SYMPOSIUM

I CHALLENGES IN THERAPEUTIC DRUG MONITORING

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I CHALLENGES IN THERAPEUTIC DRUG MONITORING

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Therapeutic Drug Monitoring in Rheumatology

PAOLA MIGLIORINI
CLINICAL IMMUNOLOGY AND ALLERGY UNIT, DEPARTMENT OF CLINICAL AND EXPERIMENTAL MEDICINE, UNIVERSITY OF PISA, PISA, ITALY

INTRODUCTION

Biological agents, either monoclonal antibodies or fusion proteins designed to target cytokines or cytokine receptors, are frequently used in rheumatology. Targets include proinflammatory cytokines, tumour necrosis factor alpha (TNFα), interleukin (IL)-1β and IL-6. TNFα inhibitors (TNFi) currently approved for the treatment of rheumatoid arthritis (RA) are etanercept, aTNF receptor fusion protein; certolizumab pegol, a humanized Fab' (variable) domain in polyethylene glycol; the fully humanised IgG1 antibodies adalimumab and golimumab; and infliximab, a chimeric antibody consisting of a mouse antigen-binding domain (Fab) and a human Fc (constant) domain (**Figure 1**) [1].

ANTI-DRUG ANTIBODIES (ADAS) TO TNF INHIBITORS

TNFi are complex molecules and demonstrate immunogenicity [2]. Regions of TNFi such as the mouse Fab' domain on infliximab can produce anti-drug antibodies (ADAs) in some treated patients. The fully humanised antibodies adalimumab and golimumab have a unique set of antigenic determinants or idiotopes on their Fab regions, which may result in development of anti-idiotype antibodies. The constant regions of TNFi have allotypic determinants that also may be immunogenic in some patients. Neo-epitopes can be generated in TNFi, resulting in the production of ADAs following therapy. Use of non-human cells during the preparation of some TNFi can lead to neo-epitopes arising from non-human glycosylation. Neo-epitopes can also arise from drug aggregates formed during the processing of TNFi and in the splicing site region of a fusion protein (etanercept).

Although TNFi are effective for treating RA, around 20-30% of patients fail to respond to the first TNFi prescribed for therapy, and around 20% of responders experience a loss of efficacy. The efficacy of biological therapy in RA is adversely affected by smoking and obesity. Co-prescription of disease-modifying anti-rheumatic drugs (DMARDs) also influences the efficacy of biologics. TNFi trough levels are strongly associated with clinical response. The lack or loss of efficacy of TNFi is often consequent to the production of ADAs.

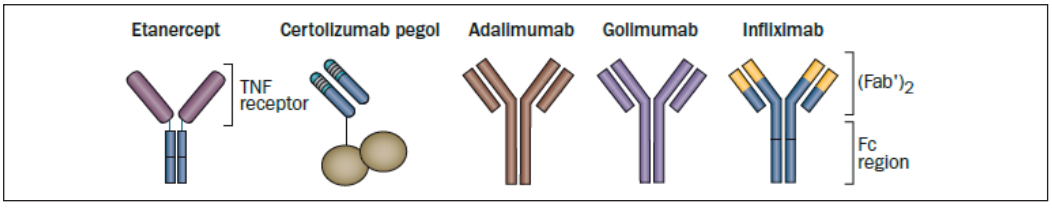

Figure 1. Structure of TNFα inhibitors used in rheumatology.

ADAs are mostly of the IgG class of immunoglobulins, predominantly the IgG1 and IgG4 subclasses (in the case of anti-infliximab and anti-adalimumab), and rarely of the IgE class. ADAs react with conformational epitopes on infliximab and adalimumab; conformational epitopes on adalimumab reside on the antigen binding site of the molecule. ADAs produced during adalimumab therapy were shown to be mainly anti-idiotype antibodies [3]. The production of IgE antibodies occurs during hypersensitivity reactions, which can be localised or systemic including the life-threatening condition anaphylaxis. IgG antibodies can be neutralizing or non-neutralizing; both types lower drug levels following the formation of small or large immune complexes which are then cleared by phagocytes. There is some evidence to suggest that formation of anti-adalimumab antibodies is associated with thromboembolic events.

The production of high affinity IgG ADAs is T-cell dependent and requires endosomal cleavage of the protein, peptide presentation by class II human leukocyte antigen (HLA) molecules and expansion of $CD4^+$ helper T cells. An evaluation of potential T cell epitopes on six monoclonal antibodies using a combination of $CD4^+$ T-cell proliferation ($[^3H]$-thymidine incorporation assay) and IL-2 secretion (immunoassay) showed that secukinumab (anti-IL-17A) and ustekinumab (anti-IL-12/-23) had the lowest T-cell response rates, whereas these rates were relatively high with both adalimumab and infliximab [4]. Similarly, evaluation of potential T epitopes using proteomics of major histocompatibility complex (MHC)-associated peptides showed that secukinumab and ustekinumab had relatively low numbers of potential T epitopes compared to adalimumab and infliximab [4].

A meta-analysis of 68 studies involving 14,651 patients in total reported a 12.7% (95% confidence interval [CI] 9.5–16.7) overall cumulative incidence of ADAs for TNFi. Cumulative incidences for individual TNFi were: 25.3% (95% CI 19.5–32.3) for infliximab; 14.1% (95% CI 8.6–22.3) for adalimumab; 6.9% (95% CI 3.4–13.5) for certolizumab pegol; 3.8% (95% CI 2.1–6.6) for golimumab; and 1.2% (95% CI 0.4-3.8) for etanercept [5]. The higher rate of ADAs associated with infliximab reflects the presence of murine sequences in the biological agent. The quantity of data available for certolizumab and golimumab is comparatively low as both biologics have been introduced relatively recently.

A review of published data for the rate of ADA development to infliximab reported values varying from 19–47% in RA, and from 25–50% in ankylosing spondylitis/psoriatic arthritis. Positivity for ADAs was associated with lower or undectable levels of infliximab, and with a lower likelihood of disease control or remission. Anti-infliximab antibodies commonly appeared within the first year of therapy, with a median time to appearance of 44 (range 16–69) weeks [6].

Published data for ADA development to adalimumab also showed wide variation in incidence rates, ranging from 5–54% in RA and from 18–45% in ankylosing spondylitis/psoriatic arthritis. Anti-adalimumab positivity was associated with lower or undetectable adalimumab levels, and with a lower likelihood of disease control or remission. Median time to ADA appearance with adalimumab ranged from 28 weeks to 1 year [6].

Methods for ADA detection

Although wide variation in the appearance of ADAs may reflect inter-patient variability, the methods

used to detect these antibodies are also responsible for this variability. The bridging enzyme-linked immunosorbent assay (ELISA) method involves ADAs present in a patient's serum forming a bridge between an immobilised biological drug (on a solid surface) and an enzymatically labelled drug. In the radioimmunoassay (RIA) antigen binding test, ADAs in a patient's serum bind to a radiolabelled biological drug with the complex being precipitated using protein A. The pH-shift anti-idiotype anti-gen-binding test involves dissociating ADA-drug complexes in a low pH environment, followed by pH neutralisation and addition of excess rabbit ADA, and finally detection of the patient's ADA using an antigen binding test.

The bridging ELISA is the most commonly used assay for ADA detection. These assays detect both neutralizing and non-neutralizing ADAs. For ADAs non-complexed with the drug, free drug may interfere with bridging ELISAs. In addition, as IgG4 antibodies are commonly monovalent, IgG4 ADAs are detected only if they remain divalent.

In contrast, cell-based assays detect functionally active TNFα and, indirectly, neutralizing ADAs. Reporter gene assay (RGA) is a test in which [7]. TNFα, with or without anti-TNFα (ADAs), is incubated with the genetically-engineered human erythroleukemic K562 cell line, transfected with a NFκB-regulated firefly luciferase reporter-gene construct which expresses the TNFα receptor. The luciferase reporter-gene is detected by luminescence [7].

A recent 12-month study investigated drug availability and presence of ADAs in 189 patients with RA (from 5 tertiary centres in Northern Italy) following treatment with three TNFi: etanercept, adalimumab, or infliximab [Data submitted for publication]. Drug availability and ADAs were evaluated by a bridging ELISA (Progenika Biopharma) and by a RGA (Biomonitor iLite). ELISA results showed significant inverse correlations between adalimumab (87.8%) and anti-adalimumab (6.8%) ($p = 0.0005$), and between infliximab (70.1%) and anti-infliximab (28.4%) ($p = 0.00003$). No statistical comparison was possible for etanercept (97.9%) and anti-etanercept (0.0%) as no ADAs were detected. Using the cell-based RGA, similar results were obtained with significant inverse correlations found for adalimumab (81.6%) and anti-adalimumab (6.1%) ($p = 0.005$); and for infliximab (52.2%) and anti-infliximab (25.4%) ($p = 0.00001$). Results for etanercept (89.4%) and anti-etanercept (2.1%) were not significant ($p = 0.106$).

Comparison of the assays for drug detection showed that concordance was generally good for most patients; 69.9% scored positive and 14.7% scored negative with both assays (**Table 1**) [Data submitted for publication]. However, there was a group of patients (13.5%) who were positive by ELISA but negative by RGA, with the difference between assays being statistically significant (McNemar's test, $p < 0.0001$). In contrast, concordance between assays for detection of ADAs was excellent; most patients scored negative for both assays (83.5%) or positive for both assays (8.0%) (**Table 2**) (McNemar's test, $p = 0.803$) [Data submitted for publication].

The relationship between disease activity (evaluated using the Disease Activity Score 28 [DAS28]) and drug or ADA levels was assessed for each assay. Patients were categorised by DAS28 scores (<3.2 or >3.2). Both assays showed a trend towards an association between higher disease activity and lower positivity for drug and ADA levels for etanercept,

Table 1. Comparison of positive and negative results for biological drugs obtained with an enzyme-linked immunosorbent assay (ELISA) and a Reporter Gene Assay (RGA) [Data submitted for publication].

	RGA		
ELISA	Positive	Negative	Total
Positive	114 (69.9%)	22 (13.5%)	136 (83.4%)
Negative	3 (1.9%)	24 (14.7%)	27 (16.6%)
Total	117 (71.8%)	46 (28.2%)	163 (100%)

Table 2. Comparison of positive and negative results for ADAs obtained with an enzyme-linked immunosorbent assay (ELISA) and a Reporter Gene Assay (RGA) [Data submitted for publication].

	RGA		
ELISA	Positive	Negative	Total
Positive	15 (8.0%)	9 (4.8%)	24 (12.8%)
Negative	7 (3.7%)	157 (83.5%)	164 (87.2%)
Total	22 (11.7%)	166 (88.3%)	188 (100%)

adalimumab, and infliximab [Data submitted for publication].

The study had some important limitations. Most patients were in remission which limited the power of the analysis. In addition, the timing of ADA appearance was not determined and the true baseline status of the patients was unknown.

Current work includes an ongoing 12-month study of TNFi-naive RA patients who are being treated with TNFi. Patients are to undergo evaluation every 3 months for assessment of drug levels and ADAs; disease activity and adverse effects are also being recorded.

Disease control is known to be poor in RA or ankylosing spondylitis following the development of ADAs to TNFi. In the case of primary or secondary failure, the key question is whether to change the drug or change the dose of the TNFi. In the presence of adequate therapeutic drug levels, the best option is probably to change the biological drug, as TNFα is unlikely to be involved in the immunopathology of disease. For low drug levels with no detectable ADAs, increasing the dose of TNFi is recommended, whereas for low drug levels in the presence of ADAs, changing the TNFi is the best option. Guidelines indicate that the dose of biological DMARDs should be tapered for patients in remission. Assessment of drug levels and ADAs may assist in identifying patients at low risk of disease flare.

CONCLUSIONS

In a 12-month study investigating drug availability and the presence of ADA in RA patients under treatment with TNFi (infliximab, adalimumab, etanercept), a significant inverse correlation was observed between drug positivity and ADA negativity detected by either ELISA or RGA. ADA assessment was

comparable between the two techniques. Drug availability measurement using the two assays showed good agreement for positive samples. Almost all patients treated with etanercept were drug-positive and ADA-negative. A higher proportion of patients receiving adalimumab versus infliximab were drug-positive. In contrast, a higher proportion of patients receiving infliximab versus adalimumab were ADA-positive. A trend between disease activity and drug levels was identified for patients undergoing therapy with adalimumab as detected by RGA and for patients undergoing therapy with infliximab as detected by ELISA.

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Therapeutic Drug Monitoring in Gastroenterology

CHARLIE LEES

**DEPARTMENT OF GASTROENTEROLOGY,
WESTERN GENERAL HOSPITAL, EDINBURGH, UK**

INTRODUCTION

Inflammatory bowel disease (IBD) affects about 1 in 200 people, although an increasing incidence of Crohn's disease (CD) has been reported in recent years, notably in the Western world. For example, in Scotland a 5-fold increase in the incidence of paediatric CD was described over a 34 year period [1]. In Asian countries, the prevalence of both CD and ulcerative colitis (UC) has more than doubled over the past 10 years [2].

IBD is an expensive disease to treat. The total annual direct healthcare cost in Europe is estimated to be €4.6–€5.6 billion. In addition, unemployment (10%), sick leave (3–6 weeks/year), and permanent work disability (2-fold increase) are more common in patients with IBD than in unaffected individuals. The economic impact of IBD is particularly high because patients are affected at an early age [3].

This review summarises our approach to the treatment of IBD at the Western General Hospital in Edinburgh, United Kingdom (UK), with particular focus on CD.

TREATMENT OF IBD

Although patients and physicians may state their treatment goals for CD somewhat differently, the goals themselves are not dissimilar. Patients desire to be symptom free, have a normal quality of life, uninterrupted schooling or work, a normal social/sex life, and no unsightly scars or stoma. Physicians wish to achieve deep remission, avoid hospitalisation and surgery, prevent complications, minimise 'bowel damage' which accumulates over time, and have no drug toxicity.

Treatment goals in CD have evolved over the years from achieving clinical remission in the 1970s to achieving remission based on patient reported outcomes (PRO) in the present day, particularly in the United States (US). The concept of biochemical remission was developed in the 1980s, with inflammatory biomarkers such as C-reactive protein (CRP) and faecal calprotectin commonly being applied in CD. Since then, endoscopic remission in the 1990s, remission based on cross sectional imaging in the early 2000s, and histological remission which was developed circa 2010 have all been applied to CD [4].

At the Western General Hospital, our main interest is to achieve deep remission with an emphasis on mucosal healing. Patients with IBD who achieve mucosal healing have better outcomes than those who do not [5-7]. Indeed, a wide range of benefits associated with mucosal healing have been reported. These include lower relapse rates, fewer hospitalizations, improved quality of life (QoL), reduced risk of cancer in UC, lower postoperative recurrence in CD, steroid sparing, and a decreased need for surgery [8-13].

The consensus treatment target in CD is a combination of clinical/PRO remission defined as resolution

of abdominal pain and normalization of bowel habit, and endoscopic remission defined as resolution of ulceration at ileocolonoscopy. Adjunctive measures of disease activity that may be useful in the management of selected patients but are not a target include CRP and faecal calprotectin. Measures of disease activity that are not a target include histology and cross-sectional imaging [14]. The consensus target in UC is a combination of clinical/PRO remission defined as resolution of rectal bleeding and normalization of bowel habit, and endoscopic remission defined as resolution of friability and ulceration (Mayo 0-1). Adjunctive measures of disease activity that may be useful in the management of selected patients but are not a target include CRP, faecal calprotectin, and histology. Measures of disease activity that are not a target include cross-sectional imaging.

Follow up of CD patients (n = 16,902) over a 40-year period confirmed the progressive nature of the disease, with stricturing and penetrating lesions developing over time [15]. In advanced disease, the bowel wall becomes fibrotic and scarred. Ulceration of the bowel wall causes development of fistulae, abscesses and other complications that respond to drug therapy. The presence of inflammatory lesions in about 70% of patients at the time of diagnosis provides a window of opportunity in which to treat patients with anti-inflammation drugs [15].

Current therapeutics for induction and maintenance of remission in IBD are summarised in **Table 1**. Induction agents include 5-aminosalicylic acid (5-ASA, mesalazine) for UC, corticosteroids for CD, and anti-TNF agents or vedolizumab for both conditions. Maintenance agents are 5-ASA for UC, methotrexate for CD, azathioprine, and the biologics, anti-TNF agents and vedolizumab. Multiple clinical trials have shown the benefits of biologic therapy in CD: fast onset of action, induction of remission, long-term remission, mucosal healing and reduced hospital admissions and operations. **Table 2** summarises key clinical trials involving the three main biologics (the anti-TNF agents, adalimumab and infliximab; and vedolizumab) which clearly induce remission in IBD [16-27]. Additional biologics for use in IBD are certolizumab pegol which is not licenced in Europe, and golimumab for UC.

Anti-TNF therapy is more effective in early CD than in late CD, which emphasizes the importance of the inflammatory window of opportunity [28-32]. The pivotal trial of anti-TNF therapy in CD was the SONIC study of patients who had not previous received immunosuppressive or biologic therapy. Patients were

Table 1. Current therapeutics for treatment of inflammatory bowel disease.

Induction	Maintenance
Corticosteroids	5-ASA (for UC only),
Aminosalicylate (5-ASA; for UC only)	Azathioprine/mercaptopurine
Anti-TNF (tumour necrosis factor) agents	Methotrexate (for CD),
Vedolizumab	Anti-TNF agents
Exclusive enteral feeding (for ileal CD)	Vedolizumab
Limited surgical resection	Smoking cessation

CD, Crohn's disease; UC, ulcerative colitis.

Table 2. Benefits of biologics: clinical trials in Crohn' disease [16-27].

	Adalimumab	Infliximab*	Vedolizumab
Induction of remission	CLASSIC-I [16]	Targan et al. [22]	GEMINI II [24] GEMINI III [25]
Fast onset of action	CLASSIC-I [16], GAIN [17]	Targan et al. [22]	GEMINI II [24]
Long-term remission	ADHERE (3 yr) [18]	ACCENT-1 (1yr) [23]	GEMINI II (1 yr) [24] GEMINI LTS (2 yr) [26]
Mucosal healing	EXTEND [19]	ACCENT-1 [23]	Arijs et al. [27]
Reduced hospital admissions and operations	CHARM/ADHERE [20], EXTEND [21]	ACCENT-1 [23]	

* Remicade™ (MSD).

randomly assigned to receive infliximab plus azathioprine, infliximab monotherapy or azathioprine monotherapy. Combination therapy significantly improved corticosteroid-free clinical remission at week 26 compared to infliximab monotherapy (p=0.02) or azathioprine monotherapy (p<0.001) [31].

The algorithm used at the Western General Hospital for initial management of CD is based on stratifying patients by disease severity (**Figure 1**). Patients with mild disease are commonly treated with corticosteroids. Azathioprine plus corticosteroids or exclusive enteral nutrition is used to treat moderate disease in the absence of risk factors. Patients with moderate disease and risk factors are treated with azathioprine plus an anti-TNF. Patients with severe disease are also treated with the combination of azathioprine and anti-TNF agent. Tight monitoring of patients throughout the disease course is critical for optimal management. Risk factors for a worse prognosis are young age [33,34]; smoking [35]; extensive small bowel disease [36]; peri-anal disease [33,34]; corticosteroids at diagnosis [33]; weight loss [34]; and deep ulcerations at endoscopy [37].

The algorithm used for maintenance therapy of CD includes options for patients with primary non-response or a secondary loss of response (**Figure 2**). Some patients receive no maintenance therapy, which is preferable to ineffective therapy. Patients with a poor initial response to anti-TNF therapy should be switched out-of-class, to vedolizumab. Patients with a satisfactory initial response to anti-TNF therapy should be switched to an alternative anti-TNF.

THERAPEUTIC DRUG MONITORING IN IBD

Prognostic methods for prediction of outcomes from baseline variables in IBD are relatively poor. Instead, the current focus is on disease monitoring, and adapting clinical practice to improve patient outcomes. Therapeutic drug monitoring (TDM) is integral to this process. TDM in IBD encompasses several elements: stratifying patients at diagnosis (despite its known flaws); selecting the 'right' drug or drug combination to use first time; monitoring patients closely; and adjusting the therapeutic strategy as necessary based on the results of monitoring.

Monitoring is important as there is discordance between underlying inflammation in IBD and the

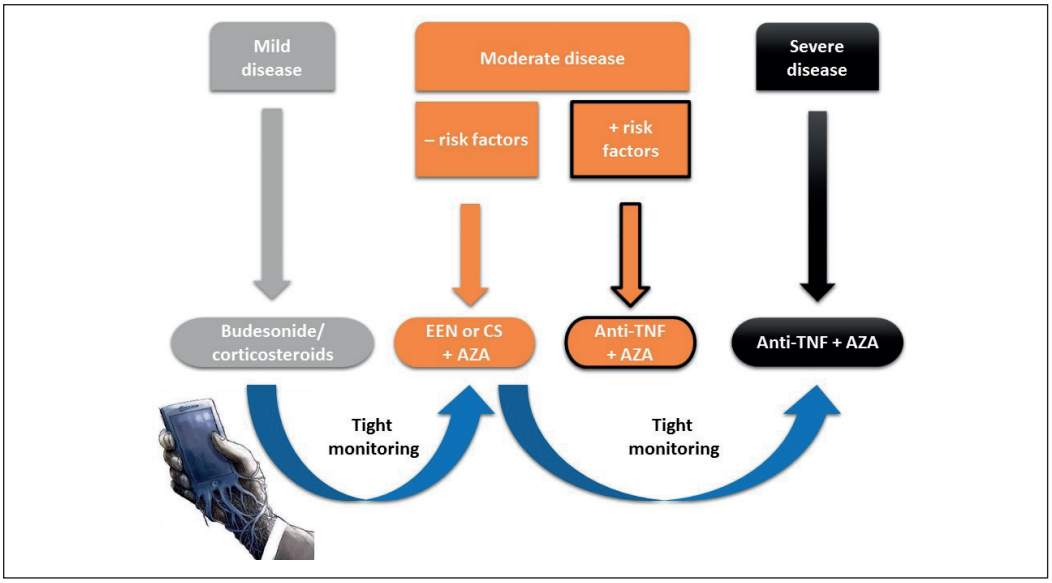

Figure 1. Algorithm for stratification and management of Crohn's disease at Western General Hospital, Edinburgh, UK. AZA, azathioprine; CS, corticosteroids; EEN, exclusive enteral nutrition.

presence of symptoms – some patients have symptoms but no inflammation, whereas others have inflammation but few symptoms [38,39]. Monitoring identifies patients who need treatment and those who do not. Disease activity is assessed by symptoms, CRP, endoscopy and histology in remission and during flares. Disease activity may still be present in patients who are symptomatically in remission. Moreover, it is becoming increasingly evident that levels of disease activity markers can vary during flares i.e. not all markers may be abnormal.

Faecal calprotectin is a critical surrogate marker for endoscopic lesions in IBD; levels of this protein are significantly correlated with endoscopic disease activity (using the Simple Endoscopic Score for Crohn's Disease) [40]. Faecal calprotectin is also an excellent marker for prediction of disease progression in CD. In the gastroenterology unit at the Western General Hospital, patients are scored clinically using the Harvey-Bradshaw index (HBI). Serum CRP and faecal calprotectin levels are both measured, together with infliximab trough levels, and anti-infliximab antibodies.

NON-RESPONSE AND LOSS OF RESPONSE IN IBD

The first step in implementing TDM is to establish definitions of efficacy/non-efficacy as this determines the next course of action. Several definitions of non-responsiveness have been devised which differ in their scope and level of stringency. The European Crohn's and Colitis Organisation (ECCO) pathogenesis workshop defined primary non-response in CD as a failure of symptoms and signs to improve after induction therapy [41]. The definition has since evolved to describe non-response as the failure to improve, after induction therapy, of objectively assessed signs of active inflammation (using CRP, faecal calprotectin, endoscopy), despite adequate drug concentrations and the absence of anti-drug

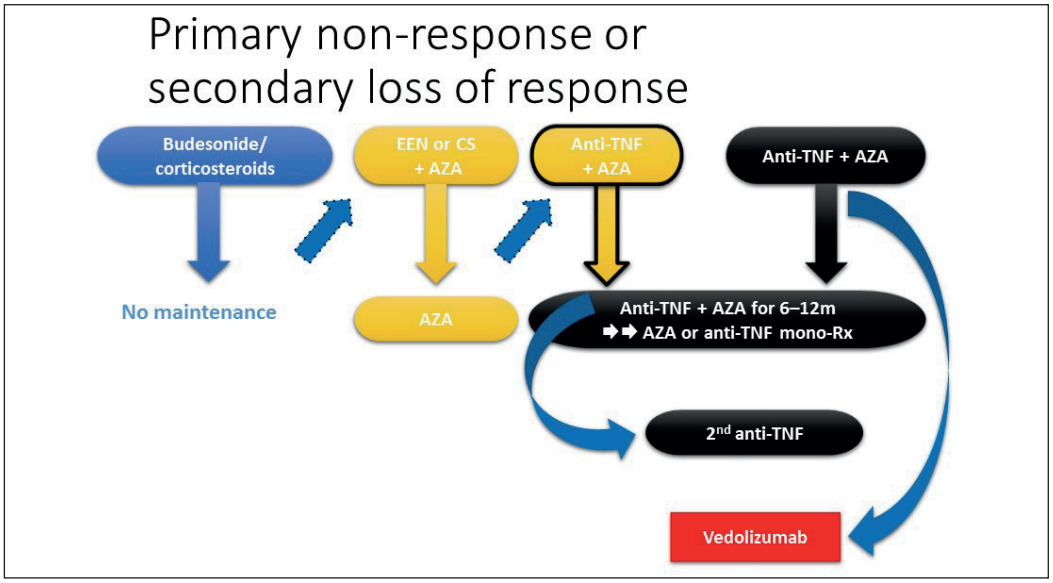

Figure 2. Algorithm for maintenance therapy in Crohn's disease at Western General Hospital, Edinburgh, UK. AZA, azathioprine; CS, corticosteroids; EEN, exclusive enteral nutrition.

antibodies [42]. This newer definition incorporates a role for TDM to ensure that drug therapy is optimized.

One definition of a loss of response in CD is the failure to maintain a response (reduction of 70 points on the Crohn's Disease Activity Index [CDAI]) after an initial response to induction therapy. A more stringent, and preferred, definition is the presence of symptomatic inflammatory IBD activity, which is of sufficient severity and duration to warrant escalation in corticosteroid, immunomodulatory, or anti-TNF therapy, or to undertake surgical resection. Loss of response (defined as the "need to intensify anti-TNF dose") to both adalimumab and infliximab has been observed in multiple key clinical trials of CD [43]. These data show that the response rate fell by 30-50% during the first 12 months of treatment [43].

Loss of response in CD occurs due to non-inflammatory mechanisms such as fibrostenotic strictures and malignancy, and to unrelated inflammatory mechanisms such as infections, vasculitis and ischaemia; these patients have adequate trough levels of the drug. Loss of responsiveness associated with low drug trough levels include IBD-related inflammatory mechanisms comprising development of anti-drug antibodies (ADAs), flares related to anti-TNF use, non-immune drug clearance and non-adherence [43].

MONITORING FOR TREATMENT FAILURE IN IBD

There are several reasons to monitor for treatment failure in IBD. At present, our ability to predict failure to anti-TNF agents is limited. Primary non-responsiveness and loss of response are common. Disease activity is more likely to respond to dose intensification or drug switching when it is detected early. In this fashion, it is possible to reduce the duration of ineffective therapy which, in turn, limits the structural

damage and morbidity associated with uncontrolled inflammation, reduces the risk of adverse drug reactions and reduces costs. The increasing number of therapeutic options available in IBD also supports monitoring for treatment failure.

To illustrate the utility of TDM, the time course of faecal calprotectin levels in a patient (DS) diagnosed with CD prior to the implementation of TDM is shown in **Figure 3**. For comparison purposes, time course graphs illustrating a primary response, primary non-response and loss of response are also shown. Combination therapy with infliximab and azathioprine was dose escalated in the patient at 6 and 12 weeks. Faecal calprotectin levels fell, and were maintained at normal levels following the second dose of intensified combination therapy (at 12 weeks). Intensified combination therapy was performed when the patient was asymptomatic. In the present day, TDM would be performed for such a case. TDM plays an important role in assessing primary non-response and loss of response, and is also implemented after therapeutic intervention to assess response [40,44-47] (**Table 3**).

Factors modifying levels of anti-TNFs in IBD patients include ADAs, inflammatory cytokines, loss of drug into the bowel stool, serum albumin, use of immunomodulators, increased degradation during active inflammation, and body mass [48]. Some of these factors are discussed in more detail below.

In patients with severe UC, primary non-responsiveness to infliximab was associated with high faecal infliximab concentrations in the first days after therapy. Patients who were clinically non-responsive

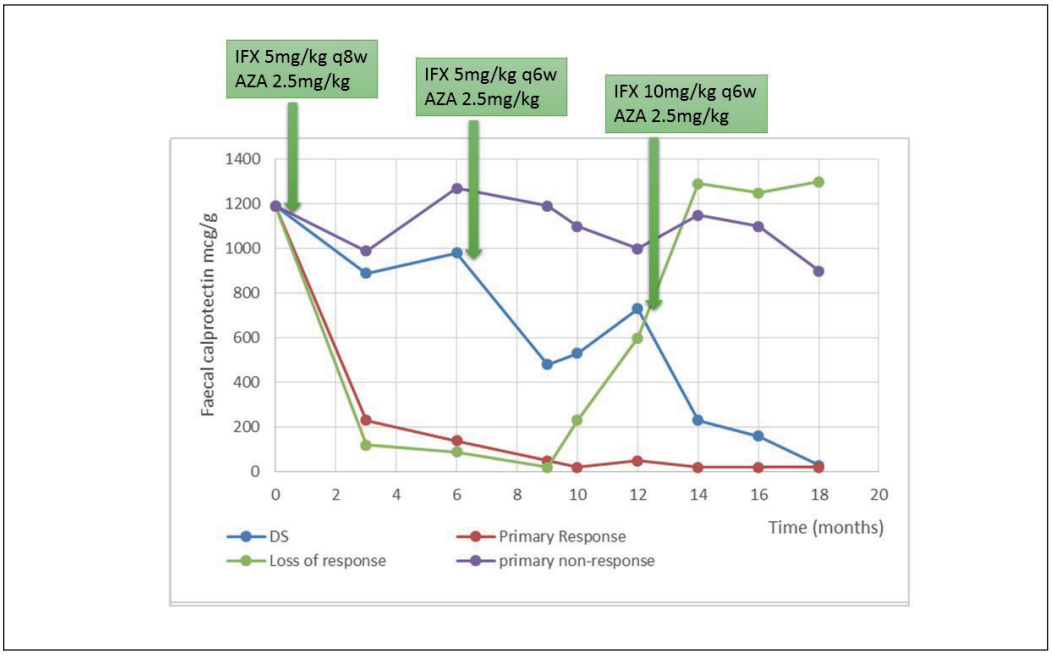

Figure 3. Time course of faecal calprotectin levels in a patient (DS) with Crohn's disease. Time course graphs illustrating primary response, primary non-response and loss of response are also shown.

Table 3. Monitoring of inflammatory bowel disease in the era of Therapeutic Drug Monitoring (TDM): targets and frequency [40,44-47].

Timing	Parameter	Outcome
Week 12–14	CRP normalisation	Mucosal healing
	CRP ≥60% decrease	Durable response
Primary non-response	TDM	
At each infusion/visit	CRP >5 mg/L	Relapse (CD)
	FC >300 mg/kg x 2	Relapse (UC)
Loss of response	CRP ≥5 mg/L	Mucosal lesions
	FC ≤250 µg/g	CDEIS ≤3
	TDM	
After intervention	CRP	Assess response to intervention
	FC	
	TDM	

CD, Crohn's disease; CDEIS, Crohn's Disease Endoscopic Index of Severity; CRP, C-reactive protein; FC, faecal calprotectin; TDM, Therapeutic Drug Monitoring; UC, Ulcerative colitis.

at week 2 had significantly higher faecal concentrations of infliximab than patients with clinical responses. This was attributable to intestinal mucosal damage with the consequent loss of infliximab into the stools of patients [49].

Trough serum levels of anti-TNF are significantly correlated with outcome. Analyses have demonstrated that a minimal trough level of 3-7 µg/mL of infliximab gives maximal clinical remission and an endoscopic response; and that a trough level of >5 µg/mL of adalimumab is optimal for promoting mucosal healing [50-52]. Data from the unpublished PANTS (Personalised Anti-TNF Therapy in Crohn's disease) study showed that trough levels of infliximab or adalimumab at week 14 are associated with a primary non-response; with 20.9% and 9.7% of infliximab- and adalimumab-treated patients, respectively, having no detectable drug in serum.

A series of known and unknown factors contribute to the immunogenicity of anti-TNF agents. Product-related factors include glycosylation, formulation, and downstream processing of drugs; patient-related factors include immune status, genetic background, and comorbidities [53,54]. Development of ADAs in anti-TNF therapy of IBD is well documented, with episodic treatment being associated with a higher prevalence of ADAs than scheduled anti-TNF treatment. The addition of an immunosuppressant also reduces the prevalence of ADAs. ADAs are more common with infliximab therapy than with other biologic agents [55-59]. In patients with IBD, antibodies to infliximab most commonly develop within the first 12 months of therapy [60]. Unpublished data from the PANTS study showed that development of ADAs to anti-TNF agents (infliximab or adalimumab) at week 5 predicted non-remission at week 54.

The TAXIT study involved 263 patients with CD or UC who had stable responses to maintenance infliximab therapy. Patients were dose optimised, and then randomised to receive either dose escalated

or dose reduced infliximab to reach a target trough concentration of 3-7 µg/mL. After 1 year, there were no significance differences in clinical and biochemical remission between the two dosing schedules [61], possibly reflecting the initial optimisation of patients' therapy. During the optimisation phase, a significantly higher proportion of CD patients achieved clinical remission (p=0.02) and had a lower CRP concentration (p<0.001) after dose escalation, compared with patients before dose escalation. These differences were not observed in UC patients. Patients with high trough levels and no ADAs who received dose reduction produced a pharmaco-economic saving [61], which has important implications for reducing costs in health care settings. Future maintenance treatment algorithms for anti-TNFs may possibly include cost savings strategies, to avoid unnecessary dosing above the optimum trough level for each drug.

A proposed algorithm based on published data [61,62-64] for primary non-response and loss of response to anti-TNF agents is shown in **Figure 4**.

A critical step is to confirm the presence of active inflammatory disease. In patients with active inflammatory disease, undetectable drug trough levels and no ADAs, non-adherence to anti-TNFs should be considered, especially with SC drugs. Drug dose should be optimised using a reduced treatment interval or increased dose. With low and high titre ADAs, the addition of an immunomodulator may be beneficial. A switch to an alternative anti-TNF should be considered for high titre ADAs.

IBD patients who develop antibodies against infliximab are more likely to develop antibodies to adalimumab following a switch from infliximab to adalimumab after treatment failure [65]. The reason for discontinuing treatment with the first anti-TNF determines the efficacy of the second anti-TNF. This was demonstrated in a systematic review and meta-analysis of 46 studies. Reasons for anti-TNF withdrawal were intolerance, secondary failure and primary failure which produced response rates of 72%, 62% and 53%, respectively [66]. In IBD patients who showed loss of response to infliximab

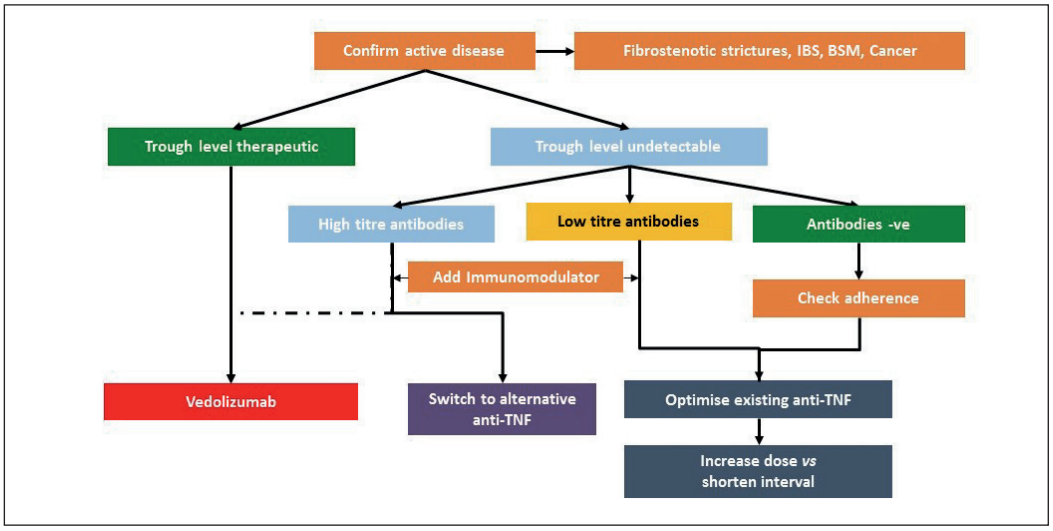

Figure 4. Proposed algorithm for anti-TNF primary non-response and loss of response.

monotherapy, the addition of an immunomodulator was effective in eliminating ADAs in serum and restoring a clinical response [67].

USE OF ANTI-TNFS AT THE WESTERN GENERAL HOSPITAL: COST SAVINGS AND FUTURE PLANS

Global expenditure on biologics in 2012 was $169 bn, representing 18% of the total spend on all prescribed medicines [68]. Newer therapies for IBD either available or currently under development include infliximab biosimilars, anti-adhesion drugs, novel anti-cytokine drugs, novel small molecules, and manipulation of diet and microbiota [69], all of which are adding to the cost of care.

At the Western General Hospital, Edinburgh, we have been addressing escalating costs with the use of an infliximab biosimilar. TDM has been an important aspect of the implementation of this drug.

The use of infliximab biosimilars in Europe has increased markedly since the beginning of 2015, with a concomitant fall in the use of Remicade®. Overall, infliximab use during this period was higher than its projected level, suggesting that it had been driven by the availability of biosimilars.

Switching from Remicade to the biosimilar, CTP13, for new patients with IBD at the Western General Hospital has generated a cost savings of around €0.6-€0.7 million per year. Prior to switching from Remicade to CTP13 for patients receiving maintenance therapy, TDM was implemented, which involved measuring infliximab trough levels and ADAs, in conjunction with a full clinical review. Preliminary data for CD patients who were switched from Remicade maintenance therapy to CTP13 maintenance

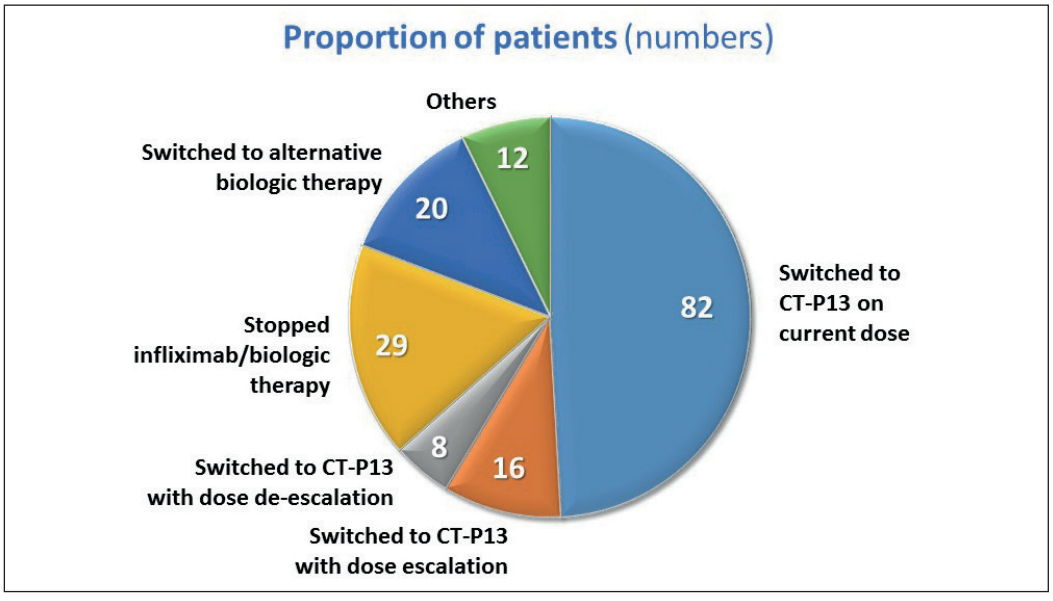

Figure 5. Infliximab biosimilar switch data from Western General Hospital, Edinburgh, UK.

therapy is summarised in **Figure 5**. Approximately half the patients were switched without a change in dose. Fewer patients were switched to CTP13 with dose escalation or dose reduction, stopped infliximab/biologic therapy, or were switched to an alternative biologic therapy. Cost savings will accrue from the lower cost of the biosimilar (62% compared to the cost of Remicade), together with dose reduction.

At the present time, TDM measurement of infliximab levels and ADAs is performed prior to the fourth dose of CTP13 (approximately 6 months after treatment initiation). Blood and faecal calprotectin levels are measured routinely every 2 months, and clinical symptoms are assessed on the day of infusion using a patient monitoring proforma. In the next phase of TDM, we will be implementing a review of patients receiving infliximab therapy and who are in remission for possible treatment discontinuation.

A similar programme for the adalimumab biosimilar will be initiated when it becomes available in the near future.

CROHN'S DISEASE: TAKE-HOME MESSAGES

Certain aspects of CD management are especially important in terms of optimising patient outcomes. Take-home messages from this review include the following:

- Time-bound management of CD is critical
- Stratify patients by risk early
- Be aware of potential missed treatment opportunities
- Monitor patients closely and act on the results
- Tailor combination therapy versus monotherapy to the individual patient
- Consider the long-term efficacy and safety profiles of immunomodulators and anti-TNF agents
- Plan drug withdrawal strategies and monitor outcomes
- If anti-TNF therapy fails, vedolizumab provides an alternative option
- Use TDM to optimise drug therapy, and stop the drug if ineffective.

CONCLUSIONS

In summary, primary non-response and loss of response to anti-TNF therapy are common in patients with IBD. Regular monitoring of CRP and faecal calprotectin allows early detection of anti-TNF failure. TDM has a critical role in guiding treatment decisions. For a primary non-response consider switching to vedolizumab (anti-TNF 'non-responsive disease'). For a secondary loss of response to anti-TNFs, TDM may clarify the mechanisms underlying anti-TNF failure and guide cost-effective interventions:

- For patients with low drug levels or those who have ADAs: switch anti-TNF or class
- For patients with low drug levels who are ADA negative: check compliance and escalate the dose
- For patients with therapeutic drug levels who are ADA negative: switch drug class.

Consider/reconsider immunomodulatory therapy for anti-TNF failures–either as combination therapy if there is evidence of immunogenicity or as monotherapy as an alternative to switching out of class.

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Cost-efficacy of Therapeutic Drug Monitoring

DORA PASCUAL-SALCEDO, PHD

IMMUNOLOGY UNIT, UNIVERSITY HOSPITAL LA PAZ, MADRID, SPAIN

INTRODUCTION

Therapeutic Drug Monitoring (TDM), as it applies to anti-tumour necrosis factors (anti-TNF) agents, is described as "a careful follow-up of the clinical response to TNF inhibitor in combination with the monitoring of drug and anti-drug antibody levels, that potentially can influence prescribing procedures" [1]. Approximately four years ago, TDM was introduced into the rheumatology clinic at the University Hospital La Paz in Madrid, Spain.

The Monitoring of Monoclonal Antibodies Group in Europe (MAGE) for inflammatory diseases, of which the author is a member, has three main aims:

- To standardize assays for drug measurement
- To perform collaborative analyses to develop algorithms for TDM
- To design clinical trials to assess comparative effectiveness in order to validate these tools.

MAGE is currently in the final stages of producing a comprehensive book about TDM which is due to be published in 2017.

HOW TO PERFORM TDM

Two designs of enzyme-linked immunosorbent assays (ELISA) for measuring levels of anti-TNF agents are in common use. In capture ELISA, TNF is captured by a solid phase monoclonal antibody to TNF, to which the biologic anti-TNF drug, present in serum, binds. The biological drug is detected using an anti-idiotype antibody which is labelled with biotin or peroxidase. Alternatively sandwich ELISA may be used. This assay uses a solid phase coated with a F(ab')2 fragment of a monoclonal antibody directed to the drug in serum. The biological drug is detected with conjugated anti-idiotype antibody [2,3].

Assays used more often to measure anti-drug antibodies (ADAs) are a bridging ELISA and a radioimmunoassay (RIA), as shown in **Figure 1**. The bridging ELISA involves coating an assay plate with the biological drug, adding serum-containing ADAs which are detected with the same biological drug conjugated with biotin. The assay detects ADAs of the IgG1, IgG2 and IgG3 subclasses. Although ADAs of the IgG4 subclass are commonly produced together with IgG1 ADAs, a specific assay for IgG4 ADAs has been developed. The RIA for ADA detection involves immobilising the serum IgG using Protein A, with the specific ADA being detected with the radiolabelled drug [4].

Figure 2 illustrates the time course in a patient treated with infliximab showing peaks and trough levels, and the association of trough levels with detectable ADAs from week 18. Trough levels of infliximab fell gradually from around 35 ng/mL at week 2, to approximately 26 ng/mL at week 6, and then to 15-16 ng/mL from week 14.

WHEN TO PERFORM TDM

TDM to measure drug levels and/or ADAs is performed at several key timepoints during the course of TNF inhibitor therapy:

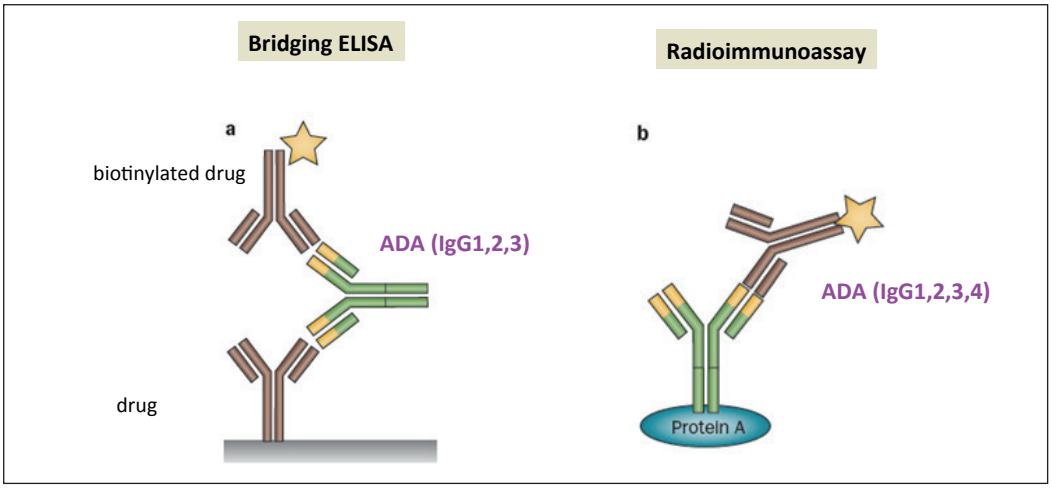

Figure 1. Assays for measuring anti-drug antibody levels (ADA). Adapted with permission from [4]. ELISA, Enzyme-linked immunosorbent assay.

- At baseline, including therapy re-introduction when it is specially important to assay for ADAs
- At treatment induction
- Regularly throughout the course of treatment
- Whenever the clinical situation recommends a change in treatment, which may be due to inefficacy (increase dose/switch drug) or efficacy (tapering/optimization).

Drug levels are assayed regularly during the first year of treatment (ADA are only assayed when drug levels are low or negative).

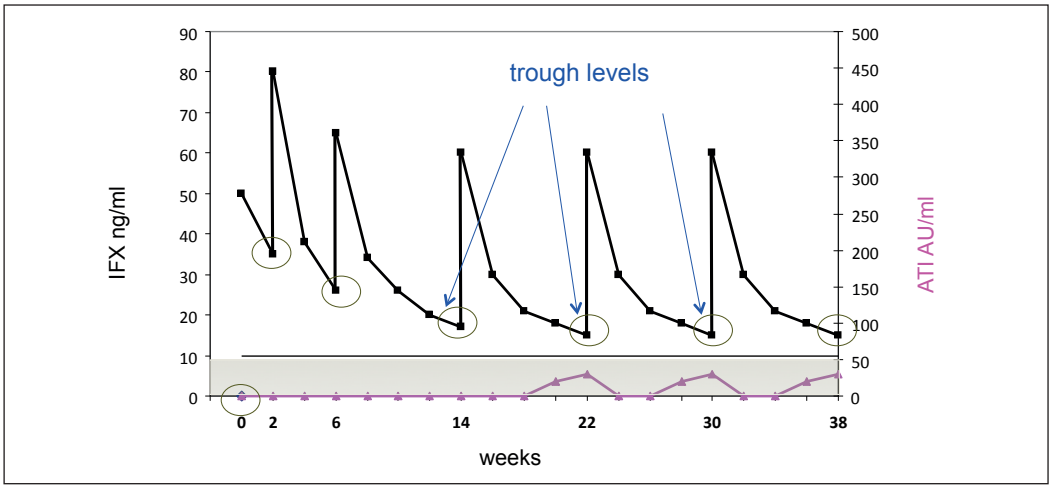

Figure 2. Time course in a patient treated with infliximab (IFX) showing peak and trough drug levels and antibodies to infliximab (ATI).

A study of 42 patients with spondyloarthritis treated with a TNF inhibitor has illustrated the effects of treatment inefficacy after switching to a second anti-TNF. At 6 months after switching, patients who had developed ADAs to the first TNF inhibitor achieved a significantly ($p = 0.002$) better clinical response (measured by the Ankylosing Spondylitis Disease Activity Score [ASDAS]) than those who had not developed ADAs. Thus, a failure to respond to the first anti-TNF due to the development of ADAs is predictive of a better clinical response to a second anti-TNF drug [5].

Similarly, patients with RA who developed ADAs to a first anti-TNF responded better when switched to a second anti-TNF [6]. Clinical outcome was assessed by the Disease Activity Score 28 (DAS28). In contrast, in patients who had not developed ADAs to the initial anti-TNF agent, there was no significant difference in clinical outcome 6 months after switching [6].

WHY TDM SHOULD BE PERFORMED

TDM facilitates treatment optimization, such that the amount of drug administered is within the therapeutic range. This avoids the development of side effects in patients, is cost saving, and increases the number of patients that can be treated within a given budget i.e. it is cost efficient.

In most patients, drug levels correlate with clinical response. Following development of ADAs, clinical efficacy decreases due to a lower level of circulating drug. Increasing the dose of an anti-TNF can lead to disappearance of ADAs in serum, as our group observed in a patient with RA. Increasing the dose of infliximab at week 14 (from 3 mg/kg to 5 mg/kg) resulted in the neutralisation and disappearance of ADAs. However, the effects of dose escalation were short lived, as ADAs reappeared after 41 weeks of infliximab treatment and were associated with an unnecessary increase in costs.

The Rheumatology Department at the University Hospital La Paz has adopted a policy of switching drugs, rather than escalating doses, following the appearance of ADAs. The short term nature of dose escalation was shown by our group in a retrospective study of 42 RA patients. Although global DAS28 disease activity showed modest improvement after dose escalation, improvement did not persist after 6 and 12 months [7].

TDM also allows for effective personalized therapy. Charting the time course of a patient with RA indicated that reducing the frequency of infliximab dosage (i.e. increasing the dose interval) resulted in a declining serum drug concentration, whilst clinical response (DAS28) whilst clinical response is maintained.

A collaborative study between our group and Dutch colleagues, in which the clinical response of patients with RA who received anti-TNF dose tapering (n=67, from Spain) were compared with patients who received a standard anti-TNF regimen (n=77, from the Netherlands), showed that disease control was similar in both groups [8]. Tapering was performed for 2 years in patients who were clinically stable for at least 6 months. At the end of the study DAS28 scores were 2.7 ± 0.9 in the tapering group and 2.5 ± 1.0 in the control group ($p=0.1$). The anti-TNF tapering strategy enabled reduction of administered drugs, with reductions of 33% for infliximab, 53% for adalimumab, and 53% for etanercept. Similar results were reported in a Spanish-Dutch collaborative study of patients with spondyloarthritis, in which

drug tapering (n= 74, from Spain) produced similar clinical outcomes to a standard drug regimen (n= 43, from the Netherlands), but reduced the amounts of drugs administered by approximately 50% [9]. For infliximab, there was a 22% reduction in dose (mean dose 4 mg/kg), and a further 28.7% reduction was made possible by increasing the interval of drug administration. Adalimumab and etanercept were reduced by 45.2% and 51.5%, respectively.

Knowledge of the optimal circulating ranges of TNF inhibitors is important, as it is cost-effective. A study of 221 patients with RA showed that adalimumab trough levels of 5-8 µg/mL were sufficient to produce an adequate clinical response [10]. Increasing the adalimumab trough level above this range was not associated with any improvements in clinical response. Likewise, in collaboration with our Dutch colleagues, we recently published a study of 70 patients with RA which showed that serum tocilizumab trough concentrations of 5-12 µg/mL were sufficient to produce an acceptable clinical response [11]. Most patients had received more drug than was necessary to achieve an acceptable clinical response [11].

Assessment of serum infliximab concentrations in 140 patients with RA treated with infliximab 3 mg/kg for 8-9 weeks showed that the majority (76%) had levels between 1-5 µg/mL, whereas 7% had levels <1 µg/mL and 17% had levels >5 µg/mL. The group with infliximab serum levels of 1-5 µg/mL had a significantly better clinical response compared to the <1 µg/mL group (p=0.005). No additional clinical benefit was associated with infliximab serum levels >5 µg/mL, suggesting that this group of patients were receiving more drug than required [12].

Optimization of biological treatment is cost-effective, as illustrated by our analysis of 78 patients with rheumatic diseases which showed that dose tapering led to significant cost-savings [13]. Patients who had low levels of clinical disease activity, or who were in remission for at least six years, were compared over two time periods: in the first period (2007-2009) with the standard dose, and in the second period (2010-2012) with a reduced dose. The drug administration interval was significantly greater in the second period for infliximab ($p<0.001$), adalimumab ($p<0.0001$), and etanercept ($p<0.05$). Clinical efficacy in RA (using DAS28) and in spondyloarthritis (using BASDAI) were similar before and after dose tapering. Overall, the cost of administered drug per patient was reduced by around 20% per year (16% infliximab, 22% adalimumab, 19% etanercept) [13].

Data from our Hospital Pharmacy Service shows that we were able to treat 59% more rheumatic patients with biological drugs in 2016 than in 2009. This corresponds with the period of anti-TNF dose tapering which delivered considerable cost savings. From 2009 to 2013 the annual spend on biological drugs for patients with arthropathies decreased by 14%. Beginning in 2013, new therapeutic drugs were introduced for which treatment has yet to be optimized. Importantly, the annual accumulated spending per patient with arthropathies fell by 38% from €11,539 in 2009 to €7140 in 2016, which is attributable to dose optimization in 52% of patients.

Compared with budgeted costs, the calculated cost savings for biological drugs administered in rheumatology, gastroenterology, and dermatology services in the Hospital La Paz compared to eight large hospitals in Madrid during 2014 was more than €770,000. In comparison, the cost of assessing drug levels using TDM was €20,000 to €200,000/year. Thus personalized TDM benefits both patients and healthcare budgets.

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Edited by: **Grifols, S.A.**
Parc Empresarial Can Sant Joan
Av. de la Generalitat, 152-158
08174 Sant Cugat del Vallès
Barcelona - SPAIN

Contact details and information:
medaffairs.diagnostic@grifols.com

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