Therapeutic Drug Monitoring in Inflammatory Bowel Disease: Current State and Future Perspectives

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Keywords: Adalimumab, Anti-drug antibodies, Anti-TNF, Biologics, Crohn's disease, Immunogenicity, Infliximab, Trough concentrations, Ulcerative colitis

Financial support and funding: NVC is a Postdoctoral Fellow of the Research Foundation - Flanders (FWO), Belgium

Abstract

Current available anti-inflammatory drugs, in particular monoclonal antibodies directed against the cytokine tumor necrosis factor α (TNF), have greatly enhanced the treatment of inflammatory bowel diseases (IBD). Although many patients respond to ant-TNF therapy, a proportion of patients will not respond (primary non-response) or will lose response to the drug over time (secondary non-response). This loss of response can be caused by patient, TNF-inhibitor, or disease-related factors influencing the pharmacokinetics and pharmacodynamics of the drug. Therefore, monitoring pharmacological parameters (i.e. therapeutic drug monitoring) may help guide therapeutic decisions. This review emphasizes interesting and important new findings, and provides an updated overview, on the subject of therapeutic drug monitoring. While exploring the hypothesis that "one size does not fit all", we focused on the first prospective studies investigating the novel approach in IBD of 'target concentration adjusted dosing' and personalized medicine.

Introduction

Most of the established and evolving therapies used in the treatment of inflammatory bowel disease (IBD) are also used to treat other chronic inflammatory conditions such as rheumatoid and psoriatic arthritis and ankylosing spondylitis. These anti-inflammatory drugs specifically interact with downstream targets of a shared inflammatory cascade. The monoclonal antibodies infliximab, adalimumab and golimumab and the antibody fragment certolizumab pegol all target the abundantly expressed cytokine tumor necrosis factor α (TNF). These biologicals remain to date the most efficacious tools in the pharmaceutical armamentarium to induce and maintain remission in patients with Crohn's disease (CD) and ulcerative colitis (UC) (1-5). Although a drug can be administered for different indications based on its mode of action, a dose and its subsequent efficacy are much more difficult to extrapolate especially in the setting of complex biological drugs.

Not only the pharmacokinetics (PK, referred to as what the body does to the drug) but also pharmacodynamics (PD, referred to as what the drug does to the body) can greatly differ between patients suffering from the same chronic inflammatory disease. From the literature, it is known that 10–30% of IBD patients do not respond to TNF inhibitors (primary non responders) (6, 7). Across different trials and clinical case-series the annual risk for loss of response to infliximab and adalimumab was calculated to be, respectively, 13 and 24% as judged by the need for dose intensification (8, 9). Despite empiric dose intensification, the median drop-out rate from infliximab treatment was calculated to be 7% per year (10). Different factors can influence the non-response rate in patients and it is important to keep in mind that, especially in the setting of biologicals, the response towards the drug can fluctuate. These factors can be related to the patient (e.g., albumin, body size, and gender), disease (e.g., type, location, and severity) and the drug itself (e.g., synergism with immunosuppressive drugs and immunogenicity) (11).

Immunogenicity is an important downside of biologic drugs, where the body recognizes the drug as non-self and the immune system develops anti-drug antibodies (ADA). These ADA hamper the

activity of the drug by causing a faster clearance and by blocking the binding site of the drug to TNF, and can also lead to allergic reactions.

The heterogeneity in PK is probably not unique to TNF inhibitors, but it might be an intrinsic property of monoclonal antibodies. Therapeutic drug monitoring (TDM) at regular intervals can shed light on what is going on with the drug *in vivo*. The preferred time point of sampling is at trough (i.e. lowest concentration of drug just before the next administration). Drug trough concentrations (TC) are a pharmacological representation of the absorption, distribution, metabolization and excretion phase of the drug since its last administration (12). It can be hypothesized that a TC needs to be sufficiently high for the drug to exert maximal efficacy. On the other hand, a TC above this threshold will not result in increased (clinical) efficacy. This concept is often referred to as the optimal therapeutic window concept (13).

Previous pivotal retrospective studies reported correlations between drug TC and clinical outcomes such as response, remission, and mucosal healing, supporting the concept of TDM in IBD clinical practice (14-17). This review's goal is to emphasize new and important findings and to give an updated overview on the subject. By doing so, we chose to focus on the first prospective studies investigating this novel approach of 'target concentration adjusted dosing' and personalized medicine.

Therapeutic Window Concept

Therapeutic drug monitoring is important for the safety of drugs that have a narrow therapeutic window. For those drugs (e.g., digoxin) it is important to monitor that drug concentrations do not exceed a certain toxic concentration. On the other hand low or undetectable drug concentrations result in low efficacy.

Anti-TNF drug and ADA concentrations can be measured using different assays. Recent comparison studies have shown that there can be differences in specificity and sensitivity among those assays

(18, 19). When measuring drug concentrations, an accurate standard can be available in the drug itself provided by the pharmaceutical company. In the case of measuring ADA, such a standard is not yet available which makes it difficult to compare absolute values obtained with different immunogenicity assays. Within the last few years, new assays have been developed which are able to measure ADA concentrations even in the presence of the drug (20, 21). Although it is still a matter of debate what the clinical relevance is of measuring ADA if an excess of active drug is still available in the patient's serum, it appears that ADA in the presence of detectable drug leads to increased clearance of the drug.

In the case of TNF inhibitors, the upper limit of the therapeutic window should be a reflection of a drug's maximal efficacy, rather than toxicity. There is a lack of data on what is the optimal upper limit for the anti-TNF therapeutic window. However, this limit could greatly influence the cost-effectiveness of anti-TNF treatment because dose reduction in patients with too high trough concentrations would result in significant cost savings. In relation to low concentrations, recent retrospective studies have suggested an optimal lower limit for infliximab and adalimumab TC in IBD patients:

Infliximab Therapeutic Cut-Off

A recent *post hoc* analysis of the ACT 1 and 2 studies showed that the proportion of UC patients achieving clinical response, remission and mucosal healing at weeks 8, 30, and 54 increased with increasing quartiles of infliximab concentrations (22). It was confirmed that this concentration-effect relationship reached a plateau. Specifically, the proportion of patients achieving clinical response, remission and mucosal healing did not increase above a certain infliximab concentration (Fig. 1). In a cohort study including 134 UC patients treated with maintenance infliximab, a TC cut-off >2 µg/ml was found to be associated with a higher rate of clinical steroid free remission (69 vs. 16%) for a median follow-up of 19.9 months (23). A meta-analysis of 2,021 serum samples from 532 CD patients included in 4 prospective randomized controlled trials or cohort studies evaluated the correlation

between infliximab concentration, ATI, and C-reactive protein (CRP) (24). Receiver operator curve analysis showed that an infliximab concentration >3 µg/ml was predictive of significantly lower disease activity, as measured by CRP. These results were corroborated by Bortlik *et al.* who found that infliximab TC greater than 3 µg/ml at start of maintenance treatment (week 14 or week 22) were predictive of sustained remission (median 2-year follow-up) with a positive and negative predictive value of, respectively, 85 and 45% in a cohort of 84 CD patients (25).

Adalimumab Therapeutic Cut-Off

For adalimumab a similar correlation between the mean trough concentrations and clinical outcome was found during the pivotal CLASSIC 1 trial but a recent *post hoc* analysis of both CLASSIC 1 and 2 trials was not able to delineate a reliable therapeutic cut-off (26). The authors attributed this to overlap in TC between Crohn's disease patients with and without remission, due to high inter- and intra-individual variability. Recently, the exposure-response relationship for adalimumab during the induction phase of treatment of UC (ULTRA 2) was investigated (27). From the 258 UC patients randomized to receive adalimumab (160/80 mg at weeks 0/2, and 40 mg every other week) the relationship between week 8 remission or response and TC was explored. The ranges of adalimumab TC quartiles were <5, 5-8.7, 8.7-11.7 and >11.7 µg/ml. Plotting the % of patients in remission per TC quartile showed a clear exposure-response relationship at week 8. Higher TC values were associated with higher rates of remission. Quartile plots for response showed that the % of patients with week 8 response was higher for the 2nd and 3rd TC quartiles compared with the 1st quartile. The percentage of patients with week 8 response did not increase beyond the 3rd quartile. The authors also observed that weight, CRP, albumin, and combination therapy with methotrexate at baseline greatly influenced the PK of adalimumab during induction which explained a part of the observed variability in drug TC. Regarding maintenance therapy, a prospective cross-sectional study from Velayos F. *et al.* including 54 IBD patients investigated the correlation between adalimumab TC and clinical outcome (28). An adalimumab TC <5 µg/ml was found to be correlated with increased levels of CRP. These

results were corroborated in a study including 66 IBD patients where elevated CRP levels were best predicted by a minimum serum adalimumab cut-off point of 5 µg/ml (29). Similarly, a study including 40 CD patients treated with maintenance adalimumab revealed that an adalimumab TC cut-off of 5.9 µg/ml was optimal to maintain negative CRP (≤3 mg/l) (30). Aside from clinical response and remission, mucosal healing has emerged as an important therapeutic endpoint in IBD. The correlation between adalimumab TC during maintenance therapy and mucosal healing was recently investigated in a cohort of 40 IBD patients (31). An adalimumab TC <4.9 µg/ml was found to be associated with absence of mucosal healing with a positive predictive value of 88% and negative predictive value of 51%.

TDM at Time of Secondary Loss of Response

Other than for 'target concentration adjusted dosing', TDM can also be used to guide therapy at time of loss of response to the biologic. The empiric approach to tackle loss of response by intensifying the treatment and, if this fails, switching to another type of TNF inhibitor is frequently suboptimal and leads to unnecessary high costs. A therapeutic strategy has several advantages over the empiric approach as it 1) avoids dose intensification in those patients who will not benefit from more drug (i.e. patients who have become immunized or patients who have a non-TNF driven disease or other causes of symptoms) 2) allows targeted dose intensification in those patients who lost response due to low concentrations of drug, and 3) directs patients with a non-TNF driven disease more efficiently to other therapeutic options. In a simulated model, the testing-based strategy has shown to be more cost-efficient compared to the empiric dose-escalation strategy in CD patients losing response to IFX (32). Both strategies yielded a similar proportion of patients in response and remission at 52 weeks, however this was achieved differently between the two groups. More patients from the testing group needed surgery compared to the empiric group (48 vs. 34% respectively). The main reasons for cost savings in the testing group resulted from 1) substantially lower use of high-dose (and high-cost)

biological therapy, and 2) greater time spent off biologic medication as compared to the empiric group.

Recently, in Denmark, a first randomized controlled study was performed where individualized therapy was compared to standard dose intensification in 69 CD patients with secondary infliximab failure (33). Treatment of patients in the active arm was based solely on infliximab drug and ADA concentrations. The study revealed that the individualized approach based on drug and ADA concentrations was more cost-effective (up to 56% reduction in cost) as compared to routine dose escalation, without any apparent effect on clinical efficacy. However, the duration of the study was limited to 12 weeks and thus long-term benefits (both pharmacoeconomical and clinical) for this approach could not be calculated or predicted.

A large multi-center, randomized controlled trial is planned in North-America, Canada and Europe including 40 investigative sites and 160 IBD patients with secondary loss of response (NCT01960426 ClinicalTrials.gov). The duration of this study will be 32 weeks and patients will have multiple time points at which treatment can be optimized based on drug and ADA concentrations. The study will also take into account adalimumab and will give a better representation of the impact of a testing-based strategy with respect to the North American healthcare model.

Recently a study by Paul and co-workers looked at infliximab TC, ADA and endoscopic improvement (mucosal healing) after dose escalation in IBD patients suffering secondary loss of response (34). This prospective observational study in 52 IBD patients showed that the restoration in infliximab TC after dose escalation was correlated with mucosal healing. They found that a cut-off of 0.5 µg/ml was associated with mucosal healing (sensitivity 88%, specificity 77%).

TDM During Induction and Maintenance Phase

One could hypothesize that better disease control could be achieved by dose optimizing patients based on individual drug TC to intervene before clinical loss of response is diagnosed. Ultimately, this might reduce the high rate of loss of response seen during anti-TNF maintenance treatment (35).

Although there is no incontrovertible proof that adverse events are associated with supratherapeutic concentrations of TNF inhibitor, an association between skin lesions, arthralgia and high anti-TNF concentrations has been suggested in IBD (36). Therefore, lowering the dose in patients with supraoptimal TC could lead to fewer side effects and a lesser cost for the health care payer. A cost-effectiveness analysis using a patient level Markov model showed important cost savings when a personalized treatment based upon drug and ADA concentrations was implemented in a cohort of rheumatoid arthritis patients treated with maintenance adalimumab (37).

Recently, the final results of the randomized controlled TAXIT (trough level adapted infliximab treatment; 2011-002061-38 ClinicalTrialsRegister.eu) study have been presented. This study investigated whether dosing of infliximab based on TC was superior compared to clinically based dosing. The study was comprised of two phases. During the optimization phase, all patients were dose-optimized using the TAXIT algorithm to achieve infliximab TC between 3 and 7 μg/ml. This revealed that dose escalation in CD patients with suboptimal drug concentrations (<3 μg/ml) leads to a better disease control as seen by a significant drop in the Harvey-Bradshaw index and CRP. Meantime, dose de-escalation was successful in both CD and UC patients with supra-optimal drug concentrations (>7 μg/ml) leading to a lower drug exposure and lower cost (38). During the maintenance phase patients were randomized 1:1 to continue drug concentration-based dosing or to switch back to clinically-based dosing (52-week follow-up). The primary end point was defined as the proportion of patients in clinical and biochemical remission in each group. This second phase of the study showed no additional benefit in utilizing an ongoing drug concentration-based dosing strategy compared to a clinically-based dosing strategy with infliximab, although the secondary endpoint

looking at need for dose optimization clearly showed a benefit for the drug concentration based dosing group (39).

It can be hypothesized that to achieve most out of TDM and 'target concentration adjusted dosing', one should perform the dose optimization of the drug early on (i.e. during or right after induction) (40, 41). A randomized controlled trial (TAILORIX) is under way in Europe, which includes anti-TNF naïve CD patients in whom infliximab therapy is initiated (NCT01442025 ClinicalTrials.gov). Dose adjustments in the active arm can already be done at week 14 after the start of the treatment based on drug concentrations and/or clinical symptoms.

In the setting of the reintroduction of infliximab therapy after a long drug holiday, adequate drug TC and absence of ADA early after restart has been shown to correlate significantly with both short- and long-term clinical outcomes (42).

Monitoring of ADA

A recent meta-analysis including 1,378 patients with IBD showed that patients who develop antibodies to infliximab have a risk ratio of 3.2 (95% confidence interval 2.0–4.9) to lose clinical response to the drug as compared to patients who did not develop antibodies. Development of ADA also resulted in lower infliximab trough concentration (43). Although the association between ADA and hypersensitivity and/or persistent loss of response was already shown a decade ago, quantitative correlations between the concentration of ADA and markers of disease activity seem to be limited to the presence or absence of ADA. This was recently confirmed in a cross-sectional study including 66 IBD patients treated with maintenance adalimumab (29). Here, detectable antibodies to adalimumab where associated with an adalimumab TC <5 µg/mL [odds ratio (OR) 8.6; 95% CI: 2.3-31.8], macroscopic mucosal inflammation [OR 3.8; 95% CI: 1.1-13.2], need for corticosteroids [OR 3.7; 95% CI: 1.1-12.9], and previous infliximab use [OR 3.9; 95% CI: 1.0-15.2]. A recent observational retrospective study including 90 IBD patients treated with infliximab revealed that, in almost 1/3 of IBD patients, antibodies disappeared over time (44). These antibodies were classified as 'transient'

and led to a discontinuation of the treatment in only 13% of the patients as compared to 68% of the patients who developed 'sustained antibodies'. Interestingly, an infliximab TC <2 µg/ml at week 14 after start of therapy predicted ADA formation later on. These results have recently been corroborated in another prospective observational cohort (45). Dose escalation to overcome low level ADA and regain adequate TC has been suggested, but it remains a matter of debate whether this is the most cost-effective option. Other options such as adding an immunomodulator (if possible) or switching to another anti-TNF have to be considered and prospective studies are warranted (46).

TDM for Non-Anti-TNF Drugs in IBD

Therapeutic drug monitoring has also been used in IBD patients treated with azathioprine (AZA) or 6-mercaptopurine (6-MP) to optimize and to restore clinical response. These drugs are inactive pro-drugs and are metabolized into the active thioguanine nucleotides (TGN) which can be monitored for therapeutic efficacy. A recent study including 189 adult IBD patients showed that the optimization of AZA or 6-MP treatment using TGN monitoring resulted in improved clinical outcomes (47). When TGN concentrations were taken into account to guide therapy, this resulted in an improved clinical effect in 90% of the patients *versus* only 33% when the treatment decision was not TGN-guided. An algorithm to optimize treatment with azathioprine or 6-methotrexate based on TDM has recently been suggested elsewhere (48). However, whether or not dose optimization in patients with subtherapeutic 6-TGN concentrations results in an increase of 6-TGN concentrations and an increased efficacy is still unclear.

Conclusions and Guidelines

Based on this literature overview, several guidelines can be formulated on how therapeutic drug monitoring could be implemented in clinical practice (Table 1).

Adequate drug concentrations early after start are associated with better long-term clinical outcomes, whereas low or undetectable drug concentrations are associated with loss of response

and anti-drug antibody formation. Prospective data are lacking whether dose optimization based on early drug concentrations can alter clinical outcomes in the long-term.

From recent concentration-effect studies in both Crohn's disease and ulcerative colitis patients, it can be suggested that the optimal therapeutic trough concentration during maintenance therapy is 3 µg/ml for infliximab and 5 µg/ml for adalimumab. For the implementation of therapeutic drug monitoring during maintenance therapy, a distinction should be made between 1) responder patients where it could help to further optimize dosing of the drug or 2) non-responder patients where it could help to guide therapeutic decisions.

Regarding the first situation, the TAXIT study showed that infliximab dosing based on drug trough concentrations results in a more efficient use of drug. However, in patients on longstanding biological therapy, it was not necessary to constantly monitor these drug concentrations as clinically-based dosing proved to be equally effective after the initial drug concentration-based dose optimization.

With regard to the second situation of loss of response during maintenance therapy, drug concentration-guided treatment adjustment is likely to be more cost-effective than empiric dose escalation at similar clinical outcomes. Given the association between the restoration of infliximab and adalimumab trough concentrations and disease response after the intervention measuring drug concentrations after dose escalation may still be useful. Therefore in the setting of secondary loss of response, consecutive measurements of drug concentrations should be considered. Moreover since anti-drug antibodies can be transient, it is useful to measure drug and anti-drug antibodies on consecutive time points to confirm this dynamic profile.

In order to better use therapeutic drug monitoring in routine clinical practice, several hurdles remain to be overcome. First, because of a large inter-individual variability in drug trough concentration, it is difficult to define a trough concentration window which is optimal for each patient. Factors influencing infliximab and adalimumab PK have been described (e.g., body weight, serum albumin

concentration, and presence of ADA) but do not account for all the variability (27, 49). Therefore, intensive PK sampling in large patient cohorts would seem necessary to define important determinants of PK. Second, it is crucial that accurate and accessible techniques can be used to measure drug and ADA concentrations. Correlations between established assays are lacking and standardization is necessary to reduce assay-related variability. The cost of these measurements is also an important factor, as this will influence the cost-effectiveness of therapeutic drug monitoring (although the cost of biologic medications is so great that even relatively expensive assays are still cost effective compared to empiric dose escalation). Third, prospective data of the implementation of a TDM approach in routine clinical practice remain scarce, but trials are under way. These results will further answer the question of whether or not therapeutic drug monitoring is superior to the empiric dose adjustment approach and which strategy is more cost-effective.

Conflict of Interest

Niels Vande Casteele has served as a consultant for MSD and Janssen Biologics. He has received payment for development of educational presentations including service on speakers' bureaus for AbbVie. Brian G. Feagan has received payment for development of educational presentations including service on the speakers' bureau for Abbott/AbbVie, JnJ/Janssen, Takeda, Warner-Chilcott, UCB Pharma. He has received travel/accommodation compensation from Abbott/AbbVie, Actogenix, Albireo Pharma, Amgen, Astra Zeneca, Avaxia Biologics Inc., Axcan, Baxter Healthcare Corp., Boehringer-Ingelheim, Bristol-Myers Squibb, Calypso Biotech, Celgene, Elan/Biogen, EnGene, Ferring Pharma, Roche/Genentech, GiCare Pharma, Gilead, Given Imaging Inc., GSK, Ironwood Pharma, Janssen Biotech (Centocor), JnJ/Janssen, Kyowa Kakko Kirin Co Ltd., Lexicon, Lilly, Merck, Millennium, Nektar, Novonordisk, Prometheus Therapeutics and Diagnostics, Pfizer, Receptos, Salix Pharma, Serono, Shire, Sigmoid Pharma, Synergy Pharma Inc., Takeda, Teva Pharma, Tillotts, UCB Pharma, Vertex Pharma, Warner-Chilcott, Wyeth, Zealand, Zyngenia. He has received compensation for his membership on scientific advisory boards for Abbott/AbbVie, Amgen, Astra Zeneca, Avaxia Biologics Inc., Bristol-Myers Squibb, Celgene, Centocor Inc., Elan/Biogen, Ferring, JnJ/Janssen, Merck, Novartis, Novonordisk, Pfizer, Prometheus Laboratories, Salix Pharma, Takeda, Teva, Tillotts Pharma AG, UCB Pharma. Ann Gils has received an IIR grant from Pfizer and speaker's fees from MSD and Pfizer. Séverine Vermeire has served as a consultant for Centocor, UCB Pharma, Merck, Abbvie. She has received grants from Centocor, UCB Pharma, Merck, Abbvie. She has received payment for development of educational presentations including service on the speakers' bureau for Centocor, UCB Pharma, Merck, Abbvie, Ferring, Shire, and Pfizer. Reena Khanna has received speaker's fees from Takeda. Dr. Sandborn reports personal fees from ActoGeniX NV, AGI Therapeutics, Inc., Alba Therapeutics Corporation, Albireo, AM-Pharma BV, Alfa Wasserman, Anaphore, Astellas Pharma, Athersys, Inc., Atlantic Healthcare Limited, Axcan Pharma (now Aptalis), BioBalance Corporation, Boehringer-Ingelheim Inc., Celgene, Inc, Celek Pharmaceuticals, Cellerix SL, Cerimon Pharmaceuticals, ChemoCentryx, CoMentis, Cosmo Technologies, Coronado Biosciences, Elan Pharmaceuticals, Eli Lilly,

Enteromedics, Exagen Diagnostics, Inc., Ferring Pharmaceuticals, Flexion Therapeutics, Inc., Funxional Therapeutics Limited, Genzyme Corporation, Gilead Sciences, Given Imaging, Human Genome Sciences, Ironwood Pharmaceuticals, KaloBios Pharmaceuticals, Inc., Lexicon Pharmaceuticals, Lycera Corporation, Meda Pharmaceuticals, Merck Research Laboratories, MerckSerono, Millennium Pharmaceuticals (subsequently merged with Takeda), Nisshin Kyorin Pharmaceuticals Co., Ltd., Novo Nordisk A/S, NPS Pharmaceuticals, Optimer Pharmaceuticals, Orexigen Therapeutics, Inc., PDL Biopharma, Procter and Gamble, Prometheus Laboratories, ProtAb Limited, Purgenesis Technologies, Inc., Relypsa, Inc., Salient Pharmaceuticals, Salix Pharmaceuticals, Inc., Santarus, Schering Plough Corporation (acquired by Merck), Shire Pharmaceuticals, Sigmoid Pharma Limited, Sirtris Pharmaceuticals, Inc. (a GSK company), S.L.A. Pharma (UK) Limited, Targacept, Teva Pharmaceuticals, Therakos, Tillotts Pharma AG (acquired by Zeria Pharmaceutical Co., Ltd), TxCell SA, UCB Pharma, Viamet Pharmaceuticals, Vascular Biogenics Limited (VBL), Warner Chilcott UK Limited, Wyeth (now Pfizer); and grants and personal fees from Amgen, Bristol Meyers Squibb, Genentech (now Roche), Glaxo Smith Kline,Janssen (previously Centocor), Pfizer, Receptos outside the submitted work.

Barrett G. Levesque has received payment for development of educational presentations including service on the speakers' bureau for Warner Chilcott, UCB Pharma, and Salix Pharmaceuticals.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Tables

Table 1 *Implementation of a therapeutic drug monitoring approach of anti-TNF drugs in the treatment of inflammatory bowel disease patients.*

		Serum Drug Concentration		
		High	**Optimal range**	**Low**
Response to treatment	**Maintained remission**	Dose reduction	Dosing scheme unchanged	Measure ADA: **Sustained ADA** Stop and consider switch out of class **Transient or Undetectable ADA** Dose optimize/switch in class Or Consider to stop and switch out of class when mucosal healing is confirmed by endoscopy
	Partial or loss of response	[a]Switch out of class	[a]Switch out of class	Measure ADA: **Sustained ADA** Stop and switch in class **Transient ADA** Dose optimize/switch in class **ADA undetectable** Dose optimize and determine cause of accelerated drug clearance (e.g., consider endoscopy[a])

ADA anti-drug antibody

[a]Rule out non-IBD causes of symptoms

Legend to figures

Figure 1 Post hoc analysis of data from ACT 1 and ACT 2 trials representing the proportion of patients achieving clinical remission by serum infliximab concentration. Clinical remission was defined as Mayo Score ≤2 points, with no individual subscore >1. X-axis represents quartiles (Q) of infliximab trough concentration in µg/ml and were for week 8: Q1 <21.3; Q2 ≥21.3-<33.0; Q3 ≥33.0-<47.9 and Q4 >47.9; for week 30: Q1 <0.11; Q2≥0.11-<2.4; Q3 ≥2.4-<6.8 and Q4 >6.8; for week 54: Q1 <1.4; Q2 ≥1.4-<3.6; Q3 ≥3.6-<8.1 and Q4 >8.1. Adapted from Reinisch W. *et al.,* Infliximab Concentration and Clinical Outcome in Patients With Ulcerative Colitis. Presented at Digestive Disease Week; May 19-22, 2013; San Diego, California. Abstract 566

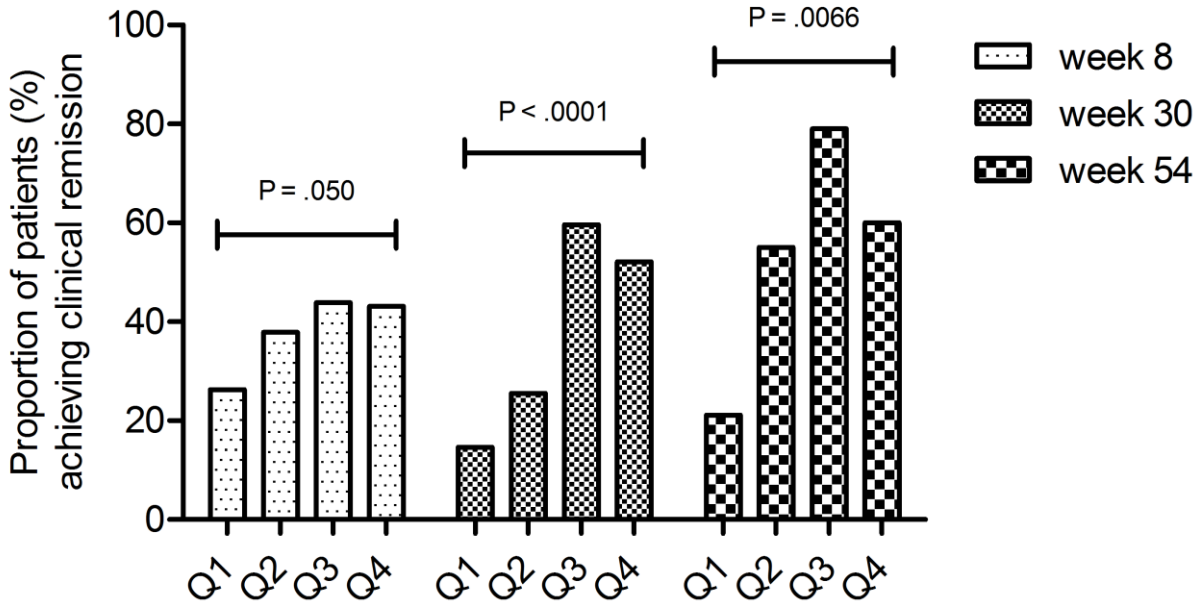
Proportion of patients (%) achieving clinical remission
100
80
60
40
20
0
P = .050
P < .0001
P = .0066
week 8
week 30
week 54
Q1
Q2
Q3
Q4
Q1
Q2
Q3
Q4
Q1
Q2
Q3
Q4

Figure 1

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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