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Therapeutic Drug Monitoring to Guide Clinical Decision Making in Inflammatory Bowel Disease Patients with Loss of Response to Anti-TNF: A Delphi Technique-Based Consensus

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Abstract: **BACKGROUND** Loss of response is frequently encountered in patients with inflammatory bowel disease (IBD) treated with antitumor necrosis factor (TNF) agents. Therapeutic drug monitoring (TDM) and antidrug antibody measurement are increasingly used in this setting. **METHODS** To establish a consensus on the use of TDM in the context of loss of response to anti-TNFs, we performed a vote using a Delphi-style process followed by an expert panel discussion among 8 IBD specialists practicing in Switzerland, Europe. Statements were rated on an even Likert-scale ranging from 1 (strong disagreement) to 4 (strong agreement), based on expert opinion and the available literature. **RESULTS** The experts agreed on the following statements: (i) loss of response is associated with inadequate drug levels in both Crohn's disease and ulcerative colitis; (ii) best timepoint for measuring drug levels is prior to the next application (= trough levels) with different thresholds for anti-TNF agents (infliximab 5 g/mL, adalimumab 8 g/mL, certolizumab pegol 10 g/mL); (iii) antidrug antibodies are predictive for loss of response; and (iv) antidrug-antibody titers and drug trough levels are key determinants in the treatment algorithm. Data about non-anti-TNF biologics were considered too limited to propose recommendations. **CONCLUSION** A Delphi-style consensus among 8 IBD experts shows that TDM and measurement of antidrug-antibody titers are useful in the context of loss of response to anti-TNF. Optimal cutoff levels depend on the type of anti-TNF. These values are critical in the decision making process. More studies are needed to address the value of such measurements for non-anti-TNF biologics.

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Therapeutic Drug Monitoring to Guide Clinical Decision Making in Inflammatory Bowel Disease Patients with Loss of Response to Anti-TNF: A Delphi Technique-Based Consensus

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Keywords

Therapeutic drug monitoring · Antidrug antibodies · Inflammatory bowel disease · Loss of response · Consensus · Antitumor necrosis factor

Abstract

Background: Loss of response is frequently encountered in patients with inflammatory bowel disease (IBD) treated with antitumor necrosis factor (TNF) agents. Therapeutic drug monitoring (TDM) and antidrug antibody measurement are increasingly used in this setting. **Methods:** To establish a consensus on the use of TDM in the context of loss of response to anti-TNFs, we performed a vote using a Delphi-style process followed by an expert panel discussion among 8 IBD specialists practicing in Switzerland, Europe. State-

ments were rated on an even Likert-scale ranging from 1 (strong disagreement) to 4 (strong agreement), based on expert opinion and the available literature. **Results:** The experts agreed on the following statements: (i) loss of response is associated with inadequate drug levels in both Crohn's disease and ulcerative colitis; (ii) best timepoint for measuring drug levels is prior to the next application (= trough levels) with different thresholds for anti-TNF agents (infliximab 5 µg/mL, adalimumab 8 µg/mL, certolizumab pegol 10 µg/mL); (iii) antidrug antibodies are predictive for loss of response; and (iv) antidrug-antibody titers and drug trough levels are key determinants in the treatment algorithm. Data about non-anti-TNF biologics were considered too limited to

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propose recommendations. **Conclusion:** A Delphi-style consensus among 8 IBD experts shows that TDM and measurement of antidrug-antibody titers are useful in the context of loss of response to anti-TNF. Optimal cutoff levels depend on the type of anti-TNF. These values are critical in the decision making process. More studies are needed to address the value of such measurements for non-anti-TNF biologics.

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Introduction

Inflammatory bowel disease (IBD) with its 2 subtypes Crohn's disease (CD) and ulcerative colitis (UC) is a chronic inflammatory disorder of the gastrointestinal tract [1]. Given a complex and yet only partially understood etiopathogenesis, IBD is considered an incurable, but treatable disease [2, 3]. The introduction of antitumor necrosis factor (TNF) with considerable higher efficacy than conventional immunomodulatory drugs has dramatically changed the therapeutic management of IBD. However, loss of response is encountered in up to 46% of IBD patients treated with anti-TNF [4, 5]. Loss of response implies a previous initial response to treatment, which is lost over time, and has to be differentiated from primary nonresponse, where such response is never achieved [4]. To undermine this difference, loss of response is sometimes referred to as secondary nonresponse. Based on the mechanisms involved, loss of response can be either classified as immune-mediated (formation of antibodies against anti-TNF) or nonimmune mediated (accelerated drug clearance due to burden of disease, weight or male gender, nonadherence, fibrostenotic disease phenotype) [4]. Therapeutic drug monitoring (TDM) and antidrug antibody measurement are increasingly used in the setting of a loss of response and data supporting their application in daily practice are emerging [6–8]. However – despite acknowledging the usefulness of TDM – current guidelines of the European Crohn's and Colitis Organisation (ECCO) lack of a clear recommendation regarding optimal time-point, adequate thresholds, and TDM's exact role in the long-term therapeutic algorithm [9, 10].

Therefore, we performed an expert panel discussion to reach a consensus statement based on the available literature about TDM. The goal of this discussion was to elaborate an algorithm for TDM in the context of biological therapy in IBD and a loss of response to such treatment. During an expert meeting, the relevance of thresholds and cutoff values for adequate drug concentrations and

antidrug-antibody titers were discussed, and a therapeutic decision pathway was elaborated. The discussion focused on TDM for loss of response only, so therapy monitoring per se was not within the scope of the panel discussion. With this consensus study, we sought to answer the following questions: (1) when and why to measure and how to interpret drug levels? (2) when and why to measure and how to interpret antidrug antibody titers? and finally, and (3) what is the best treatment algorithm in case of a loss of response to anti-TNF?

Literature Review

Definition of Loss of Response

There is no universally accepted definition of loss of response to anti-TNF treatment and hence its reported frequency is highly variable. Definitions used in clinical trials, observational studies, and reviews are (1) reemergence of clinical symptoms after induction of response, verified by an increase in clinical activity scores such as the Crohn's disease activity index (CDAI, e.g., 70 point change) or Mayo score (e.g., 3 point change) [11, 12]; (2) patient's perspective of increasing symptoms [13]; and (3) need for dose intensification or treatment discontinuation with a switch to other agents [5, 14, 15]. Current ECCO guidelines suggest the following 2 possible definitions for loss of response in CD – acknowledging that no consensus exists: For CD (1) a CDAI >150 with an increase of >70 points or (2) a CDAI increase of ≥ 100 points [9]; For UC, ECCO did not release a statement regarding the definition of loss of response [10]. However, a Mayo score of >2 or an increase of 3 or more points might be used in daily clinical practice [16, 17].

Drug Levels and Loss of Response

Several studies demonstrated higher efficacy of anti-TNFs with higher serum drug levels, both in UC and CD, as well as for infliximab and other anti-TNF agents. Most data derive from retrospective analyses of prospective trials, which have been nicely summarized in a comprehensive review by Sorrentino et al. [18] In CD, high or detectable infliximab trough levels were associated with higher rates of ongoing clinical response compared to low or undetectable levels. These rates were (1) 82 vs. 6% (for detectable vs. nondetectable) [19]; (2) 74 vs. 59% (for cutoff >3 $\mu\text{g/mL}$); [20] (3) 39 vs. 18% (for cutoff $\geq 3.5 \mu\text{g/mL}$); [21] (4) 92 vs. 14% (for cutoff >0.3 $\mu\text{g/mL}$) [22]; and (5) 100 vs. 80% (for cutoff >5 $\mu\text{g/mL}$) [22]. Moreover, there was a 66% lower likelihood to lose clinical response in case of

drug concentrations above 3 µg/mL [23]. Clinical remission rates increased after dose escalation to reach target levels of 3–7 µg/mL (from 65 to 88%) [24]. There was a longer duration of clinical response in patients with a threshold of >12 µg/mL [25]. In addition, higher rates of endoscopic remission (47 vs. 19%) were observed with detectable infliximab levels (vs. nondetectable) [19]. In UC, detectable infliximab levels were also associated with higher clinical (69 vs. 15%) and endoscopic (76 vs. 28%) response rates [26]. Patients in endoscopic remission had higher levels of infliximab (8.1 vs. 2.9) and an infliximab threshold level of >6.6 µg/mL predicted endoscopic response with an OR of 18.1 [27]. In both UC and CD, loss of response to infliximab was attributed to low drug levels in 45% [28].

Fewer studies have been performed with adalimumab. In CD, trough levels of ≥5 µg/mL have been identified as predictive for treatment continuity with an OR of 4.5 [29]. Higher trough levels were further observed with clinical remission and mucosal healing [30]. In UC, patients with histological and endoscopic inflammation had lower drug levels, while those in clinical remission and with mucosal healing showed higher serum concentrations of adalimumab [31]. A comprehensive analysis of 145 patients examined the impact of adalimumab and infliximab drug levels in both UC and CD [32]. The following rates of mucosal healing were found: (1) with infliximab 50% for >4 µg/mL, 85% for >6 µg/mL, and 90% for >8 µg/mL and (2) with adalimumab 50% for >7.5 µg/mL, 75% for >8 µg/mL, and 90% for >12 µg/mL [32]. A plateau was reached with >12 µg/mL (adalimumab) and >8 µg/mL (infliximab). For certolizumab, even fewer data are available: with higher drug levels (≥23.30 vs. <8.98 µg/mL), more CD patients were found to be in clinical remission (93 vs. 50%), endoscopic remission (75 vs. 30%), and to show endoscopic response (87.5 vs. 20%) [33].

Despite these positive data – however – in some trials, no association between drug levels and treatment outcome was seen: in the SONIC trial, no significant differences were observed in terms of remission rates at week 50 when patients with nondetectable infliximab levels (0 µg/mL) were compared with patients with higher drug levels (>6 µg/mL, 67 vs. 87%) [18, 20]. Similar findings were reported by Pariente et al. [34]. In addition, optimal cutoff values remain unclear. This is mainly attributed to the fact that many different thresholds have been used in the so far conducted trials, ranging from >1 to >12 µg/mL in case of infliximab. Different outcomes were used to define therapeutic response ranging from clinical response, remission to endoscopic response, and remission.

Since most data evolve from retrospective analyses of prospective studies, the evidence for TDM is low. The value of proactive drug level measurements and targeting infliximab treatment to a predefined serum concentration (target: 3–7 µg/mL) were evaluated in the TAXIT trial: While indeed clinical remission rates increased with dose escalation in patients with subtherapeutic drug levels, this strategy was not superior to clinically based dosing [24]. Similarly, maintaining infliximab above 3 µg/mL did not result in higher rates of steroid-free clinical remission than adapting dose based only on symptoms (TAILORIX trial) [35]. Taken together, no clear recommendations for the use of TDM and for optimal thresholds in particular exist [7]. Suggested cutoffs vary from >2 to 5–10 µg/mL. Current recommendations regarding the use of TDM and adequate threshold levels in IBD patients are summarized in Table 1 [9, 10, 36–40].

Antidrug Antibodies

Development of antidrug antibodies, a process called anti-TNF immunogenicity, may also affect the efficacy of anti-TNF treatment. Antidrug antibody formation has been observed with all anti-TNF agents used in IBD. Of note, episodic dosing resulted in higher antibody titers than did scheduled dosing [25, 41–45]. Antidrug antibodies have been linked to higher rates of loss of response and higher likelihood of transfusion reactions [25, 42, 43]. Antidrug antibody titers can be measured with commercially available tests, which are based on ELISA, RIA, or HMSA methods [6, 41, 46]. Data on the association between presence of antidrug antibodies and disease outcome are inconsistent [41]. In CD studies with episodic dosing of infliximab, higher antibody titers were linked to shorter duration of response and lower response rates, while no such association was seen with scheduled dosing except for the SONIC trial, where some improvement was observed with inconclusive antidrug antibody titers [19, 20, 25, 42–44]. In UC, even higher response rates were seen with detectable antibodies, which were probably confounded by higher trough levels in these patients [47]. No such association was found in the study by Seow et al. [26]. For adalimumab and certolizumab, no associations between antidrug antibodies and disease outcome were seen [14, 48, 49]. Detailed descriptions of these trials can be found in the thorough reviews by Scott and Lichtenstein [41] and by Khanna et al. [6, 41]. No clear cutoffs for antidrug antibodies exist due to different measurement methods and the fact that antidrug antibodies may be only transient in a considerable proportion of patients. While some studies used absence vs. presence of antibod-

Table 1. Current recommendations regarding drug levels and antidrug antibodies in IBD

	ECCO	AGA	ACG	WGO	APAGE
Use of TDM	Could be used to guide optimisation strategy if available	Reactive TDM suggested to guide treatment changes if active anti-TNF treated IBD	Should be considered in active disease	More widely available for infliximab than any other anti-TNF. It can help determine the cause of a secondary loss of response and may be adopted in dose reduction strategies	No statement
Threshold for adequate drug levels	No statement	Infliximab ≥ 5 $\mu\text{g/mL}$ Adalimumab ≥ 7.5 $\mu\text{g/mL}$ Certolizumab ≥ 20 $\mu\text{g/mL}$ Golimumab unknown	Infliximab > 7.5 $\mu\text{g/mL}$, adalimumab > 5 $\mu\text{g/mL}$, and certolizumab pegol > 20 $\mu\text{g/mL}$	No statement	No statement
Use of antidrug antibodies	Could be used to guide optimization strategy if available	No statement	Should be considered in active disease	More widely available for infliximab than any other anti-TNF. It can help determine the cause of a secondary loss of response and may be adopted in dose reduction strategies	No statement
Cut-off values for antidrug antibodies	No statement	No statement	No statement	No statement	No statement

IBD, inflammatory bowel disease; ACG, American College of Gastroenterology; AGA, American Gastroenterology Association; APAGE, Asian Pacific Association of Gastroenterology; ECCO, European Crohn's and Colitis Organisation; WGO, World Gastroenterology Organisation.

ies, others used defined threshold values. There are no clear recommendations regarding the use of antidrug antibodies in IBD treatment. In addition, there is no consensus regarding adequate threshold values (Table 1). However, antidrug antibody titers may have their value in clinical practice. A study from the Mayo Clinic revealed higher response rates for switch of anti-TNF agent compared to dose intensification in case of presence of antidrug antibodies (92 vs. 17%), while dose intensification was more effective if no antidrug antibodies were present (86 vs. 33% compared to switch of anti-TNF agent) [28]. Similarly, Roblin et al. [50] demonstrated high clinical response rates (67%) with adalimumab dose optimization in case of low trough levels and nondetectable antidrug antibodies. In addition, combined interval shortening and dose intensification appears to be particularly effective for restoring therapeutic drug levels when antidrug antibodies titers are low [51]. Nonetheless, dose intensifications can still be effective even in case of high antidrug antibody titers (in 60% compared to 74% efficacy in patients with nondetectable antidrug antibodies) [34].

Methods

Delphi-Style Consensus

To establish a consensus on the use of TDM in the context of loss of response to anti-TNF treatment, we performed a vote among IBD experts using a Delphi-style process [52]. First, we conducted a literature review using PubMed and Embase. The following key search items were used: *loss of response*, *TDM*, *anti-TNF*, *antidrug antibodies*, and *IBD*. In addition, guidelines from 5 gastroenterology societies were consulted: American Gastroenterology Association, American College of Gastroenterology, ECCO, Asian Pacific Association of Gastroenterology and World Gastroenterology Organisation. In a second step, 8 IBD specialists participated in a 3-h meeting and rated different statements on an even Likert-scale ranging from 1 to 4, based on their expert opinion and the available literature: 1 indicated strong disagreement with a specific statement, 2 disagreement, 3 agreement, and 4 indicated strong agreement. The statements included (i) reason for and optimal time-point of TDM; (ii) use of antidrug antibodies; (iii) definition of loss of response; and (iv) most adequate treatment strategies in case of loss of response to anti-TNF. A list of the statements used for the first round of voting can be found in online Supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000501930). Participants were blinded to the votes of the other IBD experts. The voting process was followed by a panel discussion to refine the statements. A statement was

Fig. 1. Thresholds for adequate drug levels according to anti-TNF agent. ADA, adalimumab; CZP, certolizumab pegol; IFX, infliximab.

considered accepted if the mean rating value was 3 or more. As data are limited for biologics beyond the anti-TNF mode of action, statements were restricted to anti-TNF treatment. The 8 IBD experts were as follows: 5 experts practice in and/or are affiliated with an academic institution (university hospital level), 2 experts practice in private practice, and 1 expert practices at a large community hospital (all in Switzerland, Europe).

Ethical Statement

This study did not include patient subjects. Therefore, as for other Delphi-technique based consensus paper, ethical approval was not required [53].

Results

TDM for Anti-TNF

After the specialist panel opinion, the following consensus on therapeutic drug levels was achieved: (1) loss of response is associated with low or undetectable serum drug concentration in 50–70% of cases (mean value 3.4, online Suppl. Fig. 1) and (2) both in CD and UC, loss of response is associated with low or undetectable serum drug levels (mean value 3.6, online Suppl. Fig. 1). There was a consensus on how anti-TNF clearance occurs: through immune-mediated reactions (with formation of antidrug antibodies, mean value 3.6) and nonimmune reactions (mean value 3.6, online Suppl. Fig. 1). There was strong agreement that nonimmune-mediated drug clearance is affected by severity and extent of IBD (mean value 3.9), male sex (mean value 3.3), BMI (mean value 3.5), and concomitant use of immunomodulators (mean value 3.8, online Suppl. Fig. 2). There was also strong consensus on when to measure drug concentrations in terms of infliximab (trough levels immediately before the administration of the next dose, mean value 4). However, there was no consensus regarding when to measure drug concentrations of subcutaneously administered anti-TNF. In terms of adequate anti-TNF levels, there was strong agreement that mucosal healing should be the target to treat. Optimal cutoff values to achieve this goal were controversially discussed (online Suppl. Fig. 3). However, there was a final agreement for infliximab (5 µg/mL),

adalimumab (8 µg/mL), and certolizumab pegol (10 µg/mL, Fig. 1). There was no agreement regarding an optimal threshold for golimumab.

Antidrug Antibodies

In a next step, use of and cutoff values for antidrug antibodies were rated and discussed. There was overall agreement that high antidrug antibody titers are predictive for adverse events and loss of response, but that they do not predict mucosal healing, CRP levels, or calprotectin levels (online Suppl. Fig. 4). There was consensus to use manufacturer's cutoff values for anti-infliximab and adalimumab antibody titers. The test provider usually indicates if levels are considered positive or negative. All positive levels are meaningful. In addition, there was an overall agreement that antidrug antibodies should be measured when drug levels are lowest to avoid the risk of complex formation. There was no consensus on specific cutoff values for certolizumab pegol and golimumab. The value of anti-vedolizumab antibodies remains unclear – and was not within the scope of the current consensus.

Loss of Response to Anti-TNF

There was overall agreement on how to define loss of response. The following parameters should be considered: symptoms (mean value 3.4), drug levels (mean value 3.1), antidrug antibodies (mean value 3.1), and imaging such as sonography (mean value 3.1), endoscopy (mean value of 3.5), and MRI (in case of Crohn's disease, mean value 3.1, online Suppl. Fig. 5). A calprotectin level of >50 µg/g was not considered to affect clinical decision making (mean value 2.6). However, after discussing optimal cut-off levels, there was a strong agreement that calprotectin levels of >200 µg/g should be taken into account, when defining loss of response.

Therapeutic Algorithm for Patients with Loss of Response to Anti-TNF

The following interventions were deemed appropriate in the context of loss of response: (1) shortening of dose interval or dose intensification in case of subtherapeutic drug levels, and absent or low antidrug antibody titers; (2) switch to another anti-TNF (= switch in class) in case of subtherapeutic drug levels, but presence of antidrug antibodies; and (3) switch to a non-anti-TNF biologic (= switch out of class) in case of therapeutic drug levels regardless of presence or absence of antidrug antibodies. In case of subtherapeutic drug levels, but absent or low antidrug antibody titers, 2 options were deemed appropriate: (1) increasing the dose (“dose intensification”) or (2) shortening the interval. The

Fig. 2. Treatment algorithm in case of loss of response to anti-TNF. ADA, antidrug antibody; CS, corticosteroids; IBD, inflammatory bowel disease; IS, immunosuppressive drugs.

experts agreed on the following: (1) dose intensification should be strived for if the clinical effect after drug administration is slow and (2) shortening the interval should be favored if a patient still responds to a maintenance dose, but experiences deterioration of IBD symptoms prior to the next drug administration. Figure 2 shows a treatment algorithm in case of loss of response to anti-TNF, which was elaborated during this expert panel discussion.

Discussion

TDM and measurement of antidrug antibodies are increasingly used in the context of loss of response to anti-TNF. As of yet, ECCO guidelines mention these novel tools but without clear recommendations about their use

[9, 10]. We herein report on the results from a Delphi-based consensus meeting among 8 IBD specialists. The final statements are summarized in Table 2.

Our expert panel reached consensus that loss of response to anti-TNF is associated with inadequate anti-TNF drug levels in both CD and UC. Indeed, despite some negative data from the SONIC trial, most published analyses showed that higher trough levels lead to better clinical and endoscopic outcomes [18, 20]. Most data are available for infliximab, but similar results have been reported for other anti-TNF agents. There was consensus that drug levels should be measured, when concentration is lowest (= trough levels). However, optimal cutoff values were discussed controversially among the panel experts. Current data are limited by the fact that studies used many different thresholds to define adequate and nonadequate drug con-

Table 2. Overview of the final statements made during the expert panel discussion

Final statements
Loss of response is associated with inadequate drug levels in both CD and UC
Best time-point for measuring drug levels is prior to the next application (trough levels)
Thresholds for adequate drug levels depend on the anti-TNF agent
Antidrug antibodies are predictive for loss of response and adverse events
Manufacturer's cutoff values for antidrug antibodies should be used and all positive levels should be considered meaningful
Antidrug antibody titers and drug trough levels are key determinants in the treatment algorithm

centrations. Nonetheless, a second voting round resulted in a consensus for infliximab (5 µg/mL), adalimumab (8 µg/mL), and certolizumab pegol (10 µg/mL). These cutoffs should be seen as guiding values. Such guidance may help clinicians to decide whether or not a current anti-TNF therapy is underdosed. A limiting factor of the current recommendation is that it may take up to 2 weeks until anti-TNF drug levels are available. Thus, an intervention is often needed and performed before the results are known. Point-of-care measures of anti-TNF may allow clinicians to take more advantage of TDM in the future.

Available data for antidrug antibodies are less consistent than they are for drug concentrations [41]. However, our expert panel reached consensus that antidrug antibody titers are useful and high titers are associated with loss of response to anti-TNF. This agreement was achieved based on (1) data from the SONIC trial [20], (2) a recent meta-analysis showing worse outcome with antidrug antibodies at least in CD [54], (3) and the fact that – if antidrug antibodies are present – switch to another anti-TNF results in better clinical response than dose intensification [28]. Thus, antidrug antibodies should be taken into consideration when it comes to define loss of response to anti-TNF. However, threshold values remain unknown. As of today, any positive result evolving from antibody testing (based on the manufacturer's protocol) should be considered clinically meaningful.

Based on these data and agreements, both trough levels and antidrug antibody titers should be seen as key determinants in the treatment algorithm. After loss of response is confirmed, drug monitoring is recommended. If thera-

peutic drug levels are detected, anti-TNF dose intensification has no benefit. Treatment should be switched out of class, high dose steroids might be started, or even surgery might be considered. In case of inadequate drug levels, antidrug antibody titers may help in clinical decision making: (1) undetectable antibody or low antibody titers justify dose intensification, while (2) high antidrug antibody titers should lead to a therapeutic switch out of class or maybe within class, but with optimization of concomitant immunomodulation. Some anti-TNF has lower immunogenic potential than others (e.g., adalimumab) [55]. This strategy is mainly based on the retrospective analysis from Mayo Clinic, where in patients with low drug levels dose intensification was superior to anti-TNF switching, but in patients with antidrug antibodies, switching to other agents was superior to dose escalation [28]. In another study – however – dose intensification was effective even in patients with high antidrug antibody titers [34].

Our consensus recommendations have several limitations. They only discuss anti-TNF treatment, since conclusive data are still missing for the newer non-anti-TNF biologics. Measuring vedolizumab levels is complicated because of saturation of the target receptor. In addition, patients may be in clinical remission despite undetectable or very low vedolizumab levels. Ustekinumab trough levels can now be measured. However, data supporting their use in clinical practice are too sparse [7]. The literature review was not conducted in the sense of a systematic review, but rather based on recent meta-analyses, reviews, guidelines, and studies in high impact journals. A further limitation of our consensus is that there is still no generally accepted definition for loss of response to anti-TNF. Therefore, the therapeutic algorithm provided in Figure 2 should be seen as guidance rather than a rule for every patient. Clinical decision making should be discussed on individual basis.

In conclusion, a Delphi-style consensus among 8 IBD experts shows that TDM and measurement of antidrug antibody titers are useful in the context of loss of response to anti-TNF. Optimal cutoff levels depend on the type of anti-TNF. These values are critical in the decision-making process. More studies are needed to address the value of such measurements for non-anti-TNF biologics.

Disclosure Statement

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Author contributions

G.R., N.Z., and S.R.V.: study design; TG, A.M.S., and S.R.V.: literature research; T.G., P.J., P.M., F.S., C.M., B.S., M.M., G.R., and S.R.V.: acquisition and interpretation of data; T.G., M.M., and S.R.V.: drafting of manuscript; P.J., P.M., F.S., C.M., B.S., M.M., G.R., and S.R.V.: expert panel discussion for the Delphi-like process. P.J., P.M., F.S., C.M., N.Z., B.S., M.M., A.M.S., and G.R.: critical review of the manuscript. T.G., M.M., G.R., and S.R.V.: supervision. All authors contributed to the critical revision and approved the final version of manuscript.

Guarantors of the Article

Thomas Greuter, MD and Stephan R. Vavricka, MD.

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