001; adalimumab: OR 0.03, 95% CI 0.01-0.12, p < 0·0001). Drug concentrations of 7 mg/L for infliximab and 12 mg/L for adalimumab at week 14 predicted better primary and long-term outcomes in these patients.

Is combination therapy better than optimized anti-TNF monotherapy?

Clinical experience has shown that combination therapy with infliximab and an immunomodulator (especially azathioprine) improves outcomes in patients naïve to biologics and immunomodulators. The immunomodulator is thought to increase the concentration of anti-TNF agent and decrease the development of antidrug antibodies. However, combination therapy with azathioprine is associated with a higher incidence of adverse events such as opportunistic infections and serious infections, and with higher rates of lymphoma and hepatosplenic T-cell lymphoma. Optimizing the anti-TNF agent concentration alone may avoid these risks and improve patient safety. In other words, optimized anti-TNF monotherapy through proactive TDM may be an alternative to combination therapy with an immunomodulator.

The Study of Biologic and Immunomodulator Naive Patients in Crohn disease (SONIC) has provided valuable evidence about the role of combination therapy in IBD [25]. In this study, biologic- and immunosuppressive-naïve patients with moderate to severe CD were randomized to receive azathioprine + placebo, infliximab + placebo, or azathioprine + infliximab. At week 26, more patients who received combination therapy were in corticosteroid-free clinical remission than those treated with infliximab or azathioprine alone: 56.8 *vs*. 44.4 *vs.* 30.0%, respectively, suggesting better outcomes with combination therapy. However, a post hoc analysis indicated that the superiority of combination therapy over monotherapy may be due to higher concentrations of anti-TNF agent [26]. Whereas combination therapy contributed more patients to higher infliximab concentration quartiles, those receiving combination therapy with undetectable infliximab drug concentrations (quartile 1) fared poorly in terms of corticosteroid-free clinical remission (25%), while those receiving infliximab monotherapy with infliximab drug concentrations ≥ 5.02 mg/L (quartile 4) fared well (78.6%) (**Figure 3**). Thus, outcomes may not depend on combination therapy versus monotherapy but, rather, on achieving adequate concentrations of infliximab. A retrospective European study which compared optimized infliximab monotherapy and optimized combination therapy (for 6-12 months)

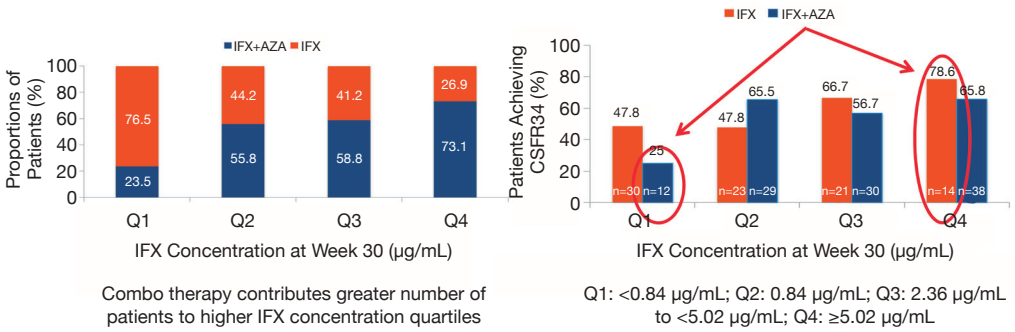

Figure 3. A post-hoc analysis of the Study of Biologic and Immunomodulator Naive Patients in Crohn disease (SONIC) suggested that infliximab drug concentration, not combination therapy, is associated with clinical outcomes. Reproduced and modified with permission from [26]. AZA, azathioprine; IFX, infliximab; Q, quartile.

in 149 patients with IBD (94 with CD) reported no significant differences in outcomes between starting strategies; however, infliximab consumption during the first year was higher in the optimized infliximab monotherapy group [27]. In the same line, Lega and colleagues showed that infliximab durability did not differ between patients on infliximab monotherapy who were dosed based on proactive TDM and patients receiving combination therapy [28].

In patients receiving combination therapy who wish to stop their immunomodulator, factors to consider include treatment cost and the potential for loss of response. In the SONIC study, discontinuing azathioprine had no effect on 1- or 2-year remission rates but was associated with lower infliximab trough concentrations and higher CRP levels [25], which replicated the findings of an earlier prospective RCT comparing withdrawal of immunomodulator in combination with infliximab in patients with controlled disease [29]. A lower infliximab trough concentration and higher CRP level is likely to eventually lead to a loss of response.

Stopping the concomitant immunomodulator has an effect on the infliximab concentration. A randomized open-label study aimed to identify the optimal dose of azathioprine required for efficacy in IBD patients receiving combination therapy [30]. The study enrolled 81 patients with CD previously naïve to infliximab or immunomodulator who had been receiving azathioprine and infliximab for at least 1 year and were in remission for at least 6 months. All patients had an infliximab trough concentration > 2 mg/L, and were receiving stable doses of azathioprine (2 to 2.5 mg/kg/day) and infliximab (5 mg/kg every 8 weeks). Patients were randomized to continue azathioprine at the usual dose, at half the dose, or stop. The primary endpoint was failure at week 52 and/or the need to change medications secondary to adverse events. The mean infliximab concentration decreased from 4.25 mg/L to 2.15 mg/L in the group that stopped azathioprine ($p = 0.02$), but showed no change in groups that continued azathioprine at full dose or half dose. Importantly, the proportion of patients with an unfavorable evolution of infliximab pharmacokinetics, defined as an infliximab trough concentration < 1 mg/L or an undetectable trough concentration with antibody formation, was significantly higher in the group that stopped azathioprine versus the groups that received half or a full dose of azathioprine: 42.3 *vs.* 14.8 *vs.* 14.3%.

Collectively, these studies make a strong case for performing proactive TDM to optimize the anti-TNF drug concentration in patients with IBD. Discontinuing an immunomodulator in patients receiving combination therapy leads to a decrease in the infliximab trough concentration, making patients prone to developing lower drug concentrations and antibodies to infliximab. Maintaining adequate trough anti-TNF concentrations is recommended at all times but, in particular, drug concentrations should be measured proactively before and after discontinuing an immunomodulator.

Proactive TDM: induction

Although most data for proactive TDM concern the postinduction or maintenance phases, the most important time to perform TDM is likely during induction when patients have active disease, require more drug and are at risk for low drug concentrations and early development of antibodies. Several studies have shown that early drug concentrations correlate with short-term and long-term outcomes, highlighting the need for early drug optimization [31]. A European study involving 19 consecutive patients with moderate-severe UC reported an endoscopic response rate of 58% at week 8 of infliximab treatment [32]. Infliximab concentrations at week 6 were higher in responders than in nonresponders (8.1 *vs.* 2.9 mg/L; $p = 0.03$). Importantly, at week 8, antibodies were present in six of eight nonresponders compared with one of 11 responders ($p < 0.01$), and were measurable as early as day 18 of treatment. Lower infliximab concentrations were associated with high CRP levels ($p = 0.001$). Similar to outcomes reported in the PANTS study [24], a prospective observational study in 58 pediatric IBD patients showed that an infliximab concentration > 7 mg/L at week 14 had a 100% positive predictive value for persistent remission [33].

WHAT TO DO WITH THE RESULTS OF TDM?

The BRIDGe group has developed a web-based tool that allows easy access to and display of responses to various permutations of drug concentrations and antidrug antibody titers in specific clinical settings. Physicians are invited to input characteristics (biologic agent, treatment phase, drug concentration, presence of antibodies, patient's clinical status) in order to view the actions and recommendations about how to proceed. The website and embedded tool is accessible on all devices (smart phones, tablets, and computers) and can be found at: www.BRIDGeIBD.com [9].

CHALLENGES AND FUTURE DIRECTIONS

Despite a better understanding of the role of TDM in the IBD setting, several questions remain. What trough concentrations of anti-TNF are optimal to achieve a desired outcome? Although higher concentrations are known to correlate with better outcomes, are there certain thresholds? Is peak concentration or area under the curve (AUC) a better measure of drug concentration during induction? Most data report trough concentrations prior to administration. Small studies are currently investigating whether peak concentration or AUC during induction may better predict outcomes. How often should proactive TDM be performed for optimal outcome? Point-of-care assays permitting rapid changes to dosing regimens are under investigation. As the move continues towards increasingly personalized patient care, other groups are exploring predictive modelling which takes into account not only drug concentration but

factors such as albumin and CRP levels, gender and weight.

CONCLUSIONS

Available evidence for TDM has advanced our approach to managing patients with IBD. The clear associations between trough concentrations and clinical outcomes and between drug concentrations and antibody formation provide the basis for management decisions in patients with IBD. Compared with empiric dose escalation, reactive TDM is more cost effective and better directs therapy. Proactive TDM is also cost effective and improves outcomes. Optimizing anti-TNF monotherapy may be an alternative to combination therapy with an anti-TNF agent and immunomodulator. Although most proactive TDM data relate to maintenance therapy, optimizing anti-TNF drug concentrations should begin early, preferably during induction, since low albumin levels, high CRP levels, and high drug clearance increase patients' risk for low drug concentrations and development of antidrug antibodies.

CONFLICT OF INTEREST DISCLOSURE

KP has received lecture fees from Mitsubishi Tanabe Pharma.

ASC has received consulting fees from AbbVie, Arena, Bacainn, Grifols, Janssen, Pfizer, Prometheus, Samsung, and Takeda; and has received research support from Inform Diagnostics.

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Evidence for the utility of vedolizumab drug level monitoring in patients with inflammatory bowel disease

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INTRODUCTION

Biological agents approved in Europe to treat inflammatory bowel disease (IBD) are the anti-tumor necrosis factor (TNF) agents infliximab, adalimumab, certolizumab pegol and golimumab, and the anti-integrin agent vedolizumab [1]. Vedolizumab selectively targets the integrin α4β7 heterodimer, which is expressed on leukocytes, and blocks its interaction with MAdCAM-1 (mucosal addressin cellular adhesion molecule-1). This prevents the capture and subsequent migration of pathologic gut-specific homing lymphocytes through gut endothelium (**Figure 1**). Vedolizumab does not prevent the migration of α4β7 lymphocytes through the gut endothelium but, rather, specifically targets the CD4 memory subpopulation that is pathogenic in IBD, while sparing other CD4 memory subpopulations and monocytes integral to immunosurveillance and host defense [2].

ROLE OF VEDOLIZUMAB IN THE TREATMENT OF INFLAMMATORY BOWEL DISEASE (IBD)

The efficacy of vedolizumab in Crohn's disease (CD) and ulcerative colitis (UC) was demonstrated in the placebo-controlled GEMINI 1, 2 and 3 trials [3-5], which led to its approval in the US and Europe. The results were later supported by open-label trials [6,7]. More recently, the randomized phase 3 VARSITY trial showed that, in patients with UC, vedolizumab was superior to adalimumab in achieving clinical remission (31.3 *vs.* 22.5%; p = 0.006) and mucosal healing (39.7 *vs.* 27.7%; p = 0.0005) at 52 weeks [8]. Moreover, the open-label VERSIFY study showed that, in CD patients, vedolizumab induced endoscopic remission and response, and complete mucosal healing at 26 and 52 weeks [9]. The 52-week endoscopic response rate (³ 50% reduction from baseline in the Simple Endoscopic Score for Crohn's disease) was 54% in the overall population (n = 56), and was higher in anti-TNFα naïve (n = 32) than in anti-TNFα failed (n = 24) patients at 66% and 38%, respectively. Complete mucosal healing rates in all patients, anti-TNFα naïve patients and anti-TNFα failed patients were 18%, 28% and 4%, respectively.

Real-world studies have demonstrated the effectiveness of vedolizumab in CD, although the proportion of patients achieving mucosal healing or endoscopic remission varied from 6% to 63% due to methodological differences such as endpoint definition and treatment duration (**Figure 2**) [10-17].

The main indications for vedolizumab are summarized in **Table 1**, and are compared with anti-TNF agents and ustekinumab (interleukin IL-12 and IL-23 antagonist) [18]. Vedolizumab is indicated for treatment of mild-to-moderate UC and luminal CD and, owing to its good safety profile, can be used in patients with serious infections and in the elderly. Data are insufficient at present to recommend vedolizumab for severe/fulminant UC, perianal fistulizing CD and postoperative prophylaxis in CD. However, vedolizumab may be effective in patients who have

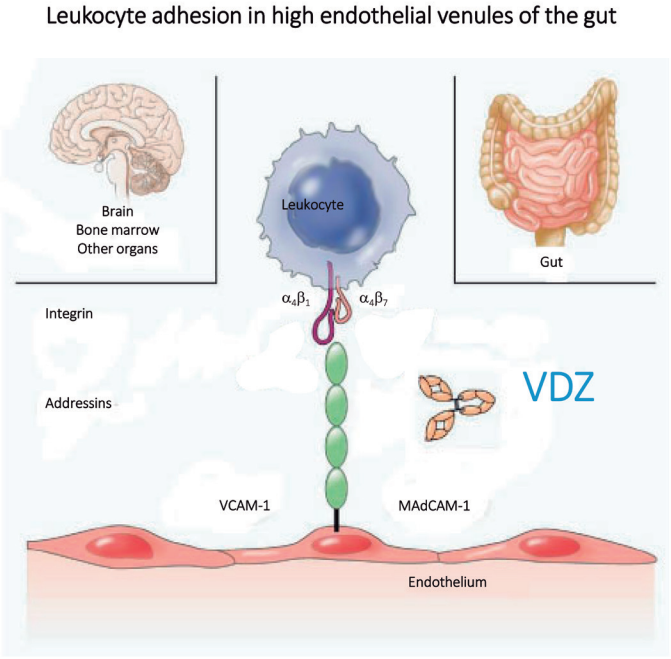

Figure 1. Vedolizumab (VDZ) targeting of α4β7. Adapted from [2].

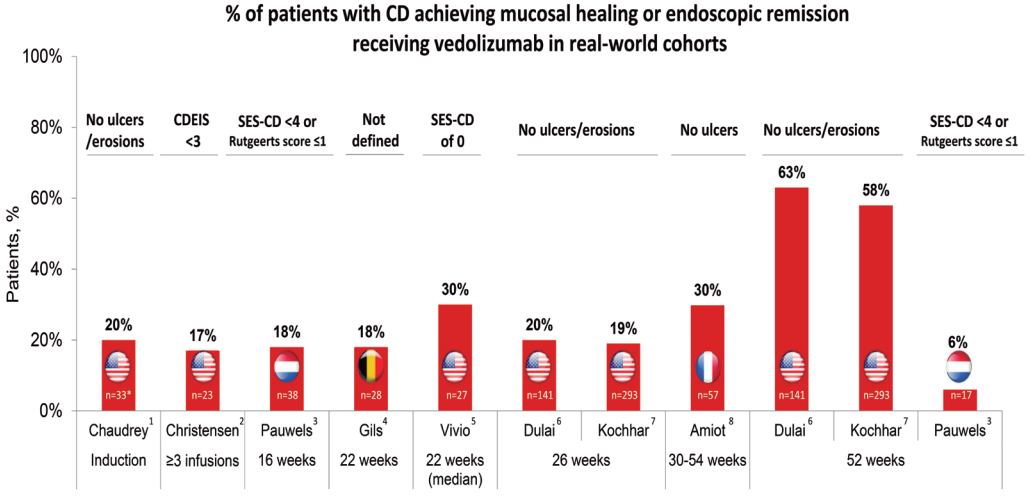

Figure 2. Proportion (%) of patients with CD achieving mucosal healing or endoscopic remission following vedolizumab treatment in real-world cohorts. [1][10], [2][11], [3][12], [4][13], [5][14], [6][15], [7][16], [8][17]. CD, Crohn's disease; CDEIS, Crohn's Disease Endoscopic Index of Severity; IBD, inflammatory bowel disease; SES-CD, simple endoscopic score for Crohn's disease. *33 patients with IBD underwent mucosal healing assessment [10].

Table 1. Positioning of available biologicals in Crohn's disease and ulcerative colitis. Adapted from [11].

Disease/Setting	Anti-TNF	Vedolizumab	Ustekinumab
Ulcerative colitis			
Mild to moderate UC	✔	✔	✔
Patient profile	• Extraintestinal manifestations • ≥ 2 immune-mediated inflammatory diseases • Children	• Serious infection • Elderly	• Extraintestinal manifestations • ≥ 2 immune-mediated inflammatory diseases • Anti-TNF-induced psoriaform lesions • Children*
Severe/ fulminant UC	Infliximab		
Crohn's disease			
Luminal CD	✔	✔	✔
Patient profile	• Extraintestinal manifestations • ≥ 2 immune-mediated inflammatory diseases • Children	• Serious infection • Elderly	• Extraintestinal manifestations • ≥ 2 immune-mediated inflammatory diseases • Anti-TNF-induced psoriaform lesions • Children*
Perianal fistulizing CD	Infliximab		
Postoperative prophylaxis†	✔		

CD, Crohn's disease; TNF, tumour necrosis factor; UC, ulcerative colitis. *Available data are for ustekinumab-treated case series only; †Available data are for anti-TNF agents only.

failed treatment with an anti-TNF, azathioprine or mesalazine.

RATIONALE FOR THERAPEUTIC DRUG MONITORING (TDM) IN THE MANAGEMENT OF IBD

Despite many advances over the past few decades in the medical management of IBD, a substantial proportion of patients treated with biologicals will experience a primary non-response or secondary loss of response. Therapeutic drug monitoring (TDM) has emerged as a promising strategy to maximize treatment response in IBD based on three key principles [19]:

1) An exposure-response relationship exists whereby higher drug concentrations are

associated with a greater magnitude of therapeutic efficacy

2) Nonresponsiveness can be mediated by pharmacokinetic failure, defined as inadequate drug exposure secondary to immune (i.e. antidrug antibody formation) or nonimmune causes (e.g. body mass index, sex, disease phenotype, concomitant immunosuppression, degree of systemic inflammation) which lead to accelerated drug clearance
3) Nonresponsiveness can be mediated by mechanistic failure due to alternative pathways of inflammation in disease pathogenesis, which is the main driver for changing therapies.

Reactive TDM relates to patients with treatment failure after previous successful therapy. It is used to guide decisions based on pharmacokinetics and pharmacodynamics which may involve intensifying the dose, changing to an agent in the same drug class, or switching to an agent in a different drug class. Proactive TDM is performed in patients in remission with the aim of adjusting treatment intensity according to individual pharmacokinetic and pharmacodynamic parameters to minimize the risk of treatment failure.

Use of reactive TDM in IBD was conditionally recommended in the 2017 American Gastroenterological Association (AGA) guidelines as a means of guiding treatment changes in adult patients with active IBD receiving anti-TNF agents [20], and was accompanied by a clinical decision support tool [21]. However, the AGA made no recommendations regarding use of routine proactive TDM in adult patients with quiescent IBD receiving anti-TNF agents [20].

The degree of acceptance and uptake of TDM in clinical practice may reflect a lack of clarity on certain issues. First, it is unclear whether TDM performed during induction or proactive TDM for patients in symptomatic remission improves long-term outcomes or the cost-effectiveness of biological agents. Second, the role of TDM for small molecule therapies and biological agents with a non-anti-TNF driven mechanism of action is unclear. Third, thresholds of therapeutic drug concentrations used to inform dose escalation or temporary drug suspension have not been fully validated. At present, there is no agreement among guideline groups about TDM thresholds for anti-TNF agents (**Table 2**) [20,22].

The Australian Inflammatory Bowel Disease Consensus Working Group has developed an algorithm for reactive TDM in IBD patients with a secondary loss of response to anti-TNF agents [19]. Based on drug concentration (therapeutic or subtherapeutic) and the presence or absence of antibodies, the algorithm guides management decisions which include escalating the dose, switching agent in or out of class, and adding an immunosuppressant (**Figure 3**). Conversely, the recently published European Crohn's and Colitis Organisation (ECCO) guidelines state that evidence is insufficient to recommend for or against the use of proactive or reactive TDM to improve clinical outcomes above those achieved with routine care in CD patients [23]. However, the guidelines acknowledge data suggesting that cost savings generated by reactive TDM with biosimilars may justify the approach.

Following publication of the 2017 AGA guidelines, a group of IBD experts from the US commented on the assertion that proactive TDM cannot be recommended due to 'limited data' and potential 'concern for harm' [24]. The authors referenced several studies which support the use of proactive TDM. In particular, the

Table 2. Therapeutic drug concentrations thresholds for anti-tumor necrosis factor biologicals.

Agent	2017 American Gastroenterological Association guideline suggestions [20]	2017 Australian Inflammatory Bowel Disease Consensus Working Group suggestions [22]
Infliximab	≥ 5 µg/mL	3-8 µg/mL
Adalimumab	≥ 7.5 µg/mL	5-12 µg/mL
Certolizumab	≥ 20 µg/mL	Not stated
Golimumab	Unknown	Not stated

authors underlined that, despite the TAXIT (Trough Concentration Adapted Infliximab Treatment) study having failed to reach its primary endpoint (clinical and biochemical remission at 1 year) due to methodological issues in study design including dose optimization in all patients prior to randomization, several secondary endpoints favored trough concentration-based dosing (i.e. proactive TDM) over clinically-based dosing according to symptoms and C-reactive protein (CRP) levels [25]. A subsequent retrospective analysis of long-term TAXIT outcomes showed that concentration-based dosing was associated with less drug discontinuation, immunogenicity and IBD-related surgery than clinically-based dosing [26]. The findings aligned with a previously published retrospective single-center study which reported

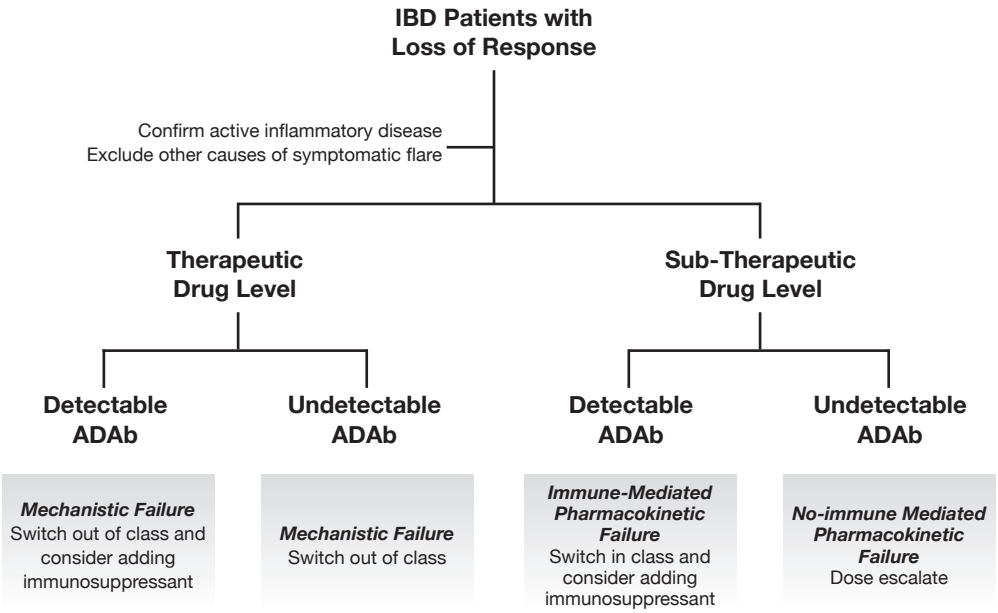

Figure 3. Algorithm for use of reactive therapeutic drug monitoring (TDM) in IBD patients with secondary loss of response to TNF antagonists [19]. ADAb, anti-drug antibodies.

greater drug persistence among patients receiving proactive TDM versus standard of care [27]. More recently, a retrospective multicenter study reported greater infliximab durability, less IBD-related surgery or hospitalization, lower risk of immunogenicity, and fewer serious infusion reactions with proactive versus reactive TDM [28]. In addition to routine monitoring of patients in remission to prevent treatment failure, other potential applications of proactive TDM are to support immunomodulator withdrawal in patients receiving anti-TNF combination therapy, stopping the anti-TNF agent in patients in deep remission, and restarting anti-TNF therapy after a drug holiday [24].

RATIONALE FOR TDM IN MANAGING IBD PATIENTS TREATED WITH VEDOLIZUMAB

Interindividual variability in vedolizumab drug clearance has been demonstrated, with differences in body weight, serum albumin levels, and inflammatory burden having been shown to affect drug pharmacokinetics, similar to that observed with infliximab and adalimumab. The presence of persistent antibodies also increases vedolizumab clearance although, interestingly, immunogenicity to vedolizumab appears attenuated compared to that with infliximab or adalimumab. In the GEMINI trials, approximately 12% of patients randomized to placebo in the maintenance arm developed anti-vedolizumab antibodies after exposure in induction, and 10% of patients in the active treatment arm developed antibodies at week 66 (14 weeks after the last dose of vedolizumab) [19].

Vedolizumab exposure levels and clinical outcomes

Analysis of data from the GEMINI-1 RCT of vedolizumab in patients with UC found that vedolizumab concentrations at week 6 were consistently associated with clinical remission at weeks 14 and 52 [29]. A similar exposure-response relationship was demonstrated in CD patients enrolled in GEMINI 2 although the association was less robust: 1 year clinical remission rates in the highest (> 33.7 µg/mL) and lowest (≤ 16 µg/mL) vedolizumab drug concentration quartiles were 22% and 6%, respectively [30]. During maintenance treatment, a dose-response relationship was evident in both UC and CD patients receiving 8-weekly dosing, but was less evident in patients receiving 4-weekly dosing.

A retrospective study of IBD patients reported a correlation between vedolizumab exposure and response [31]. Vedolizumab trough concentrations of > 30.0 mg/mL at week 2, > 24.0 mg/mL at week 6, and > 14.0 mg/mL during maintenance therapy were associated with a significantly ($p < 0.05$) higher probability of achieving effectiveness endpoints in patients with UC or CD. Higher body mass and biomarkers of more severe disease (CRP, albumin and/or hemoglobin) at the start of treatment were associated with lower trough concentrations of vedolizumab over a 30-week treatment period and, in turn, with a significantly ($p < 0.05$) lower probability of achieving mucosal healing.

A cross-sectional study of 258 patients with IBD demonstrated an association between vedolizumab trough concentrations during maintenance therapy and corticosteroid-free remission [32]. Patients in clinical and biochemical remission had significantly higher vedolizumab trough concentrations than those with active disease (12.7 µg/mL *vs.* 10.1 µg/mL, $p = 0.002$). Vedolizumab concentrations during maintenance therapy were also higher in patients with endoscopic (14.2 µg/mL *vs.* 8.5 µg/mL, $p = 0.003$) or deep (14.8 µg/mL *vs.* 10.1 µg/mL, $p = 0.01$) remission relative to their

counterparts with active disease. After controlling for potential confounders, patients with vedolizumab trough concentrations > 11.5 µg/mL during maintenance therapy were nearly 2.4 times more likely to be in corticosteroid-free clinical and biochemical remission. An antibody incidence of 1.6% suggested low immunogenicity with vedolizumab.

A systematic review and meta-analysis of the association between vedolizumab trough concentrations and clinical outcomes in IBD found that patients with UC achieving clinical or endoscopic remission had significantly higher vedolizumab trough concentrations during maintenance therapy [33]. In patients with CD, vedolizumab trough concentrations during maintenance therapy were numerically but not significantly higher in patients who achieved clinical or endoscopic remission. Based on the results of the meta-analysis, the authors proposed a treatment algorithm for applying TDM to vedolizumab (**Figure 4**). Proposed trough concentrations are < 20 mg/mL and < 12 mg/mL for induction and maintenance therapy, respectively, although may vary depending on the targeted treatment endpoint: clinical response, and clinical, endoscopic or histologic remission.

A recent retrospective analysis investigating endoscopic outcomes in anti-TNF naïve and anti-TNF exposed patients with IBD (n = 336) receiving vedolizumab showed a clear relationship between vedolizumab exposure and endoscopic remission [34]. The probability of endoscopic remission at weeks 6, 12 and during maintenance increased with higher vedolizumab trough concentrations, although not all patients benefited from treatment intensification suggesting the need for additional biomarkers to predict treatment response. A multicenter prospective observational study reported that a vedolizumab trough level > 18 µg/mL at week 6 was the only independent variable associated with mucosal healing within the first year of treatment (odds ratio 15.7, 95% confidence interval

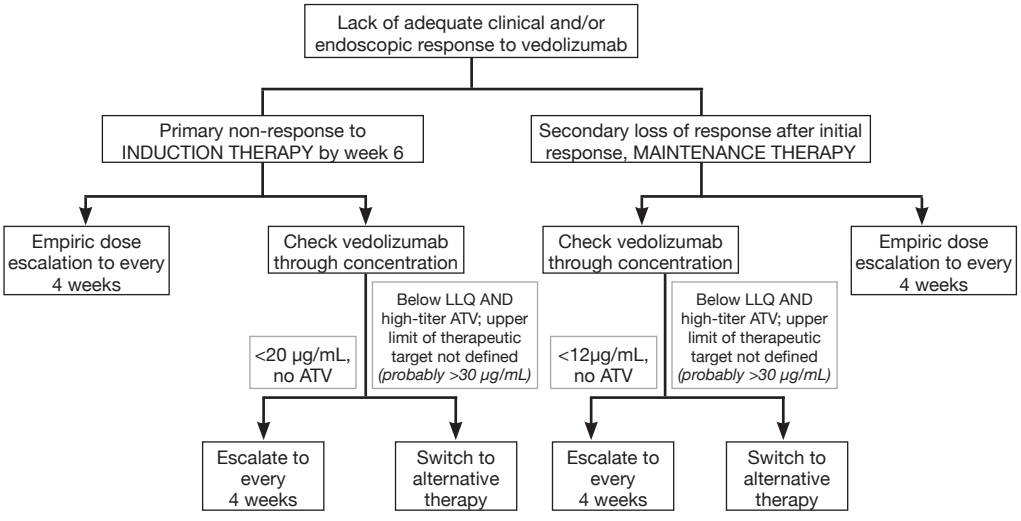

Figure 4. Proposed algorithm for applying therapeutic drug monitoring (TDM) to vedolizumab [33]. ATV, antibodies to vedolizumab; LLQ, lower limit of quantification.

2.4-173.0, p = 0.01), supporting early TDM as a means of detecting patients who may benefit from dose intensification [35]. Histological remission is a relatively recent treatment goal in IBD. A small single-center retrospective study found that higher vedolizumab trough levels during maintenance therapy were associated with histological remission in UC (p = 0.02). A vedolizumab trough level of 25 μg/mL predicted histological healing with an accuracy of 74% [36].

CONCLUSION

There is a growing body of evidence from recent RCTs and real-world studies for an exposure-efficacy relationship and low immunogenicity with vedolizumab. In parallel, there is increasing knowledge about factors that influence vedolizumab drug clearance and serum levels. At present, however, heterogeneous data about target vedolizumab trough levels continue to be a limitation toward establishing TDM-based management of IBD patients treated with vedolizumab. Further studies, particularly RCTs, are required to explore the effect of dose optimization on objective disease markers and changes in vedolizumab drug concentrations on clinical outcomes in patients with IBD.

Conflict of interest disclosure

ES has received lecture or consultancy fees from Abbvie, Alfasigma, Amgen, Aurora Pharma, Bristol-Myers Squibb, EG Stada Group, Fresenius Kabi, Grifols, Innovamedica, Janssen, Johnson & Johnson, Malesci, Medtronic, Merck & Co, Novartis, Reckitt Benckiser, Sandoz, Shire, SILA, Sofar, Takeda, and Unifarco.

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Therapeutic drug monitoring of biosimilars: validation studies

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INTRODUCTION

Biologicals are large, complex, highly specialized molecules produced in human cells using advanced biotechnological processes. Due to their inherent variability, it is not possible to produce exact copies of biologicals during manufacturing runs, in contrast to small molecule chemical medicines such as aspirin which are easily copied. Biologicals have been in use for more than 200 years, beginning with the smallpox vaccine in 1796. Insulin was first extracted from pig in the 1920s to treat diabetes in humans. Over time, biologicals have diversified into sophisticated medicines used to improve health outcomes in many diseases. Examples include hormones, blood products, cytokines, growth factors, vaccines, genes, fusion proteins and monoclonal antibodies.

Biological brands have patent protection for a limited period. Upon patent expiry, other manufacturers can develop a copy or 'biosimilar' of the innovator biological. Several biosimilars may be developed for the same reference product. As a biosimilar is not wholly identical to the original biological, the manufacturer of the biosimilar must demonstrate similarity to the reference product in terms of quality, activity, safety and efficacy.

Main differences between an innovator biological and its biosimilar include the time and cost of development which are reflected in the higher cost of the reference product (**Box 1**). Development costs of innovator biologicals include regulatory requirements to conduct clinical studies in each indication to evaluate quality, safety and efficacy. Conversely, clinical data generated with innovator biologicals are extrapolated to biosimilars prior to regulatory approval, hence the lower cost.

Box 1. Main differences between innovator biologicals and biosimilars.

Innovator biological	Biosimilar
Novel	Bioequivalent
15 years to develop	8-10 years to develop
$1–2 billion cost	$0.1 billion cost
Clinical studies for each indication	Clinical data extrapolated
Patentable	Non-patentable
Reference price	Reduced price

Since first approval in 2006 of a biosimilar in Europe, more than 50 other biosimilars have been approved. In the United States (US), the first biosimilar was approved in 2015, followed by more than 20 others. Increasingly complex biosimilar molecules have been developed including monoclonal antibodies (MAbs). Biosimilar MAbs approved to treat rheumatic diseases and inflammatory bowel disease (IBD), together with their reference biologicals, are summarized in **Table 1** [1].

Table 1. Common reference monoclonal antibody biologicals and their approved biosimilars in Europe and United States. Data from [1].

Product	Europe		United States	
	Reference	Biosimilars	Reference	Biosimilars
Adalimumab	Humira	Amgevita Halimatoz/Hefiya/ Hyrimoz Hulio Idacio/Kromeya Imraldi	Humira	Amjevita (adalimumab-atto) Cyltezo (adalimumab-adbm) Hyrimoz (adalimumab-adaz)
Etanercept	Enbrel	Benepali Erelzi	Enbrel	Erelzi (etanercept-szzs) Eticovo (etanercept-ykro)
Infliximab	Remicade	Flixabi Inflextra/Remsima Zessly	Remicade	Inflectra (infliximab-dyyb) Renflexis (infliximab-abda) Ixifi (infliximab-qbtx)
Rituximab	Mabthera	Blitzima/Ritemvia/ Rituzena/ Truxima Rixathon/Riximyo	Rituxan	Truxima (rituximab-abbs)

Treatment with a biological can begin with either an innovator or biosimilar. A common concern with use of biosimilars is their interchangeability, which refers to substituting a reference biological with a biosimilar expected to have the same clinical effect (or vice versa), or exchanging one biosimilar with another. A second important issue is cross immunogenicity, specifically whether antidrug antibodies (ADA) generated against the reference biological will also react with the biosimilar. A third issue relates to therapeutic drug monitoring (TDM) used to optimize treatment and clinical outcomes. Can TDM still be applied when a patient is switched from a reference biological to a biosimilar? These issues are examined in more detail.

INTERCHANGEABILITY OF REFERENCE ANTI-TNF AGENTS AND BIOSIMILARS

A recent systematic review of 178 studies, which included randomized controlled trials (RCTs) and real-world observational studies, reported no major efficacy, safety or immunogenicity issues associated with a single switch from a reference product to a biosimilar. Most studies (n = 132) involved switching to a biosimilar from an anti-tumor necrosis factor alpha (anti-TNFα) reference biological: infliximab (n = 100), etanercept (n = 25), or adalimumab (n = 7) [1].

Equivalent efficacy of a biosimilar with innovator infliximab (Remicade®) was first shown in

pivotal RCTs of the biosimilar CT-P13 (Inflectra®, Remsima®) in patients with rheumatoid arthritis (PLANETRA study) [2] or ankylosing spondylitis (PLANETAS study) [3] prior to regulatory approval. The pharmacokinetic and safety profiles, and prevalence of ADA to infliximab and CT-P13, were also equivalent [2,3].

Concerns about extrapolating data generated with reference biologicals to biosimilars have prompted clinical studies of biosimilars in IBD. In the large prospective observational PROSIT-BIO study, three groups of patients were compared: patients naïve to anti-TNFα therapy (n = 459, Group A), patients previously treated with biologicals (n = 196, Group B), and patients switched from reference infliximab to CT-P13 (n = 155, Group C) [4]. The results showed no differences in clinical response or treatment persistence between groups. The effectiveness and safety profile of CT-P13 was comparable to that reported in the existing literature for reference infliximab. Estimated cost savings with biosimilar use were about €4 million per year [5]. A Norwegian RCT (NOR-SWITCH) of patients with Crohn's disease, ulcerative colitis, ankylosing spondylitis or rheumatic diseases compared switching from originator infliximab to CT-P13 in patients on stable treatment with originator infliximab [6]. The absence of significant differences in disease control between responders in each group indicated that switching to a biosimilar for non-medical reasons does not compromise the effectiveness or safety of biological treatment in immune-mediated inflammatory disorders. Collectively, these results support implementing a biosimilar to reduce treatment costs.

Similar studies were conducted for another infliximab biosimilar, SB2 (Flixabi®, Renflexis®), in patients with moderate to severe rheumatoid arthritis. A RCT comparing reference infliximab with SB2 showed comparable disease activity assessed by American College of Rheumatology 20, 50 and 70 responses, 28-joint disease activity score and European League against Rheumatism (EULAR) response at week 30. The incidence of ADA, and the safety and pharmacokinetic profiles of reference infliximab and SB2, were similar between groups [7]. Efficacy, safety, and immunogenicity and pharmacokinetic profiles were comparable up to week 78 in patients who continued SB2 or reference infliximab therapy, and in patients who switched from reference infliximab to SB2 at week 54 [8]. In a real-life setting, clinical efficacy was maintained in IBD patients who switched from reference infliximab to SB2. Infliximab trough levels were comparable before and after switching, and switching to SB2 was not associated with increased immunogenicity. SB2 was well tolerated and its use generated substantial cost savings [9].

The efficacy, safety and immunogenicity of reference adalimumab (Humira®) is comparable to ABP501, GP2017 and SB5 biosimilars in rheumatic diseases. Equivalence between reference adalimumab and biosimilars has been shown in RCTs involving biological-naïve patients and in patients switching from reference adalimumab to a biosimilar [10-16].

CROSS-IMMUNOGENICITY OF REFERENCE BIOLOGICALS AND BIOSIMILARS

Demonstrating equivalent immunogenicity between innovator biologicals and biosimilars is of utmost clinical importance to maintain use of the agent. To detect antibodies to infliximab (ATI), Grifols has developed specific enzyme linked immunosorbent assays (ELISAs) for reference infliximab (Promonitor ANTI-IFX CE-marked kit), CT-P13 and SB2 (**Figure 1**). ATI were

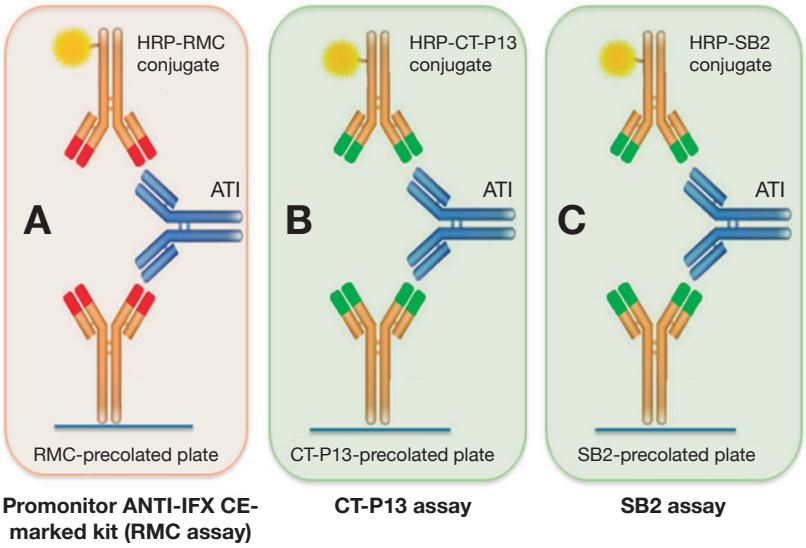

Figure 1. Three enzyme-linked immunosorbent assays for detecting antidrug antibodies reacting with reference infliximab, CT-P13 and SB2 [17,18]. ANTI-IFX, anti-infliximab; ATI, antibodies to infliximab; CE, Conformité Européene; HRP, horseradish peroxidase; RMC, Remicade®.

compared in IBD patients receiving reference infliximab or CT-P13 therapy and in infliximab/CT-P13 switchers. ADA raised against reference infliximab fully cross-reacted with those formed against CT-P13 and SB2. Likewise, antibodies raised against CT-P13 fully cross-reacted in ELISAs for reference infliximab and SB2 biosimilars. The magnitude of ADA levels in the three ELISAs were comparable [17,18]. The results suggested that immunodominant epitopes involved in stimulating an immune response to reference infliximab are responsible for the same degree of reactivity when patients are exposed to CT-P13 or SB2. The studies also showed that biosimilars cross-react with each other. It can be concluded, therefore, that CT-P13 and SB2 are interchangeable and that switching between biosimilars and reference drug will not lead to differences in ATI production.

Other studies have demonstrated cross-immunogenicity of antibodies to reference infliximab against CT-P13 in patients with IBD, ankylosing spondylitis (PLANETAS study) or rheumatoid arthritis (PLANETRA study) [19,20]. Application of reference infliximab- and CT-P13-tagged immunoassays showed cross-reactivity of ADA and neutralizing antibodies against CT-P13 and reference product [20].

Although data are limited regarding cross-immunogenicity of adalimumab antibodies with biosimilars, a poster presented at EULAR in 2019 showed that antibodies formed against reference adalimumab cross-reacted with the biosimilar ABP 501, and that antibodies to ABP 501 cross-reacted with reference adalimumab [21].

Collectively, the results suggest no immunogenicity concerns regarding use of commercial kits for comparative studies of reference products and biosimilars. Moreover, ADA positive patients treated with the reference agent should not be considered for

switching to a biosimilar treatment, since pre-existing ADA will interact with the new drug, enhancing clearance and potentially leading to loss of response.

TDM TESTS: UTILITY AND VALIDATION

TDM is an important clinical tool for optimizing therapy and guiding personalized medicine. As TDM relies on accurate determination of serum drug and antidrug concentrations, it is important to demonstrate that commercialized kits can be applied for TDM of biosimilars. In 2015, Promonitor was the first TDM test validated for CT-P13 concentrations and anti-CT-P13 antibody levels [17]. Since then, numerous peer reviewed publications have reported use of Promonitor and other commercial tests in gastroenterology and rheumatology.

Recently, a comparison of four widely used commercial immunoassays (Immunodiagnostik-ALPCO, Ridascreen, Lisa-Tracker and Promonitor) for infliximab detection showed a high correlation between tests for serum samples spiked with SB2, CT-P13 or reference infliximab [22], indicating that TDM for biosimilar infliximab can be performed adequately using kits currently in use or available in clinical laboratories.

Each kit for use in TDM of biosimilars must be validated. For example, the Promonitor-IFX assay has been shown to measure reference infliximab or any approved biosimilar (CT-P13, SB2, GP1111) with similar sensitivity, precision and accuracy. Bias is acceptable for comparisons of reference infliximab with each biosimilar, being less than the analytical variability of these assays (**Table 2**).

A similar validation was performed using the Promonitor-ADL assay for adalimumab biosimilars. Promonitor-ADL measured reference adalimumab or approved biosimilars (ABP 501, SB5, GP2017) with the same sensitivity, precision and accuracy. Bias was very low for comparisons between reference adalimumab and each biosimilar (**Table 3**).

Promonitor ELISA kits have been validated with any approved biosimilar of infliximab, adalimumab, etanercept and rituximab following standard Clinical and Laboratory Standards Institute guidelines (**Table 4**).

Point of care tests (POCT) have been developed as they are quicker to use than conventional immunoassays and have been applied for TDM. The Promonitor Quick ANTI-IFX POCT was validated in whole blood and serum from patients treated with reference infliximab and the biosimilars CT-P13 and SB2. The POCT detected ADA raised against these three molecules and showed strong agreement with the gold standard ELISA [23,24].

COST SAVINGS WITH BIOSIMILARS

As biosimilars can be offered at lower prices than reference products, their use may generate cost savings and potentially increase patient access to biological treatment. For instance, at the University Hospital Southampton, UK, savings from switching from reference infliximab to biosimilar CT-P13 were estimated to be approximately £2.1 million over a 3-year period [25]. A reduction in drug costs after switching from originator biological to biosimilar has indeed been reported in numerous studies according to a large systematic review (n = 54 studies), although the authors concluded that assessing associated healthcare service needs (e.g. medical and administrative) in addition to drug costs is necessary to quantify the full economic impact of switching [26].

Table 2. Therapeutic drug monitoring validation of the Promonitor test between reference infliximab (Remicade, RMC) and CT-P13, SB2 and GP1111 biosimilars. Validation was performed following Clinical & Laboratory Standards Institute (CSLI) guidelines: EP17-42 (lower limit of quantification) and EP10-A3 (imprecision and bias).

Bias between Remicade and CT-P13					
Drugs compared	**Infliximab nominal concentrations (µg/mL)**				
	1	**7**	**14**		
Bias RMC-Inflectra, µg/mL (% difference)	+0.12 (9.2%)	+0.62 (6.5%)	+0.94 (5.6%)		
Bias RMC-Remsima, µg/mL (% difference)	+0.03 (2.3%)	–0.06 (0.6%)	+0.82 (4.8%)		
Bias between Remicade and SB2					
Drugs compared	**Infliximab nominal concentrations (µg/mL)**				
	0.5	**1**	**3**	**7**	**12**
Bias RMC-SB2, µg/mL (% difference)	+0.10 (18.2%)	+0.004 (0.3%)	–0.51 (13.7%)	–1.37 (15.3%)	–0.55 (4.2%)
Bias between Remicade and GP1111					
Drugs compared	**Infliximab nominal concentrations (µg/mL)**				
	0.5	**1**	**3**	**7**	**12**
Bias RMC-GP1111, µg/mL (% difference)	+0.03 (6.5%)	+0.01 (1.1%)	+0.02 (0.9%)	+0.40 (6.1%)	–0.78 (7.1%)

Brand names are Inflectra/Remsima for CT-P13; Flixabi/Renflexis for SB2; and Zessly for GP 1111.

CONCLUSIONS

Biosimilars are structurally similar to their reference product and have been shown to have similar efficacy, safety, immunogenicity, and interchangeability. As biosimilars are less expensive to produce than reference products, associated cost savings may enable more patients to access treatment with biologicals leading to better health outcomes, although more comprehensive pharmacoeconomic data are required to reach definitive conclusions. Biosimilars are becoming increasingly available and current evidence suggests that clinicians can be confident in their use in routine practice.

CONFLICT OF INTEREST DISCLOSURE

B R-A is a fulltime employee of Progenika Biopharma – Grifols.

Table 3. Therapeutic drug monitoring validation of the Promonitor test between reference adalimumab (Humira) and ABP 501, SB5 and GP2017 biosimilars. Validation was performed following Clinical & Laboratory Standards Institute (CSLI) guidelines: EP17-42 (lower limit of quantification) and EP10-A3 (imprecision and bias).

Bias between Humira and ABP 501					
Drugs compared	**Adalimumab nominal concentrations (µg/mL)**				
	0.8	**1.5**	**5**	**8**	**10**
Humira-ABP 501, µg/mL (% difference)	−0.0 (0.4%)	−0.12 (6.9%)	−0.33 (6.1%)	-0.35 (4.0%)	-0.9 (6.7%)
Bias between Humira and SB5					
Drugs compared	**Adalimumab nominal concentrations (µg/mL)**				
	0.8	**1.5**	**5**	**8**	**10**
Humira-SB5, µg/mL (% difference)	0.02 (2.7%)	0.02 (0.9%)	0.55 (10.0%)	0.86 (10.0%)	−0.06 (0.5%)
Bias between Humira and GP2017					
Drugs compared	**Adalimumab nominal concentrations (µg/mL)**				
	0.8	**1.5**	**5**	**8**	**10**
Humira-GP2017, µg/mL (% difference)	0.04 (4.9%)	−0.03 (1.7%)	0.19 (3.5%)	0.75 (8.6%)	−0.93 (8.5%)

Brand names are Amgevita/Amjevita for ABP 501; Imraldi/Hadlima for SB5; and Hyrimoz for GP2017.

Table 4. Therapeutic drug monitoring validation of Promonitor ELISA kits: validation of reference biologicals with approved biosimilars.

Biosimilar (brand, molecule)	**Promonitor product**					
	IFX	**ANTI-IFX**	**ADL**	**ANTI-ADL**	**ETN**	**RTX**
Inflectra®/Remsima® CT-P13, infliximab	✔	✔				
Flixabi®/Renflexis® SB2, infliximab	✔	✔				
Zessly® GP 1111, infliximab	✔					
Amgevita® ABP 501, adalimumab			✔	✔		
Imraldi® SB5, adalimumab			✔			
Hyrimoz® GP 2017, adalimumab			✔			
Benepali® SB4, etanercept					✔	
Erelzi®, etanercept					✔	
Truxima® CT-P10, rituximab						✔

IFX, infliximab; ADL, adalimumab; ETN, etanercept; RTX, rituximab.

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