SYMPOSIUM

III CHALLENGES IN THERAPEUTIC DRUG MONITORING

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III CHALLENGES IN THERAPEUTIC DRUG MONITORING

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The patient's journey: new opportunities for therapeutic drug monitoring in rheumatic disease

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INTRODUCTION

Therapeutic antibodies, or biopharmaceuticals, are macromolecules with a structure similar to that of immunoglobulins. They may be full-length monoclonal antibodies, antibody-drug conjugates, antigen-binding fragments, or fusion proteins [1]. Unlike small molecule drugs, therapeutic antibodies are not metabolised by the liver but are recycled, which explains their prolonged half-lives [2]. Therapeutic antibodies are formulated for intravenous or subcutaneous administration.

Therapeutic antibodies are produced by genetic modification and have high specificity for their target. Monoclonal antibodies targeting tumour necrosis factor (TNF) are commonly used in rheumatic disease; however, antidrug antibodies (ADAbs) against TNF inhibitors (TNFi) can develop. ADAbs are directed toward amino acids located at the paratope (antigen-binding site) of the monoclonal antibody, impairing target binding. ADAbs also increase drug catabolism resulting in under-exposure to the therapeutic antibody.

PRINCIPLES OF THERAPEUTIC DRUG MONITORING

Therapeutic drug monitoring (TDM) is the process of measuring drug concentrations at designated intervals to maintain a specific concentration [3]. The concept of TDM can be explained by basic pharmacology, in particular the inter-relation between pharmacokinetics and pharmacodynamics. Pharmacokinetics is the study of the time course of the drug in the organism or 'What the body does with the drug'. Upon intravenous administration of a drug, parameters such as volume of distribution, clearance rate, intercompartmental exchanges rates, elimination half-life, and area under the concentration-time curve can be estimated. Pharmacodynamics is the study of the time course of the biological response or 'What the drug does to the body'. The inter-relation between these pharmacological processes is illustrated by Gabrielsson J, et al. 2009 [4].

The principle of TDM is to adjust the drug dosing regimen according to a patient's individual characteristics (e.g. disease activity) in order to obtain a target concentration and improve clinical outcomes, under the assumption that a relationship exists between dose and concentration and between concentration and therapeutic effects [5]. TDM can be reactive or proactive. Under reactive TDM, the drug is administered, reaches steady state, and elicits a response; if the clinical response is lost, the drug concentration is measured and the dose is adapted to regain response. Under proactive TDM, the drug is measured at the beginning of treatment and, thereafter, systematically, prior to steady state and before a response is achieved. Using pharmacokinetic and pharmacokinetic-pharmacodynamic models, the dose can be anticipated based on the patient's characteristics before the start of treatment, and then adjusted during the induction phase to achieve the target concentration.

Three main arguments support implementing TDM of TNFi in patients with inflammatory diseases [5].

Pharmacokinetic variability. Serum concentrations of TNFi vary considerably among patients, including undetectable levels. For example, among 86 patients with active rheumatoid arthritis (RA) in the ATTRACT trial who were allocated to receive infliximab 3 mg/kg every 8 weeks, 26% had undetectable serum trough concentrations at 54 weeks, suggesting that some patients require higher doses or a shorter interval between doses (e.g. 6 *vs* 8 weeks) [6].

Concentration-response relationship. The relationship between serum concentration and therapeutic response varies among patients. An assessment of response in 121 consecutive patients with RA treated with adalimumab for up to 28 weeks showed that good responders had significantly higher median serum adalimumab concentrations than moderate responders (p = 0.021) and non-responders (p = 0.001) [7]. Nevertheless, at the same concentration of adalimumab (e.g. 10 mg/L), all three levels of response (i.e. non, moderate, good) were observed, and good responses were observed at relatively low serum adalimumab concentrations (**Figure 1**). Serum concentration is thus an important, but not sole, determinant of response to therapeutic antibodies.

Narrow therapeutic range. Monoclonal antibodies have a narrow therapeutic range. Administering therapeutic antibody at a low concentration at treatment initiation increases the risk of developing immunogenicity, as demonstrated with infliximab in patients with RA or spondyloarthritis (SpA) [8,9]. Conversely, high concentrations of infliximab during treatment were found to correlate with a 2- to 3-fold

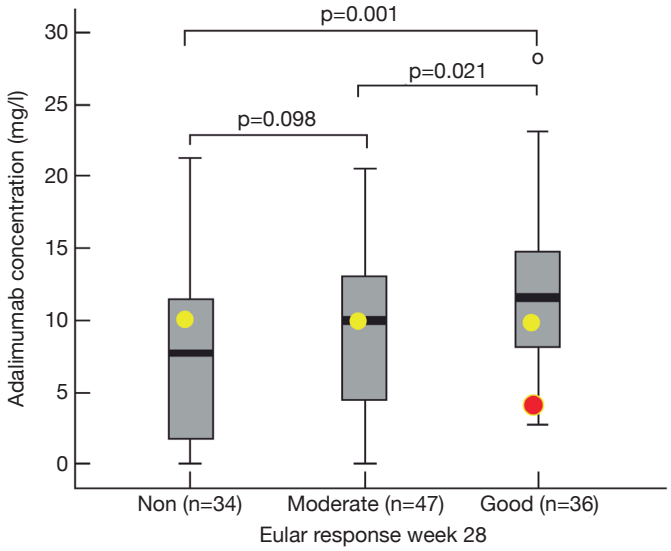

Figure 1. Serum adalimumab concentrations (mg/L) in non-responders, moderate responders, and good responders, according to European League Against Rheumatism (EULAR) response criteria at week 28 of treatment. All three levels of response were observed at the same adalimumab concentration (10 mg/L) (●). Good responses were observed at relatively low adalimumab concentrations (●). Adapted from [7].

greater risk of a first infection episode in patients with SpA [10] and a 1.5-fold greater risk of all infections in patients with RA [11].

INTEREST IN TDM OF MONOCLONAL ANTIBODIES IN INFLAMMATORY DISEASES

A primary reason for implementing TDM of therapeutic antibodies in inflammatory diseases is to improve the clinical response. Some years ago our group in Tours developed an algorithm to adapt the infliximab dose according to control of disease activity (optimal, acceptable, inadequate) and serum trough concentration (< 2.0, ≥ 2.0 to < 8.0, ≥ 8.0 µg/mL) (**Figure 2**). The algorithm was subsequently tested prospectively in patients with RA. Increasing the infliximab dosage, based on the serum trough concentration of the previous infusion, was associated with a 20% decrease in disease activity at the following two infusions as measured by the 28-joint disease activity score (DAS28) [12]. However, this was uncontrolled study in only 24 patients. Moreover, application of the algorithm in patients with SpA had no effect on control of disease activity as measured by the Bath Ankylosing Spondylitis Disease Activity Index [13].

Implementation of TDM is also expected to increase the cost-effectiveness of biologic therapy. A personalised treatment algorithm, which was developed from European League Against Rheumatism (EULAR) clinical responses and serum drug concentrations at 6 months in a cohort of 272 adalimumab-treated patients with RA, was used to determine whether adalimumab should be continued at a specific dose or discontinued or whether the patient should be switched to another biologic agent [14]. Outcomes were simulated using a patient-level Markov model, with 3 month cycles. Application of the algorithm resulted in greater treatment efficacy and lower treatment cost (**Figure 3**), leading the authors to conclude that tailoring biologic therapy using serum trough concentrations and short-term outcomes as guidance in individual patients with RA starting adalimumab is cost-effective. However, the study was limited by its retrospective design.

More recently, the same group from Amsterdam studied adalimumab concentrations prospectively in patients with RA [15]. Consecutive patients who had received adalimumab 40 mg every other week for at least 28 weeks were eligible for participation in this open label, randomised, parallel, non-inferiority

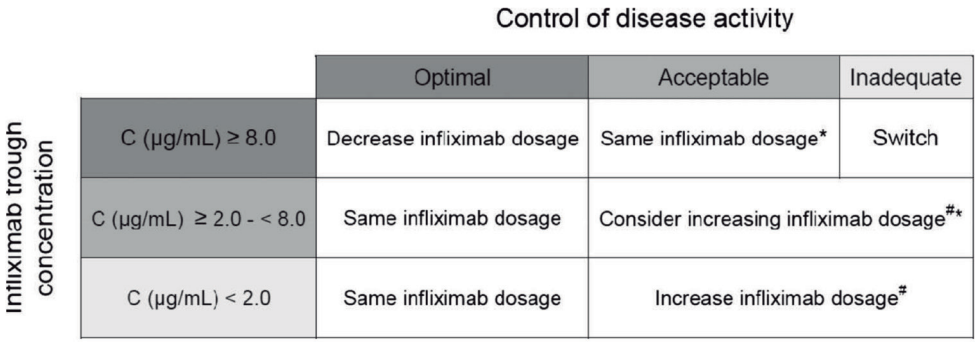

Figure 2. Algorithm to adapt infliximab dose according to control of disease activity and infliximab serum trough concentration in rheumatic diseases. Adapted from [12].

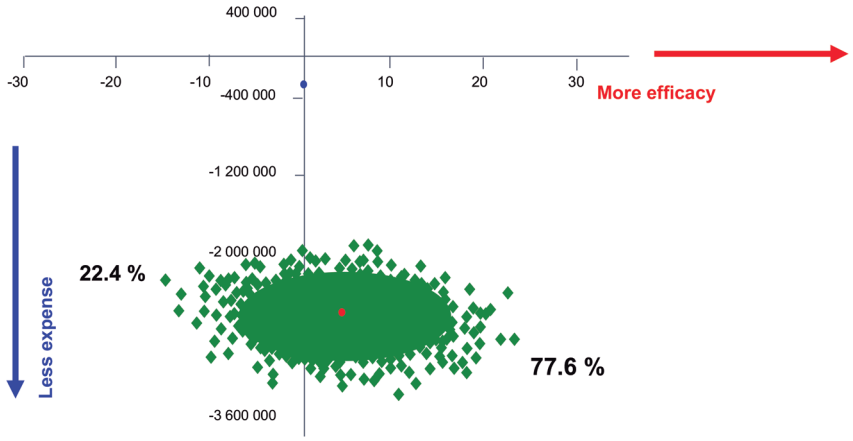

Figure 3. Application of a personalised treatment algorithm, developed from clinical responses and serum drug concentrations in patients with rheumatoid arthritis treated with adalimumab, resulted in greater treatment efficacy and lower treatment cost. Adapted from [14].

clinical trial. Of 147 patients screened, 55 patients with serum trough concentrations > 8 µg/mL were randomised to continuation of adalimumab 40 mg every 2 weeks (standard interval) or to dose prolongation of adalimumab 40 mg every 3 weeks (prolongation). Despite a significant decrease in the serum adalimumab trough concentration in the prolongation group, the mean change from baseline in the DAS28 did not differ statistically between groups. Thus, in adalimumab-treated patients with serum trough concentrations > 8 µg/mL, the dosing interval can be prolonged to once every 3 weeks without loss of disease control, suggesting potential for cost-savings, although larger-scale prospective randomised studies are required to confirm this supposition.

In a post hoc analysis of the SATRAPE study (ClinicalTrials.gov identifier: NCT00234234) [16], our group measured adalimumab concentrations in 127 blood samples taken from 30 patients with RA who had received adalimumab subcutaneously every other week [17]. Using a direct Emax inhibition pharmacokinetic-pharmacodynamic model to describe the concentration-response relationship, we studied the relationship between adalimumab concentrations and DAS28 results (141 in total) measured at baseline, 12, 24, and 52 weeks after the start of treatment. The estimated baseline DAS28 and concentration of adalimumab leading to a 50% decrease in the baseline DAS28 (adalimumab IC_{50}) were 5.7 and 11.8 mg/L, respectively. In other words, for an example patient with a baseline DAS28 of 5.7, a serum trough concentration of 11.8 mg/L would reduce the baseline DAS28 by 50% (**Figure 4**). Using these estimates, we could manipulate the equation to identify the target concentration of adalimumab required to decrease the baseline DAS28 to 3.2 (low disease activity) according to each individual's baseline disease activity. Whether this approach will inform the selection of individual target concentrations of adalimumab in patients with RA remains to be confirmed in larger studies.

CONCLUSION

Therapeutic antibodies are large, complex, immunogenic compounds that exhibit peculiar pharmacokinetics relative to small molecule drugs, and are

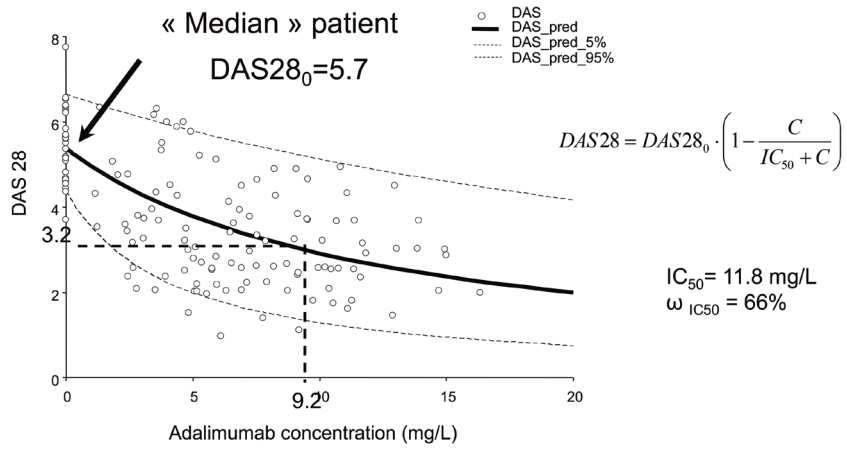

Figure 4. A direct Emax inhibition pharmacokinetic-pharmacodynamic model was used to describe the concentration-response relationship between adalimumab concentrations and the 28-joint disease activity score (DAS28). For an example patient with a baseline DAS28 of 5.7, a serum adalimumab trough concentration of 11.8 mg/L would reduce the baseline DAS28 by 50%. Adapted from [17].

expensive, underlying the need to implement TDM in rheumatic and other inflammatory diseases. As advances are made in understanding the implications of serum trough concentrations in individual patients, TDM might be expected to become 'standard of care' for patients receiving therapeutic antibodies. At present, more studies are needed to warrant implementing TDM in clinical practice.

DISCLOSURES

During the last 36 months DM has given lectures on behalf of his institution; received consultancy fees from Grifols, Novartis, and Pfizer; attended international congresses at the invite of Janssen-Cilag; and received research grants from the Lions Club Tours Val de France.

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Treat-to-target and patient management: how therapeutic drug monitoring can support clinical practice

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NATURAL HISTORY OF IBD

The term inflammatory bowel disease (IBD) encompasses two major chronic progressive conditions, Crohn's disease (CD) and ulcerative colitis (UC). Crohn's disease is characterised by inflammatory activity and digestive damage [1-3]. Along the disease course, most patients develop a stricturing or perforating complication [4]. As the natural history of CD varies widely among patients, and prognostic tools are limited, managing CD is a challenge for gastroenterologists. Selecting the optimal treatment for individual patients, while factoring in costs and potential adverse effects, is not a straightforward process.

During the evolution of CD from inflammation to strictures, the function of the intestinal tract becomes altered, resulting in a permanent symptom burden. The presence of symptoms due to fibrosis and scarring in the absence of a therapeutic target (e.g. inflammation) rules out a symptoms-based approach to determine disease activity. To minimize negative long-term outcomes in CD, it is necessary to intervene at the time of diagnosis and early disease. Current treatment recommendations advocate an early top down approach consisting of immunomodulators + biologics in individuals with high-risk disease prognosticators (e.g. young age onset disease, fistulising disease at first presentation, perianal disease, smoker). Biologics used to treat IBD include tumor necrosis factor (TNF) inhibitors (infliximab, adalimumab, golimumab), and anti-integrin (vedolizumab) and anti IL12/23 (ustekinumab) agents.

CHALLENGES IN ANTI-TNF-BASED TREATMENT OF IBD

Improved outcomes with anti-TNF-based treatment in patients with IBD are counterbalanced by the high incidence of biologic failures. About one-third of patients treated with TNF inhibitors (TNFi) exhibit primary non-response (failure to respond to induction therapy) at 3 to 4 months. Among treatment responders, around 40% will experience secondary loss of response (defined by the need to intensify the TNFi dose) at 12 months [5].

TNFi drug failures are either mechanistic or pharmacokinetic in nature. Mechanistic failures occur when TNF is not a major mediator of the inflammatory process. As CD evolves, TNF can become a less important mediator of inflammation; whether this occurs at the outset of disease in some patients is uncertain. Pharmacokinetic failures are either drug- or patient-related. In terms of drug-related factors, the molecular structure of monoclonal antibodies and their mode of delivery confer immunogenicity risk and drive the formation of anti-drug antibodies (ADAbs). However, most failures of TNFi occur due to patient-related factors which increase drug clearance and lead to prolonged periods of low/underdosed drug. High disease activity increases the rate of drug utilisation ('inflammatory sink') and drug loss (e.g. through an inflamed and leaky gut). Other

patient factors that influence drug utilisation are obesity, low serum albumin concentration, smoking, and immunomodulator treatment.

Using the same dose of TNFi in all patients with IBD irrespective of their individual clinical characteristics has no sound rationale. Conversely, personalizing the TNFi dose through therapeutic drug monitoring (TDM), especially during induction therapy, may reduce the incidence of primary non-response and secondary loss of response.

TDM KEY CONCEPTS

TDM is based on the existence of a relationship between drug concentration (pharmacokinetics) and clinical effect (pharmacodynamics) [6]. Individualising the drug dosage to maintain plasma concentrations within a targeted therapeutic range can improve therapeutic effectiveness.

TDM is particularly important in gastroenterology due to the limited armamentarium of biologic agents relative to other therapeutic areas (e.g. rheumatology); maximizing the efficacy of available treatments is therefore essential. As the likelihood of a treatment response is limited after the first biologic failure, it is necessary to invest time and resource to ensure that patients initiating biologic treatment gain maximum benefit. However, many challenges exist. Given that many symptoms in CD are driven by fibrosis and scarring, robust objective disease activity scores are lacking. Patient-reported outcome measures are also lacking. Many patients with CD have ongoing inflammation that, even if not causing symptoms, presents a high inflammatory burden radiologically. Recognising this situation and treating the patient appropriately is challenging. Since the pharmacokinetic variability of biologics is greater in IBD than in other inflammatory diseases, a current research focus is to identify biomarker-based treat-to-target strategies.

WHAT'S THE EVIDENCE THAT SERUM DRUG CONCENTRATIONS INFLUENCE CLINICAL OUTCOMES?

Several studies have provided evidence that serum TNFi concentrations influence clinical outcomes in patients with IBD.

A post hoc analysis of the key pivotal studies ACT-1 and ACT-2 in patients with UC examined the association between serum infliximab concentrations and the proportions of patients treated with 5 mg/kg who achieved efficacy outcomes according to serum infliximab concentration quartiles at induction week 8, and maintenance weeks 30 and 54 [7]. Infliximab concentrations of 41 μg/mL at week 8 and 3.7 μg/mL at steady-state were associated with optimal outcomes. Interestingly, at week 54 of maintenance therapy, the fourth quartile of infliximab concentration (≥ 8.1 μg/mL) was associated with less benefit than the third quartile (3.6 to < 8.1 μg/mL) in terms of clinical response, mucosal healing and clinical remission (**Figure 1**). Major differences in target concentrations of infliximab during induction and maintenance therapy, and relatively narrow therapeutic window during maintenance therapy, emphasize the importance of TDM.

An early TDM study in a consecutive cohort of patients with moderate-to-severe refractory inflammatory and/or perianal fistulising CD examined clinical outcomes after scheduled maintenance therapy beyond 52 weeks according to the presence or absence of a detectable serum infliximab trough concentration [8]. Ninety patients were followed

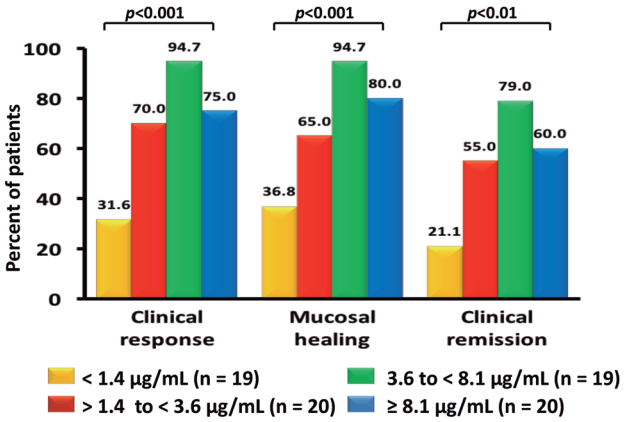

Figure 1. Proportion of patients with ulcerative colitis achieving efficacy endpoints at maintenance week 54 according to serum infliximab trough concentration quartiles. Data from [7].

for more than 12 months and median follow up was 23 months. A detectable serum infliximab trough concentration was associated with better outcomes in terms of remission rate (82 *vs* 6%; p < 0.001), C-reactive protein (CRP) concentration (2.0 *vs* 11.8 µg/mL; p < 0.001), and proportion of patients with endoscopic improvement > 75% (88 *vs* 33%; p < 0.001). In this same study, the induction protocol was infliximab 5 mg/kg intravenously at 0, 2, and 6 weeks for fistulising disease and either 3-dose induction or a single infusion of infliximab 5 mg/kg for inflammatory disease. Following induction, 82 patients received infliximab 5 mg/kg at regularly scheduled intervals of 6, 7, or 8 weeks, and 23 patients received infliximab at the time of disease relapse. Serum infliximab trough concentrations and anti-infliximab antibodies were measured. After a median of 14 infusions, 21% of patients had detectable antibodies, 25% were negative for antibodies, and results were inconclusive in 54%. Antibody development was more common after episodic versus scheduled treatment (39 *vs* 16%; p = 0.036) and was associated with a higher frequency of infusion reactions (50 *vs* 21%; p = 0.018). Antibody formation was associated with lower serum infliximab trough concentrations.

A multi-centre retrospective cohort study which investigated the association of serum trough concentrations with outcomes in patients with UC during infliximab maintenance therapy found high rates of endoscopic (Mayo endoscopic subscore of ≤ 1) and histologic (no or only focal mild active inflammation) healing at infliximab trough concentrations of > 12 µg/mL [9]. Elsewhere, a group examined whether optimizing serum concentrations of TNFi would improve mucosal healing in patients with IBD [10]. This cross-sectional study involved patients treated with infliximab (n = 78) or adalimumab (n = 67) at a single centre from 2009 through 2014. Retrospective data from colonoscopy examinations indicated a significant association between higher serum TNFi trough concentrations and mucosal healing (simple endoscopic score of < 3 or Mayo score of ≤ 1). The authors proposed that serum concentrations of 6–10 µg/mL for infliximab and 8–12 µg/mL for adalimumab are necessary to achieve mucosal healing in 80%–90% of patients with IBD (**Figure 2**).

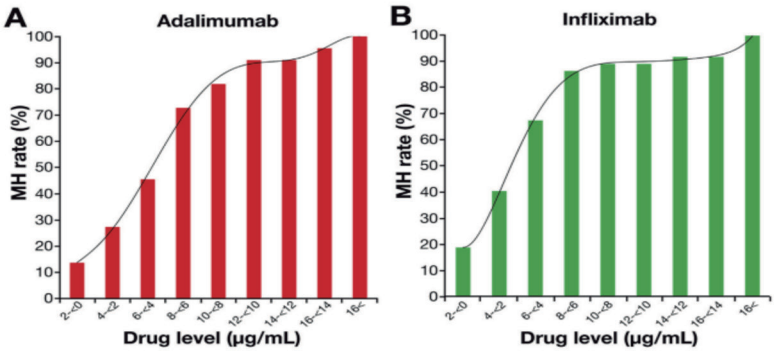

Figure 2. Mucosal healing (MH) rate according to serum concentrations of (A) infliximab (n = 67) and (B) adalimumab (n = 78) in patients with inflammatory bowel diseases. Data from [10].

USE OF TDM IN ROUTINE CLINICAL PRACTICE

The two main TDM strategies are reactive and proactive [11]. Reactive strategies are appropriate to assess partial response and secondary loss of response, whereas pro-active strategies are intended to guide decisions about dose intensification/dose de-escalation/drug withdrawal in order to prevent primary non-response and secondary loss of response.

Reactive TDM

In patients with disease relapse, measuring serum TNFi trough concentrations and ADAbs (i.e. reactive TDM) can guide treatment decisions, as demonstrated in a retrospective study involving paediatric and adult patients with IBD and suspected loss of response to infliximab or adalimumab [12]. A low serum TNFi trough concentration and no ADAbs should prompt the clinician to consider a dose increase. In the event of a low serum TNFi trough concentration and low ADAbs, options are dose intensification (increase dose or shorten dosing interval) and possibly adding immunomodulators. A low serum TNFi trough concentration and ADAb positivity indicates immunogenicity; in this scenario the only option is to switch to another TNFi (or a biologic with a different mechanism of action). The presence of therapeutic serum TNFi trough concentrations without ADAbs points to a mechanistic failure of therapy. As TNF is no longer driving the inflammatory process, an out-of-class switch is superior to attempting dose optimisation or a within-class switch. The algorithm for reactive TDM of TNFi used by NHS Scotland, which is based on an algorithm published originally in *Frontline Gastroenterology* [5], is shown in **Figure 3** although similar iterations are available in gastroenterology services worldwide.

Proactive TDM

Currently there is a move towards proactive TDM with the aim of preventing primary non-response and secondary loss of response through dose intensification/dose de-escalation/drug withdrawal based on serum TFNi trough concentrations. Evidence is accumulating to show the importance of aggressive induction therapy and personalising TNFi doses.

A prospective single-centre study performed in patients with IBD who started treatment with

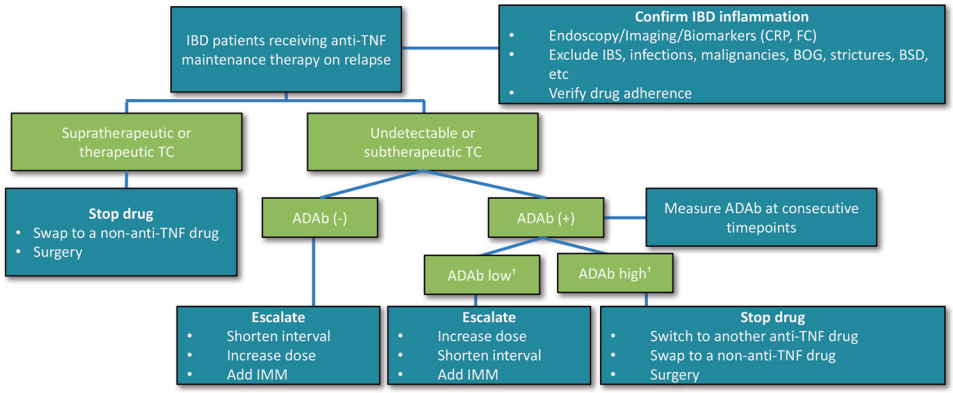

Figure 3. Reactive anti-TNF therapeutic drug monitoring algorithm of NHS Scotland. Modified from [5].
†Titre depends on the assay used: > 8 Qg/mL-eq for ELISA and > 9.1 U/mL for HMSA.
ADAb, anti-drug antibody; BOG, bacterial overgrowth; BSD, bile salt diarrhoea; CRP, C-reactive protein; eq, equivalent; FC, faecal calprotectin; HMSA, homogeneous mobility shift assay; IMM, immunomodulators; TC, trough concentrations; TDM, therapeutic drug monitoring; TNF, tumour necrosis factor.

infliximab (n = 17) or adalimumab (n = 18) showed that trough concentrations after induction were predictive of treatment response [13]. Response rates were 70.6% for infliximab and 33.3% for adalimumab. The mean infliximab trough concentration after induction was significantly higher in responders than non-responders (16.4 *vs* 5.3 µg/mL; p = 0.026), and the area under the curve for the association of trough concentrations with clinical response was 0.864 (p = 0.0001). A similar association was observed between adalimumab concentration after induction and response or no response (6.6 *vs* 3.0 µg/mL), although the difference was not statistically significant. Overall, investigators found that higher TNFi trough concentrations at week 4 increased the chances of a primary response, reduced the risk of developing ADAbs, and increased the chance of a sustained response during maintenance treatment.

A study which examined the influence of early serum adalimumab concentrations on immunogenicity and long-term outcomes in patients with CD highlighted the importance of early TDM to guide dose optimisation [14]. Among 116 patients with moderate CD, those with serum concentrations of < 8.3 µg/mL at week 4 were significantly more likely to be ADAb positive by week 12 than those with concentrations of ≥ 8.3 µg/mL (46.7 *vs* 13.0%, p = 0.009). Patients positive for anti-adalimumab antibodies by week 12 had greater need for dose escalation (p < 0.001) and higher rates of primary non-response or secondary loss of response (p = 0.02). Early monitoring of adalimumab serum concentrations, and dose optimisation, may prevent immunogenicity and influence long-term outcomes.

Drug concentrations during maintenance treatment have also been shown to correlate with clinical outcomes. Plevris and colleagues examined 160 CD patients treated with adalimumab for at least 12 weeks after induction [15]. Adalimumab trough concentrations of > 8.5 µg/mL were independently associated with biological remission (odds ratio [OR] 5.27; 95% CI: 2,43-11.44; p < 0.0001). Higher adalimumab concentrations were also associated with normalisation

of CRP ($p < 0.0001$), faecal calprotectin (FC; $p = 0.004$), and achievement of biochemical remission (CRP < 5 mg/L + FC < 200 mg/g; $p < 0.0001$) and deep remission (Harvey-Bradshaw Index < 5 + CRP < 5 mg/L + FC < 200 mg/g; $p < 0.0001$) [16]. Another group reported similar findings [17]. In patients with CD, adalimumab trough concentrations of ≥ 12 µg/mL (OR 8; 95% CI 2–31.9; $p = 0.003$) and ≥ 12.2 µg/mL (OR 9.6; 95% CI 1.7–56.1; $p = 0.012$) during maintenance therapy were independently associated with endoscopic and histologic remission, respectively. In patients with UC, an adalimumab trough concentration threshold of 10.5, 16.2, and 16.2 µg/mL was able to stratify patients with or without biochemical, endoscopic, or histologic remission, respectively.

Given that most supporting evidence for dose intensification/dose de-escalation/drug withdrawal of TNFi therapy is retrospective, TAXIT (Trough level Adapted infliXImab Treatment) is a landmark study as it was the first to show prospectively that serum infliximab trough concentrations can guide dosing in patients with IBD [18]. This randomised controlled trial involved 263 patients with IBD who were either full or partial responders to maintenance infliximab. At the start of the trial, all patients were dose optimised, meaning that their infliximab dose was adjusted to a trough concentration of 3–7 µg/mL before randomisation to maintenance therapy. Investigators examined the difference in outcomes between clinically-based (n = 123) and trough-based (n = 128) dosing. Among 76 patients with infliximab trough concentrations of < 3 µg/mL, 69 (91%) achieved a concentration of 3–7 µg/mL after dose escalation during the optimisation phase, resulting in a significant decrease in median CRP (3.2 *vs* 4.3; $p < 0.001$). Eight of 12 patients with detectable ADAbs were successfully dose escalated. Among 72 patients with infliximab trough concentrations of > 7 µg/mL, 67 (93%) achieved a concentration of 3–7 µg/mL after dose reduction during the optimisation phase, resulting in a 28% reduction in drug cost. However, clinical remission at 12 months (primary endpoint) did not differ between clinically-based and concentration-based dosing. The study's strength in terms of optimising infliximab doses in patients prior to randomisation is, in fact, also its weakness. As a consequence, the follow-up period was too short to show a difference between groups. Kaplan-Meier curves for relapse-free survival during maintenance therapy began to show separation at about 26 weeks. Extension of outcomes evaluation to 104 weeks is likely to have shown a clear separation between groups in favour of concentration-based dosing.

Proactive vs. reactive TDM

A multicentre, retrospective study attempted to determine which TDM approach (reactive or proactive) was associated with better outcomes in patients with IBD receiving infliximab maintenance therapy [19]. Patients underwent reactive (n = 134) or proactive (n = 130) drug monitoring, which was based on measurements of first infliximab concentration and anti-infliximab antibodies. Over 5 years' follow-up, proactive monitoring was associated with greater drug durability, less need for IBD-related surgery or hospitalisation, and lower risk of anti-infliximab antibodies or serious infusion reactions. However, methodological flaws in terms of higher rates of dose escalation and pre-existing ADAbs in the group randomised to reactive TDM may have contributed to overstating the benefits of a proactive approach.

NHS Scotland has also implemented a proactive TDM algorithm (**Figure 4**) [20-22], which again is

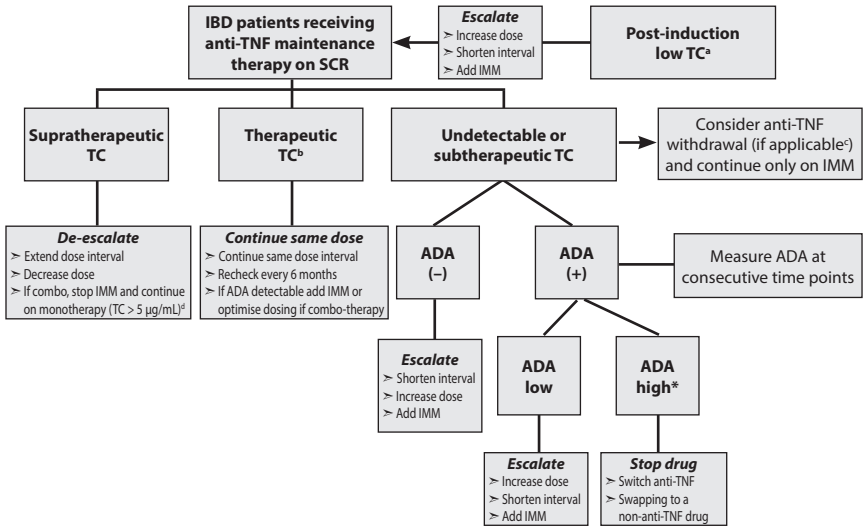

Figure 4. Proactive anti-TNF therapeutic drug monitoring algorithm of NHS Scotland [20]. Modified from [5].
a. Consider testing trough concentration and ADAbs early (from week 4) in non-responders to induction treatment.
b. For suggested values refer to guidance document.
c. Stable remission with undetectable / low trough concentration considered low risk for relapse after anti-TNF withdrawal. Advise check faecal calprotectin, CRP if considering drug withdrawal/holiday.
d. Based on data from [21,22].
e. For ADAb titre values refer to guidance document.
ADAb, anti-drug antibody; IBD, inflammatory bowel disease; IMM, immunomodulators; SCR, sustained clinical remission; TC, trough concentration; TDM, therapeutic drug monitoring; TNF, tumour necrosis factor.

based on an algorithm published originally in *Frontline Gastroenterology* [5].

WHAT DO GUIDELINES RECOMMEND FOR TDM IN CLINICAL PRACTICE?

Guidelines published in 2017 by the American Gastroenterological Association Institute [23] and IBD Sydney Organisation and Australian Inflammatory Bowel Diseases Consensus Working Group [24] provide a useful overview and appraisal of the available evidence, as well as recommendations for TDM of therapeutic antibodies in patients with IBD. It is noteworthy that both groups advocate reactive TDM as part of standard care of patients with IBD, although they qualify this stance by explaining that additional evidence is required to justify implementing a proactive TDM strategy in routine care. My personal approach to selecting a strategy to monitor TNFi in patients with IBD is summarised in **Box 1**.

UNDERSTANDING TREAT-TO-TARGET

In the biologic era, treatment goals have been evolving steadily from clinically-based outcomes to objective markers of mucosal healing (**Box 2**) [25]. Currently, demonstrating mucosal healing requires an invasive procedure such as colonoscopy or magnetic resonance imaging. In future, a shift is anticipated towards deep remission (histological remission) as the treatment goal, with use of

Box 1. Personal recommendations for TDM of TNFi in patients with IBD.

Approach	Infliximab	Adalimumab
Reactive	Primary non response Loss of response/flare	Primary non response Loss of response/flare
Proactive	Early induction? (week 2-4 or earlier) End of induction (usually week 14) Maintenance treatment – every 16-24 weeks (usually every 2-3 doses) Following dose adjustment	Early induction? (week 4) End of induction (usually week 14) Maintenance treatment – every 12-24 weeks Following dose adjustment

IBD, inflammatory bowel disease; TDM, therapeutic drug monitoring; TNFi, tumour necrosis factor inhibitor.

non-invasive biological markers in order to avoid subjecting patients to invasive procedures on a regular basis.

Treat-to-target can be described as a collaborative (including the patient) disease management strategy which aims beyond symptom resolution to address underlying inflammation and improve patients' quality of life [26]. The strategy has five distinct steps:

- Assess risk factors
- Set appropriate target/s
- Treat in a timely manner
- Monitor regularly
- Optimise therapy as necessary

The treat-to-target approach is already established in chronic inflammatory diseases other than IBD, with well-defined treatment targets of remission/low disease activity in rheumatoid arthritis (RA) [27,28]; body surface area, psoriasis area severity index, physician global assessment, and dermatology life quality index in psoriasis [29-31]; and remission/low disease activity in psoriatic arthritis [32,33].

More than a decade ago, the TICORA study demonstrated the value of tight control of disease activity in patients with RA [34]. This randomised controlled trial allocated patients with active disease to intensive management or routine care for 18 months. Patients under intensive management (n = 55) had a clinical visit each month; if their disease activity score was > 2.4, therapy was escalated as per protocol. Patients under routine care (n = 55) had a clinic visit every 3 months with no calculation of their disease activity score; if a patient was symptomatic, therapy was

Box 2. Treatment goals in inflammatory bowel disease. Adapted from [25].

Clinical	Mucosal healing	The future
Sustain remission Reduce corticosteroid use	Corticosteroid-free remission Decrease hospitalisations Decrease surgery Improve quality of life	Deep remission Reduce and prevent intestinal damage Reduce and prevent disability

escalated at the investigator's discretion. Compared with routine care, intensive management reduced disease activity and radiographic disease progression, and improved physical function and quality of life, at no additional treatment cost.

The gastroenterology community has a long history of learning from rheumatology and dermatology services which strategies can best be incorporated into daily practice. An organisation called STRIDE (Selecting Therapeutic Targets in IBD) has proposed several targets and "treatment ambitions' as a means of generating discussion within the community about appropriate treat-to-target endpoints to apply in CD (**Box 3**) [35]. These endpoints are currently proposals and are not yet agreed.

The randomised controlled phase III CALM study has provided the first prospective evidence of the value of a treat-to-target approach in IBD [36]. In this multicentre open-label study, patients (n = 244) with moderate-to-severe CD were randomised to tight control of disease activity which involved optimisation of TNFi based on biomarkers (CRP, FC), corticosteroid use and clinical symptoms (measured with Crohn's Disease Activity Index [CDAI]); or to clinical management which involved optimisation of TNFi based on corticosteroid use and clinical symptoms (CDAI) alone. At 48 weeks after randomisation, a significantly higher proportion of patients under tight control achieved the primary endpoint of mucosal healing (Crohn's Disease Endoscopic Index of Severity < 4) with absence of deep ulcers compared to patients receiving clinical management (45.9 *vs* 30.3%; p = 0.010). Subsequent analyses of the CALM study results have reported significant improvements with tight control versus clinical management in quality of life measures [37] and long-term cost effectiveness [38]. Nevertheless, expressed in opposite terms, the CALM results indicate that 54% and 70% of patients under tight control or clinical management, respectively, did not achieve mucosal healing. Thus, if treat-to-target is to lead the way in patient care, strategies must be developed to improve clinical outcomes in a greater proportion of patients.

A notable omission from the CALM study methodology was a role for TDM. Serum concentrations

Box 3. Proposed target recommendations for Crohn's disease: treat beyond symptoms* [35].

Clinical/PRO remission	Endoscopic remission:
Resolution of abdominal pain and normalisation of bowel habit Assess at least every 3 months during active disease	Resolution of ulceration Assess at 6–9 month intervals during the active phase
Biomarkers: CRP and FC are adjunctive measures of inflammation for monitoring CD (not targets). Failure of CRP or FC normalisation should prompt further endoscopic evaluation, irrespective of symptoms.	

*Symptoms resolution alone is not a sufficient target; objective evidence of inflammation of the bowel is necessary when making clinical decisions.

CD, Crohn's disease; CRP, C-reactive protein; FC, faecal calprotectin; PRO, patient-reported outcome.

of biologic agents are a useful biomarker for treat-to-target strategies in the wake of evidence demonstrating that monitoring TNFi trough concentrations can assist in achieving clinical response, clinical remission, biochemical remission, endoscopic remission, and mucosal healing. Irrespective of which outcome is ultimately selected as the target in IBD, TDM of TNFi concentrations can help achieve the treatment goal.

LOOKING AHEAD IN IBD MANAGEMENT

Gastroenterologists are increasingly aware of the window of opportunity for timely intervention in patients with CD before development of complications and bowel damage (**Figure 5**) [2,3]. A current research focus is to develop algorithms to stratify patients by disease severity much earlier in the disease course, facilitating early intervention to prevent recurrent flares and change the natural history of the disease. The next step in IBD management is to develop practical treat-to-target algorithms incorporating TDM which engage the patient, assess and stratify risk, identify the therapeutic target, and build in timely and cyclical assessment of disease activity. To maximize benefit for more patients, a treat-to-target approach in IBD must include a role for TDM which targets appropriate TNFi concentrations during induction and maintenance therapy, acknowledges different trough targets in different scenarios/diseases, and incorporates clear steps for treatment optimisation based on drug concentration testing coupled with patient-reported outcomes and non-invasive tests. Future developments for TDM include point-of-care testing of drug concentrations, TDM-based pharmacokinetic models, improved assays (wider concentration ranges), standardised approach to antibody testing, and TDM-based personalised dosing in induction and maintenance.

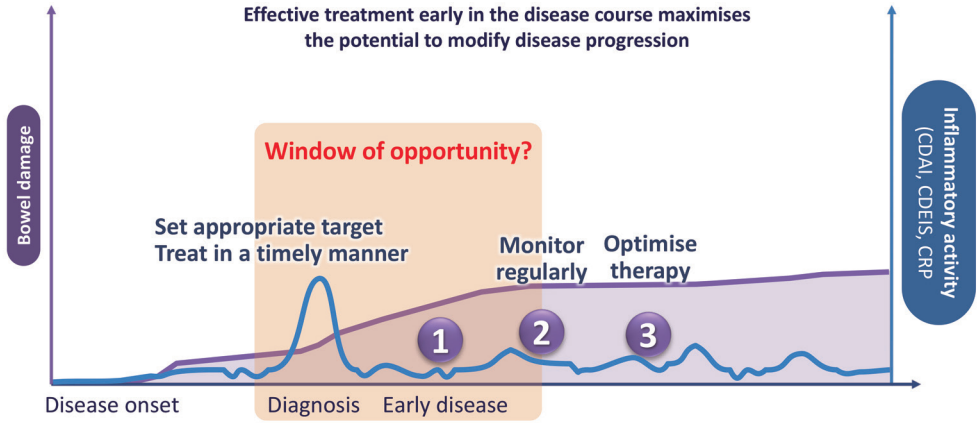

Figure 5. Window of opportunity for timely intervention in Crohn's disease before development of complications and bowel damage. Incorporating treat-to-target principals and therapeutic drug monitoring has the potential to slow disease progression and prevent damage. Adapted from [2,3].
CDAI, Crohn's disease activity index; CDEIS, Crohn's disease endoscopic index of severity; CRP, C-reactive pro

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Interchangeability in regard to immunogenicity between reference biologics and biosimilars

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INTRODUCTION

Biosimilars are an integral component of the therapeutic armamentarium to treat chronic inflammatory diseases such as inflammatory bowel disease (IBD). A biosimilar is a copy of an original (reference) biologic medicine with an expired patent. It is comparable in quality, safety and efficacy to the existing biologic medicine, but it is not a clone. The molecular complexity, method of manufacture, and testing and registration process of biosimilars means that they cannot be regarded as 'generics' [1].

Biosimilars are registered in the European Union (EU) by the European Medicines Agency (EMA), and in the United States (US) by the Food & Drug Administration (FDA) [2-4]. The first biosimilar monoclonal antibody to gain approval in the EU was biosimilar infliximab in 2013, followed by biosimilar adalimumab in 2016 (**Table 1**). Many other biosimilars are expected to follow in upcoming years.

The concept of biosimilarity has four main components: identity, safety, potency, and purity. The EMA and FDA are in full agreement with respect to the characteristics of biosimilars; specifically, that a single change in the primary amino acid sequence relative to the originator molecule denies biosimilarity; that the potency of the biosimilar must match that of the reference product; that the route of administration of the biosimilar must be the same as the reference product; and that higher-order structures, post-translational modifications and other potential variants "must be as similar as possible to the reference product with adequate analyses performed to demonstrate that any differences do not impact on clinical efficacy, safety, immunogenicity" [5].

Table 1. Status of biosimilars for inflammatory bowel disease.

Biosimilars for infliximab	Biosimilars for adalimumab
European Union	
Inflectra® (CT-P13): authorised 10 September 2013 Remsima® (CT-P13): authorised 10 September 2013 Flixabi® (SB2): authorised 26 May 2016	Amgevita® (ABP501): authorised 22 March 2017 Solymbic® (ABP501): authorised 22 March 2017 Imraldi® (SB5): authorised 24 August 2017
United States	
Inflectra® (CT-P13) [infliximab-dyyb]: approved by FDA in April 2016; available since November 2016 Renflexis® (SB2) [infliximab-abda]: approved by FDA in April 2017; available autumn 2017	Amjevita® (ABP 501): approved by FDA in September 2016 but not marketed as of April 2017

Conversely, the agencies differ to some extent with regard to methodological requirements for studies designed to demonstrate bioequivalence in pharmacokinetics, pharmacodynamics, efficacy, safety and immunogenicity [5].

Biologic medicines in general have the potential to be recognised as 'foreign' by the body and, as such, can cause unwanted immune reactions. Their composition and large molecular size confer risk for immunogenicity which exists for all biologic medicines, not biosimilars alone. Antidrug antibodies (ADAbs) can develop against monoclonal antibodies (infliximab, adalimumab) used to treat inflammatory diseases. ADAbs interfere with tumour necrosis factor inhibitor (TNFi) treatment by decreasing the functional concentration of the biologic agent (neutralising ADAbs); by forming immune complexes which increase drug clearance leading to loss of response; by inducing an infusion reaction or allergic reaction at the infusion site.

Clinical studies of immunogenicity are performed before and after approval of biosimilars. Post-marketing follow-up of biosimilars over 10 years has indicated safety profiles comparable to those of reference biologics [6].

INTERCHANGEABILITY OF REFERENCE BIOLOGIC AND BIOSIMILARS

The term interchangeability refers to the possibility of exchanging one medicine for another medicine expected to have the same clinical effect. In practice, this can mean replacing a reference product with a biosimilar (and vice versa) or replacing a biosimilar with another biosimilar. Replacement can be achieved by *switching* which describes a prescriber's decision to exchange one medicine for another medicine with the same therapeutic intent, or by *substitution* which describes the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber. Clinical scenarios that may prompt a decision to switch biologics are outlined in **Box 1**.

In 2017, the European Crohn's and Colitis Organization (ECCO) published an updated position statement on the use of biosimilars in IBD [7]. In terms of interchangeability, statements 5 and 7 are most relevant:

> Statement 5: "Adverse events and loss of response due to immunogenicity to a biologic drug cannot

Box 1. Clinical scenarios for switching biologics.

New start	Prescriber choice of reference product or biosimilar
Primary non-responder	Prescriber elects to switch to biosimilar Prescriber elects to switch to another biologic
Stabilized responder	Prescriber elects to maintain original biologic or to switch to a biosimilar
Loss of response	If attributed to high-titre ADAbs, a switch to a biosimilar should not be considered Prescriber elects to switch to another therapy

ADAbs, antidrug antibodies.

be expected to be overcome with a biosimilar of the same molecule".

Statement 7: "Switching from the originator to a biosimilar in patients with IBD is acceptable. Studies of switching can provide valuable evidence for safety and efficacy. Scientific and clinical evidence is lacking regarding reverse switching, multiple switching, and cross-switching among biosimilars in IBD patients".

The fact that originator drug and biosimilars are recognised as having similar immunogenicity validates the need to perform therapeutic drug monitoring (TDM) in patients treated with a biosimilar before and after switching to avoid loss of response or to change to a biosimilar with a different mechanism of action. TDM is the "clinical practice of measuring specific drugs at designated intervals to maintain a constant concentration in a patient's bloodstream, thereby optimizing individual dosage regimens" [8].

CLINICAL UTILITY OF TDM DURING SWITCHING

New information has recently become available about switching of infliximab in patients with IBD [9]. In the absence of cross-reactivity data between reference infliximab and biosimilars CT-P13 and SB2, prescribers had uncertainty about switching. To address these concerns, a study was performed to examine whether anti-infliximab antibodies to different infliximab products would cross-react. Sera samples were obtained from IBD patients participating in the BIOSIM01 study who were treated with reference infliximab (n = 13), CT-P13 (n = 9), or originator infliximab followed by a switch to CT-P13 (n = 12). A bridging enzyme-linked immunosorbent assay (ELISA; Promonitor-ANTI-IFX, Progenika-Grifols, Spain) was used to detect antibodies to infliximab in sera samples. This assay exploits the bivalency of immunoglobulin subclasses 1, 2, and 3 to crosslink intact infliximab molecules used as capture (coated on the plate) and detection (conjugated to horseradish peroxidase) reagents. Infliximab trough concentrations were measured in parallel using a capture ELISA assay (Promonitor-IFX, Progenika-Grifols, Spain) at three different settings for the three products. Identical cross-reactivity was observed among products (**Table 2**), supporting full interchangeability between reference infliximab, CT-P13, and SB2 (and between CT-P13 and SB2) with regard to immunogenicity. The *in vitro* cross-reactivity results were supported by similarities among products with respect to clinical outcomes (loss of response, infusion reactions) and antibody titres. However, as this was a short-term study, long-term follow-up of the effects of switching on clinical outcomes is required.

Knowledge of a patient's anti-infliximab antibody titre raises numerous clinical questions: What is the meaning of a high or low titre? Is it an indication to stop therapy? Optimize therapy? Add an immunomodulator? What is the meaning of a high or low anti-infliximab antibody titre relative to the serum infliximab trough concentration? Does switching have a boosting effect or a washing-out effect on anti-infliximab antibody titres?

Some of these questions already have answers. Since achieving and maintaining a response to infliximab requires either no or low anti-infliximab antibody titres and high or medium-high serum infliximab trough concentrations [10], both concentrations must be measured to inform treatment decisions.

Table 2. Cross-reactivity results for antibodies to infliximab. Adapted from [9].

Patient group (no. of samples)		Assay		
		Assay #1 (reference infliximab)	Assay # 2 (CT-P13)	Assay #3 (SB2)
Reference infliximab (60)	Samples positive for ATI, n	30	30	30
	Median ATI level (AU/mL)	190	216	240
CT-P13 (28)	Samples positive for ATI, n	14	14	14
	Median ATI level (AU/mL)	90	103	116
Reference infliximab, switch to CT-P13 (64)	Samples positive for ATI, n	32	32	32
	Median ATI level (AU/mL)	203	216	228

ATI, antibodies to infliximab.

Because antibodies to infliximab can still be detected in patients at least 1 year after treatment discontinuation [9], testing must be conducted before and after a switch. Unresolved issues with use of infliximab in IBD include, among others, the relationship between anti-infliximab antibody titres and serum infliximab trough concentrations, any potential boosting effect of switching in patients with low anti-infliximab antibody titres, infusion reactions on switching, optimal duration of drug treatment, serial measurements before and after switching, and the effect of combination therapy (e.g. azathioprine, methotrexate) on anti-infliximab antibody development.

The clinical utility of TDM when switching is thus to confirm the absence of ADAbs to originator/biosimilar product before switching and to monitor for ADAbs after switching [11]:

- When switching between biologics (originator product to biosimilar)
- During reverse switching (biosimilar to its originator)
- During cross-switching (switching between two biosimilars).

CHANGING ATTITUDES OF GASTROENTEROLOGISTS' TOWARDS BIOSIMILARS

The attitudes and beliefs of gastroenterologists towards biosimilars have undergone a major shift as illustrated by ECCO surveys conducted in 2013 and again in 2015 [12]. Of note, substantial decreases were observed in the proportion of gastroenterologists who believed that biosimilars act differently from, or exhibit a different immunogenicity pattern than, reference product. In parallel, substantial increases were observed in the proportion of gastroenterologists who reported being totally confident (28.8 *vs* 5.0%) or very confident (17.8 *vs* 7.6%) using biosimilars. Thus, education, and accumulating clinical trial evidence about biosimilars, altered gastroenterologists' perceptions markedly in a short time frame. Even greater acceptance of biosimilars might be expected if the survey were to be repeated today.

CONCLUSIONS

TDM represents genuine and tangible progress in the management of patients with chronic inflammatory diseases such as IBD. Knowledge of ADAbs titres and serum TNFi trough concentrations informs decision making during induction and maintenance therapy and resolves many clinical dilemmas. The strong link between treatment optimisation early in the disease course and better patient outcomes underscores the importance of 'getting things right from the start'. To gain full advantage of the benefits of TDM, standardized methodology for measurement frequency during induction and maintenance therapy is required, and optimal cut-off points must be identified. Guidelines and clinical practice points are urgently required for all specialities, not only gastroenterology. Implementing TDM of biologic therapies into routine practice offers opportunity to optimize treatment and generate cost-savings.

Key messages about TDM when switching from reference product to biosimilar include the following:

- TDM must be performed before and after switching to a biosimilar to avoid loss of response or to change to a biosimilar with a different mechanism of action.
- ELISA assays (e.g. Promonitor) are able to detect equally ADAbs of originator product and its biosimilars.
- TDM provides a safe guide to rapid treatment optimisation during switching by enhancing the probability of a treatment response.
- TDM clarifies relative efficacy and safety when switching between different therapies with the same mechanism of action and between therapies with different mechanisms of action.
- TDM drives quick and safe decisions in the field of IBD therapeutics.

CONFLICT OF INTEREST

KHK has received honoraria for consulting services including educational services, scientific articles, participation in advisory boards and clinical trials from AbbVie, Aenorasis, Ferring, Genesis, Grifols, Janssen, MSD, Shire and Takeda.

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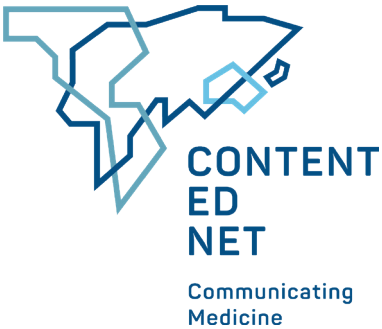

III Challenges in therapeutic drug monitoring

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