SYMPOSIUM

II CHALLENGES IN THERAPEUTIC DRUG MONITORING

November 21st 2017
Grifols Headquarters, Sant Cugat (Barcelona)

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Scientific presentations from the Symposium sponsored by Grifols, held at the Grifols Corporate Office, Sant Cugat del Vallès, Barcelona, Spain, October 21st 2017

Writing assistance was provided by ContentEdNet (Madrid, Spain) with funding from Grifols S.A.
The authors have received support from Grifols for their presentation.

II CHALLENGES IN THERAPEUTIC DRUG MONITORING

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Introduction to therapeutic drug monitoring: application and benefits

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INTRODUCTION

Biologics in current clinical practice have transformed the treatment of inflammatory diseases such as rheumatoid arthritis (RA), psoriatic arthritis, inflammatory bowel disease (IBD) and psoriasis. These agents are highly effective at controlling inflammation and dramatically improve patients' functional status and quality of life. However, biologics are expensive, currently representing the highest drug expenditure in Europe across all disease areas. A cost evaluation of single drugs in England for 2015/16 ranked three tumor necrosis factor alpha (TNF-α) biologics in the top five most costly drugs. The total cost to the National Health Service in 2015/16 for the top-ranked drug, adalimumab, was £417 million (€476 million) [1], or approximately £10,000 (€11,400) per patient per year.

There are more than 10 biologics available for therapeutic use in RA which have shown similar efficacy in clinical trials. However, these drugs can produce significant adverse events (e.g. serious infections) and, over time, a loss of response may develop. As such, there is a need to develop predictive biomarkers for treatment response in routine clinical practice.

IMMUNOGENICITY AND THE DEVELOPMENT OF ANTI-DRUG ANTIBODIES

Immunogenicity is defined as the ability of compounds such as exogenous proteins (including therapeutic proteins) to mediate an immune response. For therapeutic proteins, this may result in the production of anti-drug antibodies (ADAbs). The immunogenicity of therapeutic proteins has been recognised for more than 30 years following production of ADAbs to insulin in type 1 diabetic children. Human insulin had lower immunogenicity than porcine insulin, as evidenced by lower titres of ADAbs found in patients treated with human insulin [2].

Rates of ADAb formation differ widely between various therapeutic proteins, and also between investigative studies depending on the type of assay used and the timing of sampling. Factors which influence the immunogenicity of therapeutic proteins include: the origin of the protein (human or non-human); the presence of protein fragments, conjugates or additives; the route of administration and dose regimen including concomitant therapy; the genetic background and immunocompetence of the patient; and the type of disease (**Figure 1**) [3,4].

The development of ADAbs can also have drug safety implications. For example, the incidence of the life-threatening complication pure red-cell aplasia in patients with chronic renal failure treated with recombinant epoetin was associated with the development of neutralizing anti-erythropoietin antibodies. A relatively small change in the formulation of recombinant epoetin was associated with an increase in the incidence of ADAbs in these patients [5,6].

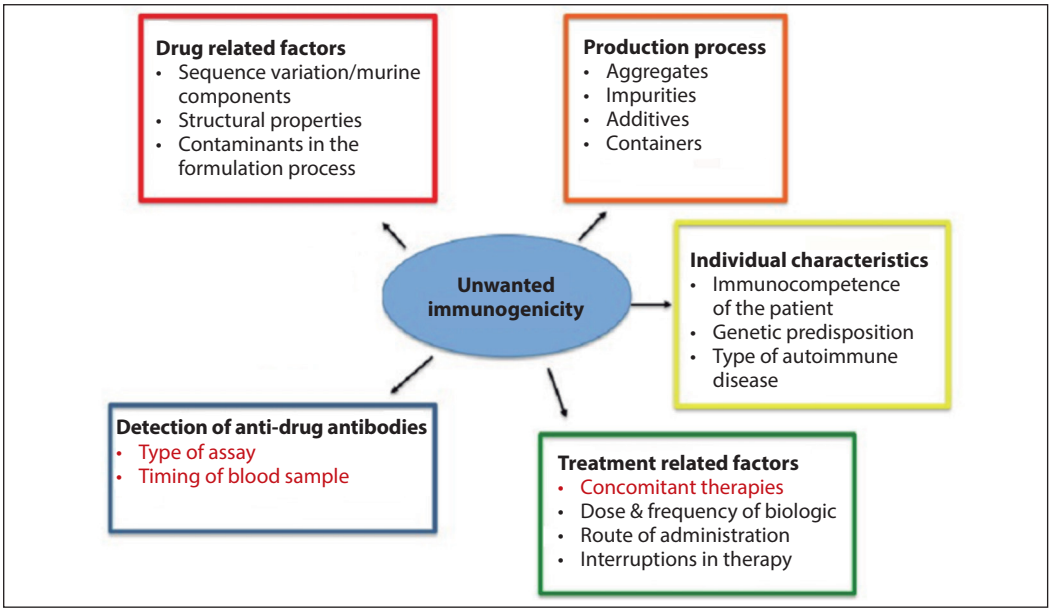

Figure 1. Factors affecting immunogeniticity.

The development of ADAbs to therapeutic proteins has been described in multiple therapeutic areas. For example, ADAbs to the humanized monoclonal antibody natalizumab (anti-α4 integrin), which is used in combination with interferon beta-1a for relapsing multiple sclerosis, resulted in a loss of efficacy and an increase in infusion-related adverse events [7].

Immunogenicity assessment is now mandatory before approval of new biotherapeutics by the US Food and Drug Administration and the European Medicines Agency.

TUMOR NECROSIS FACTOR INHIBITORS

Tumor necrosis factor (TNF) inhibitors commonly used in RA and other inflammatory conditions include infliximab, adalimumab, golimumab, certolizumab pegol and etanercept. Etanercept is less immunogenic than the other TNF inhibitors, with infliximab, adalimumab, golimumab and certolizumab all known to produce ADAbs [8].

The relevance of ADAb development to therapeutic drug monitoring (TDM) was illustrated in a study of adalimumab for treatment of RA, in which a significant association between ADAb development and trough serum levels of adalimumab was described. In addition, patients with high-titre anti-adalimumab antibodies (> 100 arbitrary units (AU)/mL) had lower trough adalimumab serum levels than patients with low to medium titre ADAbs (13-100 AU/mL). ADAb development was also associated with adverse clinical outcomes, most particularly a lower likelihood of achieving minimal disease activity and clinical remission [9].

IMPACT OF ANTI-DRUG ANTIBODIES ON TNF INHIBITOR EFFICACY IN RA

The impact of ADAb development and low anti-TNF levels on TNF inhibitor efficacy was evaluated in a long-term (12 month) study of RA patients who were treated with adalimumab or etanercept with/

without methotrexate combination therapy [10]. ADAbs developed in 25% of patients receiving adalimumab, whereas no ADAbs were detected in etanercept-treated patients. The presence of anti-adalimumab antibodies was significantly associated with lower serum adalimumab levels. ADAb development was also significantly associated with longer disease duration (14.0 *vs* 7.7 years), and with a lower dose of methotrexate (15 *vs* 20 mg/week). Multivariate analysis indicated that adalimumab serum non-trough levels were significantly ($p = 0.009$) associated with a change in the 28-joint Disease Activity Score (DAS28) at 12 months.

At 3 months after treatment onset, the best predictor of a response at 12 months, defined using European League Against Rheumatism (EULAR) criteria, was a low adalimumab level plus the presence of ADAbs. An optimal treatment response, estimated using an adalimumab concentration-effect curve for change in the DAS28 over 12 months, was found for serum adalimumab concentrations of 5.1-10 µg/mL. This range was similar to that obtained by Pouw and colleagues who reported an adalimumab concentration of 5-8 µg/mL for an adequate clinical response [11]. Although etanercept levels were associated with a EULAR response at 12 months, the association was not statistically significant following adjustment for confounders.

After adjustment for multiple confounders, ADAb status ($p = 0.005$) remained the strongest predictor of low drug levels in adalimumab- and etanercept-treated patients, followed by body mass index ($p = 0.003$); poor adherence was a negative predictor ($p = 0.028$) [10].

In RA patients treated with certolizumab pegol, higher certolizumab drug levels were associated with an improved EULAR response at 12 months, and TDM may predict long-term treatment response. ADAbs were detected in 37% of patients and were significantly associated with lower drug levels [12].

POTENTIAL IMPACT OF TNF INHIBITOR IMMUNOGENICITY ON DRUG SAFETY

It is well-documented that ADAbs are associated with infusion reactions, particularly for patients treated with infliximab. Serum sickness following TNF inhibitor infusion is also well-documented. The relationship between injection site reactions and the presence of ADAbs is unclear. One case series has suggested that thromboembolic disease and digital vasculitis are associated with ADAbs [13], although these findings have not been replicated.

Anti-TNFs may induce antinuclear antibodies (ANA) in as many as 40% of patients, as well as anti-double-stranded DNA antibodies (anti-dsDNA). Both ANA and anti-dsDNA may be a surrogate for ADAbs [14,15]. Anti-TNFs may also induce systemic lupus erythematosus (lupus) or vasculitis [16].

The risk of immune-mediated adverse events arising in RA patients treated with anti-TNFs was assessed by analysis of the British Society for Rheumatology Biologics Register. There was a time-dependent risk of both lupus-like events and vasculitis-like events, with the highest risk of both arising in the first six months of TNF inhibitor treatment. The incidence of these immune-mediated adverse events was rare: 10 per 10,000 patient years for lupus-like events, and 16 per 10,000 patient years for vasculitis-like events. Following adjustment for confounders, the incidences of lupus-like events and vasculitis-like events were not significantly different from those calculated for patients who had received

non-biologic disease-modifying anti-rheumatic drugs (DMARDs) [17].

In univariate analyses, sulfasalazine use was significantly associated with a lower risk of lupus-like events, and use of methotrexate and sulfasalazine were independently significantly associated with a lower risk of vasculitis-like events [17].

USE OF TDM IN OTHER DISEASES – PSORIATIC ARTHRITIS

Analysis of 75 patients with psoriatic arthritis treated with adalimumab or etanercept showed a significant association between serum adalimumab levels and change in the DAS28 [18]. Anti-adalimumab antibodies were detected in around 20% of patients but were not associated with treatment response. Etanercept levels were also not predictive of treatment response. An adalimumab concentration-effect curve at 6 months indicated that an adalimumab dose of 4-8 μg/mL may be associated with an optimal response in psoriatic arthritis. Only ADAb status and body mass index were associated with low drug levels.

IMPLEMENTATION OF TDM IN CLINICAL PRACTICE

Cost-effectiveness

The cost-effectiveness of TDM in clinical practice was estimated in a Finnish study of RA patients treated with adalimumab or infliximab which measured drug trough levels and ADAbs. A Markov model predicted that, within 3 years, 40% of adalimumab-treated and 50% of infliximab-treated patients would need treatment modifications. The economic impact of clinical decision-making was modelled in the short-term (3-6 months) based on 100 hypothetical patients. TDM was estimated to be cost effective if a treatment decision was affected in 2-5 individuals per 100 patients [19].

TDM has a potential use for dose tapering which would reduce treatment costs. A recent study of 55 RA patients with high serum adalimumab trough concentrations (> 8 μg/mL) found that increasing the standard dosing interval to 3 weeks had no effect on disease control compared to standard dosing [20].

In the UK, the National Institute for Health and Care Excellence (NICE) recently assessed ProMonitor® (Grifols, Barcelona, Spain) for monitoring patients' treatment response to biologics in RA. The report identified several uncertainties concerning the system, with no available studies showing the direct effect of monitoring, no agreed cut off levels for adjusting drug treatment, and a lack of a standard NHS drug monitoring pathway [21].

DEVELOPING ALGORITHMS BASED ON BIOMARKER STRATIFICATION

A preliminary algorithm has been developed for use of ADAb status to guide therapeutic decisions in RA patients receiving anti-TNF therapy [22]. The algorithm was based on reactive testing of ADAbs, based on low anti-TNF levels, which would reduce costs [22]. However, as the algorithm has not been fully tested in other cohorts it has not been adopted by EULAR or the British Society for Rheumatology.

An algorithm developed by the American Gastroenterological Association for TDM in IBD recommends that reactive TDM be used to guide treatment changes in adults with active IBD treated with anti-TNF agents [23].

CONCLUSIONS

TNF inhibitor drug levels appear to be a promising biomarker in predicting future treatment response. Implementation of these tests in clinical practice is feasible with huge potential for personalised medicine, clinical decision making, and potential cost-savings. No international guidelines which incorporate TDM algorithms have been published for RA or rheumatic diseases. Future research is required to inform these unmet needs.

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Therapeutic drug monitoring in clinical practice: rheumatic patients

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INTRODUCTION

The pharmacokinetic properties of tumour necrosis factor (TNF) inhibitors differ from those of conventional drugs on account of their route of administration (subcutaneous injection or intravenous infusion) which influences bioavailability, and their route of elimination which is mainly by the reticuloendothelial system in the liver and spleen. In addition, these large proteins circulate preferentially in plasma and only escape to inflamed tissues by vasodilatation, which is a major difference from conventional drugs.

PHARMACOKINETICS OF BIOLOGICAL DRUGS

Pharmacokinetic modelling of infliximab in patients with rheumatoid arthritis (RA) showed high intra- and inter-individual variability in serum trough drug concentrations [1]. Higher doses and shorter dosing intervals of infliximab were associated with lower variability of serum trough drug concentrations.

Factors influencing anti-TNF concentrations include the disease being treated, dose and route of administration of the TNF inhibitor, genetics, disease-modifying anti-rheumatic drug (DMARD) treatment, and body mass index (BMI) (**Figure 1**). However, the two most important determinants of variability are antigenic burden (disease activity) and immunogenicity (presence of anti-drug antibodies [ADAbs]).

There is an inverse relationship between disease activity and anti-TNF trough levels in the inflammatory sink. High disease activity is associated with concomitantly high levels of TNF in inflamed tissues,

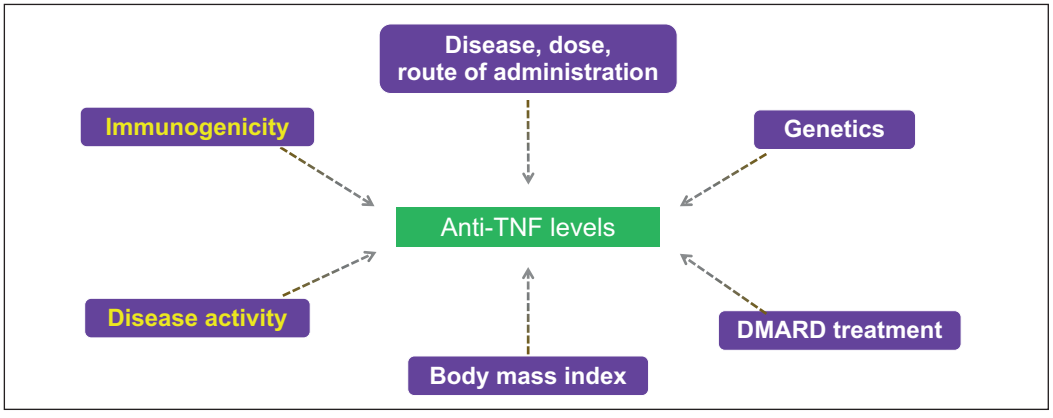

Figure 1. Factors influencing anti-TNF levels. DMARD, disease-modifying anti-rheumatic drug.

which depletes circulating TNF inhibitors resulting in comparatively low serum trough levels of anti-TNF agents. This situation is reversible: when disease activity is reduced, less anti-TNF escapes the joint and serum trough levels are therefore raised. Effective treatment lowers the level of TNF in inflamed tissue, so that subsequent fixed doses of anti-TNF will produce higher trough levels of anti-TNF than the first dose.

This relationship between anti-TNF and disease activity was shown in RA patients, with negative correlations observed between serum trough infliximab concentrations and pre-treatment C-reactive protein (CRP) levels [2]; and between serum trough adalimumab concentrations and 28-joint Disease Activity Score (DAS28) values [3]. The adalimumab concentration required to achieve low disease activity was dependent on the baseline DAS28, with higher doses required for cases with higher disease activity [3].

All therapeutic proteins are potentially immunogenic, with the immune response resulting in production of transient or long-lasting ADAbs. Clinical problems arise when ADAbs completely neutralise the action of the anti-TNF, resulting in low anti-TNF serum levels [4,5]. Long-term administration of adalimumab to RA patients showed that development of ADAbs was significantly associated with lower serum adalimumab concentrations, which was dependent on ADAb titre. The presence of ADAbs was also associated with a lower likelihood of minimal disease activity or clinical remission [6].

SERUM LEVELS OF ANTI-TNF ARE RELATED TO EFFICACY

Clinical data from the pharmacokinetic modelling study by St Clair and colleagues [1] showed that clinical improvement from infliximab therapy in RA patients was associated with serum concentrations of infliximab. In common with pharmacokinetic data, there was considerable inter-individual variability, with 24% of patients with high infliximab concentrations (> 10 μg/mL) showing a minimal clinical response (< 20% American College of Rheumatology [ACR] improvement), and 10% of patients with undetectable infliximab levels (< 0.1 μg/mL) showing a good clinical response (≥ 70% ACR improvement) [1].

Studies of RA patients treated with infliximab [7,8], adalimumab [9], and etanercept [10] have all shown a significant correlation between serum anti-TNF level and clinical improvement. However, the high inter-individual variability observed in these studies makes use of serum anti-TNF trough levels as a predictive marker of clinical response difficult to implement in clinical practice.

THERAPEUTIC DRUG MONITORING

The main steps in therapeutic drug monitoring (TDM) are blood sampling, laboratory measurement of analyte(s), and clinical decision-making based on communication and interpretation of the results [11]. The entire process needs to be conducted quickly in order to inform clinical decisions about possible changes to a patient's treatment.

For any given drug, TDM needs to fulfil specific criteria: a reliable method to measure both drug and ADAb; a narrow therapeutic range of the drug; a lack of good clinical or biological markers of response allowing individual dose adjustment; intra- and inter-individual variability in pharmacokinetics; and a known relationship between drug levels and therapeutic and toxic effects [12].

Enzyme-linked immunosorbent assays (ELISAs) are the most economical, easiest to use, and most widely available of the assays used for TDM. Surface-immobilised TNF is used to capture and measure TNF inhibitors, but the presence of ADAbs may interfere with the assay. ADAbs to TNF inhibitors can be measured directly by ELISAs by coating the plate assay wells with the drug of interest, or can be measured using a radioimmunoassay which is less susceptible to ADAb interference [13,14].

The therapeutic window for TNF inhibitors is defined by upper safety and lower inefficacy boundaries (**Figure 2**). The smooth profiles are completely within the therapeutic window and therefore are not a cause of concern. In contrast, the acute profile may yield safety concerns in the form of adverse event onset at drug concentrations above the upper boundary limit and may be sub-effective at drug concentrations below the lower boundary limit [15]. The therapeutic range for a TNF inhibitor must differ between patients with active disease and those who are in remission due to differences in TNF production in inflamed tissues.

Although the target trough concentration range for maintenance therapy of certain TNF inhibitors has been determined for some immune-mediated inflammatory disorders (IMIDs) e.g. infliximab in inflammatory bowel disease (IBD), and adalimumab in IBD, RA, spondylarthritis, and psoriasis, these data are unavailable for most TNF inhibitors/IMIDs [11]. Thus, clinical experience determines the target range for the treatment of many IMIDs with TNF inhibitors.

FIRST THERAPEUTIC SCENARIO: PREDICTING RESPONSE AFTER TREATMENT INITIATION

A recent study of 66 patients with RA found that low serum trough infliximab levels at treatment initiation predicted outcomes at 1 year. Patients with infliximab levels > 4.44 μg/mL at week 6 had better clinical outcomes at 1 year with significant improvement in DAS28 scores, than patients with infliximab levels below this value (< 4.44 μg/mL) [16].

SECOND THERAPEUTIC SCENARIO: TREATMENT MONITORING

TDM has not yet been applied in RA, although infliximab trough concentrations have been used to

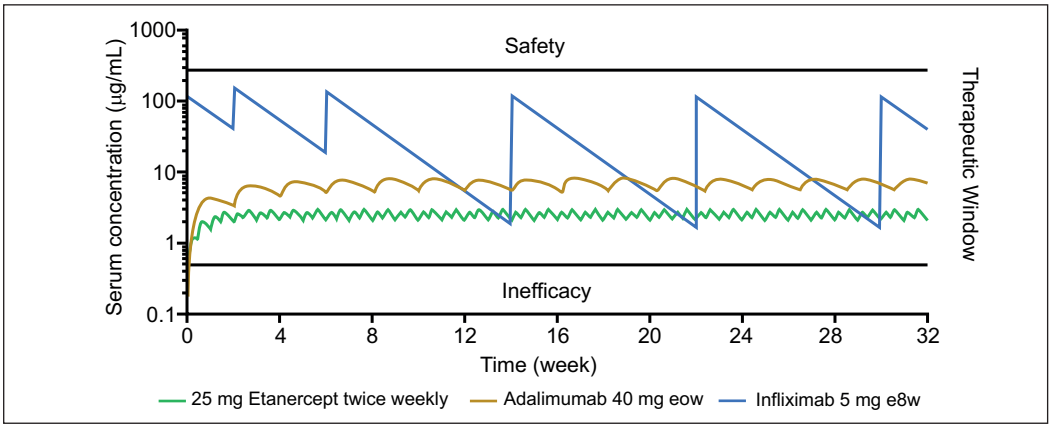

Figure 2. The therapeutic window for TNF inhibitors exemplified by three anti-TNF inhibitors. eow, every other week; e8w, every 8 weeks.

guide dosing for patients with IBD. Targeting infliximab trough concentrations of 3–7 μg/mL resulted in more efficient use of the drug. After dose optimization, continued dosing of infliximab based on trough concentrations was not superior to clinically-based dosing for achieving remission after 1 year, but fewer IBD flares were observed during treatment with TDM [17].

THIRD THERAPEUTIC SCENARIO: PREDICTING RESPONSE TO SECONDARY BIOLOGIC DISEASE-MODIFYING ANTIRHEUMATIC DRUG (BDMARD)

A TDM-based algorithm for an inadequate response to TNF inhibitors was published by Plasencia et al. in 2015 [18]. The algorithm is based on measurement of trough levels of the TNF inhibitor and, if low, measurement of ADAbs, However, the algorithm is not supported by data from randomized clinical trials of patients with RA.

One option for inadequate response to anti-TNF therapy is dose escalation. The impact of dose escalation was evaluated in a retrospective study of 42 RA patients who lacked or lost efficacy to infliximab, which was not attributable to ADAbs. Patients were stratified into undetectable, low (< 1.1 μg/mL) or high (> 1.1 μg/mL) serum trough levels of infliximab during treatment. Dose escalation from 3 mg/kg to 6 mg/kg produced a modest improvement in disease activity (DAS28) in each group, which was not sustained after 12 months' treatment. Escalation produced a significant increase in serum infliximab levels in the high trough level group alone. Thus, dose escalation of infliximab was ineffective in producing clinical improvement in these patients, with the response being independent of the initial infliximab trough serum concentration [19].

A second option following failure of first-line TNF inhibitor therapy is switching to an alternative anti-TNF. Patients with RA who developed antibodies to infliximab or adalimumab had a better DAS28 clinical response after switching to etanercept, compared with RA patients without ADAbs receiving etanercept [20]

FOURTH THERAPEUTIC SCENARIO: MAINTENANCE OF LOW DISEASE ACTIVITY AFTER DOSE REDUCTION

Dose tapering of TNF inhibitors is an option for patients who have low disease activity or are in remission, but the range of serum drug trough concentrations for maintenance therapy still needs to be established.

Retrospective studies have supported the utility of TNF inhibitor serum drug trough concentrations for dose tapering in RA patients. The therapeutic response of patients in remission or with low disease activity to dose reduction of adalimumab was predicted by drug trough levels. Baseline adalimumab levels were significantly higher in patients in remission (median 10.5 μg/mL) or with low disease activity (4.5 μg/mL) than in patients with disease flare (0.9 μg/mL) [21].

Drug tapering of infliximab, adalimumab and etanercept in RA patients with low disease activity reduced serum drug levels for each anti-TNF. These reductions of TNF inhibitors produced cost savings, and comparable disease control, compared with patients on the standard regimen [21].

The results of the first randomized clinical trial of TDM in rheumatology were recently published [22]. Screening of adalimumab-treated RA patients

in remission showed a high variability of adalimumab serum concentrations. In patients with high trough concentrations (> 8 µg/mL), prolonging the dosing interval of adalimumab from every two weeks to every three weeks maintained disease control, which was comparable to patients on the standard regimen. In clinical practice, tapering is performed in patients in clinical remission with lower adalimumab trough concentrations (e.g. 4-8 µg/mL), and further research is needed to establish whether drug tapering maintains disease control in these patients.

CONCLUSIONS

In RA, the dose–response relationship is supported by all studies of TNF inhibitors performed to date. The two most important determinants of variability of anti-TNF levels are disease activity and immunogenicity. Immunogenicity of biologics has a clear effect on pharmacokinetics and clinical response. Drug strategies based on algorithms have been proposed for RA, but evidence supporting these algorithms is low. To date, no randomized controlled trials have been performed to definitively support the effectiveness and cost utility of TDM compared with current clinical practice. Comparative effectiveness research in this field is a priority before TDM of biopharmaceuticals in clinical practice in RA can be implemented.

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Therapeutic drug monitoring in clinical practice: gastroenterology

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OVERVIEW OF INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) comprises two different diseases –ulcerative colitis (UC) and Crohn's disease (CD)– which have some pathogenetic pathways in common. IBD arises in genetically susceptible individuals, with more than 200 risk alleles identified, many of which are shared by UC and CD. Environmental factors also play a role; tobacco has an apparent protective effect in UC, whereas it increases the risk of, and adversely affects the evolution of, CD. Other environmental factors (e.g. diet and use of antibiotics in early life) may also play a role by adversely altering the gut microbiota.

A feature of IBD is immune dysfunction, with many of the identified risk alleles known to play a role in the innate or adaptive immune response e.g. autophagy, colon defensin secretion and lymphocyte apoptosis.

Most patients with IBD are diagnosed during adolescence or early adulthood. The prevalence of IBD is increasing: currently, approximately 800 per 100,000 inhabitants in Europe are affected [1].

Phenotypic classification of CD depends on several factors: the age of onset, with paediatric onset having the worst prognosis; the location of lesions, with lesions most commonly localised in the ileum, colon or both; and the type of lesion (inflammatory, stricturing or penetrating) [2].

CD is a progressive condition. Inflammation is present in asymptomatic as well as symptomatic individuals, which leads to cumulative tissue damage before the development of complications such as fistulas, abscesses and intestinal strictures. Most patients with CD who present with inflammatory lesions progress to stricturing and penetrating lesions, which are commonly treated surgically [3].

Patients with UC are phenotypically classified by the extent of disease. Involvement of the rectum is termed ulcerative proctitis; involvement beyond the rectum to the splanchnic flexure is termed left-sided or distal colitis; and involvement above the splanchnic flexure is termed extensive colitis. Patients with ulcerative left-sided UC, and particularly those with extensive colitis, have a higher risk of colectomy due to refractoriness to pharmacological therapy, dysplasia and the risk of colorectal cancer [2].

UC is a remitting-relapsing disease. Nearly 60% of patients have severe flares at disease onset, which subside over time to milder flares. About a third of patients have repeated severe flares [4].

MANAGEMENT OF IBD

Treatment of most patients with IBD follows a step-up algorithm: aminosalicylates, corticosteroids, immunomodulators, biological agents and, finally, surgery (**Figure 1**). About 50% of UC patients are managed successfully with aminosalicylates (mesalazine and sulphasalazine). More than 80% of CD

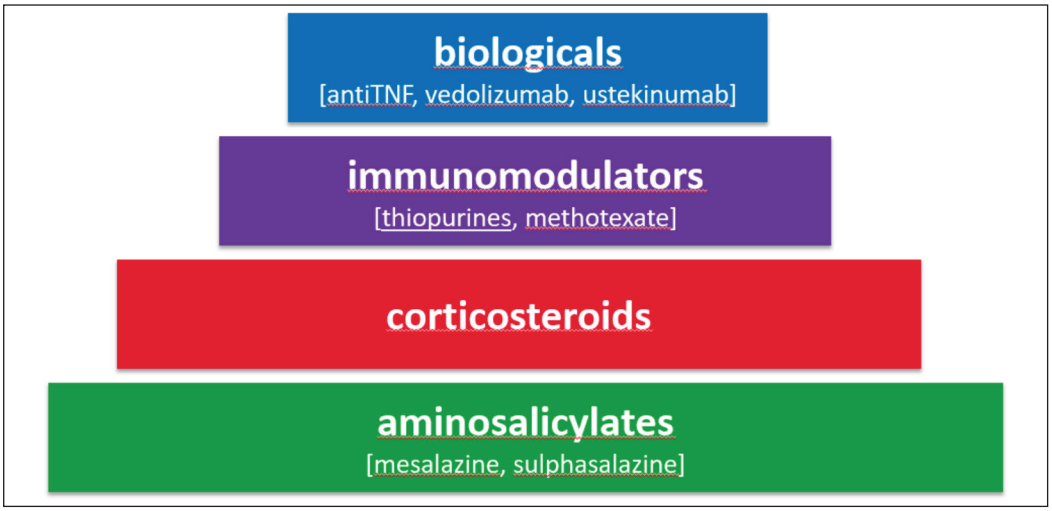

Figure 1. Therapeutic armamentarium in IBD.

patients are treated with at least one course of corticosteroid therapy and about 50- 60% of UC patients receive corticosteroid therapy. Around 75% of CD patients, and about a third of UC patients, are treated with immunomodulators. In contrast to rheumatoid diseases, thiopurines are first-line immunomodulators and methotexate is a second-line agent in IBD. Biological agents are used to treat around 40% of CD patients and 10-15% of UC patients. Three tumor necrosis factor (TNF) inhibitors have been approved for use in IBD: infliximab for CD (1999) and UC (2005); adalimumab for CD (2007) and UC (2012); and golimumab for UC (2014). Regulatory approval has also been given for the 'gut-selective' anti-integrin α4β7, vedolizumab, for both CD and UC (2014), and for anti-interleukin (IL)-12/IL23, ustekinumab, for CD (2017). This limited number of available options for biological therapy in IBD contrasts with other immune-mediated inflammatory diseases (IMIDs). Another major difference between IBD and other IMIDs is that disease activity is assessed invasively using colonoscopy, with biomarkers also having an important role.

Experience with anti-TNF therapy has identified several issues regarding its use. These are: primary non-response which is a lack of improvement after the induction phase; partial response, or primary non-remission; secondary loss of response which is loss of remission or disease flare during maintenance therapy; and adverse effects including acute infusion reactions, and non-infectious and non-neoplastic adverse events. A secondary loss of response which occurs in 30-40% of IBD patients can be due to development of anti-drug antibodies (ADAb) which is termed immunogenicity; accelerated clearance of the drug; or a switch to inflammatory pathways in IBD which do not involve TNF.

Immunogenicity in IBD

Infliximab is the most extensively studied biological agent in IBD therapy. Combination therapy of infliximab plus azathioprine or infliximab monotherapy were both significantly more effective in producing corticosteroid-free clinical remission in CD patients than azathioprine monotherapy [5]. Interestingly, in

this trial (SONIC), median serum infliximab concentrations were significantly higher in patients receiving infliximab plus azathioprine combination therapy than infliximab monotherapy. Meta-analyses of patients with IBD showed that combination therapy reduces the likelihood of developing ADAbs [6]; and that antibodies to infliximab in IBD are significantly associated with a loss of clinical response and lower serum infliximab concentrations [7]. Antibodies to infliximab can be transient or persistent. A retrospective study of 90 infliximab-treated IBD patients found that 59% developed ADAbs, with most appearing soon after initiation of maintenance infliximab therapy (median of 4 infusions). Patients with ADAbs most commonly had undetectable serum infliximab trough levels. Most ADAbs (72%) were persistent, and had higher titres than transient ADAbs. Persistent ADAbs were associated with a secondary loss of response leading to discontinuation of infliximab therapy [8]. Antibodies to infliximab commonly arise within the first 12 months of therapy, although transient ADAbs may develop at any time during infliximab therapy [9]. Consequently, the probability that ADAbs arising after 1 year of therapy will be clinically relevant is low.

Therapeutic range for infliximab in IBD

The lower limit of the therapeutic range for infliximab in IBD is largely defined by retrospective studies. A meta-analysis of 12 studies found that a serum trough infliximab level > 2 μg/ml during maintenance therapy was associated with a greater probability of clinical remission (risk ratio [RR] = $p < 0.001$) and endoscopic remission (RR = 3.0, 95% CI: 1.4–6.5; $p = 0.004$) [10]. However, these results do not translate to data from clinical trials. In the SONIC clinical trial of infliximab in CD, patients were stratified based on their median trough infliximab concentrations [5]. There was no correlation between median trough infliximab concentrations and the proportion of patients in corticosteroid-free clinical remission at 1 year.

THERAPEUTIC DRUG MONITORING IN IBD

Potential applications of therapeutic drug monitoring (TDM) in IBD include: reactive assessment of partial responders and secondary loss of response; proactive prevention of primary non-response and secondary loss of response; and to inform decisions about dosing interval and treatment cessation. TDM is most effective when serial measurements of serum trough anti-TNF levels have been taken.

Prevention of primary non-response

Several studies have shown that higher serum trough infliximab levels early in the induction phase of infliximab therapy are associated with better outcomes. A retrospective analysis of UC patients found that a trough infliximab level ≥ 15 μg/mL at week 6 of induction therapy was independently associated with early mucosal healing at week 14 [11]. In a prospective study of patients with moderate-to-severe UC receiving infliximab induction therapy, 7 of 19 patients (37%) developed antibodies to infliximab as early as 4 days after the second infusion. Pharmacokinetic studies showed that patients with ADAbs had accelerated infliximab clearance which reduced the serum concentration of infliximab and was associated with non-responsiveness [12]. In many UC patients receiving induction therapy (25/30; 83%), infliximab was lost into the faeces. High faecal concentrations of infliximab after the first days of induction therapy were associated with a primary non-response [13].

In cases with high inflammatory burden, TNF is expressed at high levels and acts as a sponge in neutralising anti-TNFs. High inflammatory burden is also associated with increased activity of the reticulo endothelial system which leads to increased metabolism of TNF inhibitor. High inflammatory burden also increases the number of lesions in the intestinal mucosa leading to the detection of infliximab in the faeces. A combination of these mechanisms results in rapid clearance of infliximab [14].

Studies which investigated predictors of primary non-response in IBD have reported that, whereas neither trough infliximab levels nor ADAbs have predictive value during infliximab induction therapy, surrogate markers of inflammatory burden have predictive value. Multiple logistic regression analysis found that, in CD, the ratio of TNF/C-reactive protein (CRP) at baseline was predictive for primary non-response to infliximab at week 14 [15].

Assessment of partial responders

Many studies have demonstrated that IBD patients who are in clinical remission have higher trough anti-TNF levels than patients who are not in remission. In CD patients, infliximab trough levels were associated with the degree of response or remission [16]. Significant associations were observed for biochemical remission ($p = 0.003$) and faecal calprotectin normalisation ($p < 0.0001$), and a non-significant trend was observed for clinical remission ($p = 0.081$). However, there was overlap in infliximab trough levels between patients showing a response/remission and non-response for each parameter.

An ongoing study of CD patients receiving maintenance therapy compared different strategies for infliximab dose intensification based on TDM (biomarker analysis and serum infliximab concentrations) plus clinical symptoms, or clinical symptoms alone [17]. TDM did not improve corticosteroid-free clinical remission compared with maintenance therapy based on clinical symptoms alone.

Prevention of secondary loss of response

Data from three studies which measured infliximab trough levels in patients with clinically stable IBD showed that around 50% of patients were within the therapeutic range, 30-50% were below, and 5-25% were above the therapeutic range [18-20].

The infliximab target trough concentration in the TAXIT randomised controlled trial (RCT) of IBD was 3-7 µg/mL; patients with drug levels of < 3 µg/mL received dose escalation. Following dose escalation, 91% of CD patients achieved trough concentrations within the therapeutic range, which resulted in an increased proportion of CD patients in remission and reduced median CRP concentrations. These changes were not found in UC patients. IBD patients with through concentration above the upper limit of the therapeutic range received dose reduction, which maintained clinical remission and had no significant effect on CRP concentrations. After 1 year, TDM optimised dosing had no benefit over clinically based dosing for achieving clinical remission, but it reduced the frequency of disease flares during therapy [18].

Further RCTs need to be conducted involving patients with a higher probability of developing a secondary loss of response.

Decisions about dosing interval and treatment cessation

Data regarding the potential adverse effects of high levels of anti-TNF are limited, with one study

suggesting that higher anti-TNF trough levels may be associated with impaired quality of life (QoL) [21]. IBD patients receiving infliximab or adalimumab maintenance therapy who had anti-TNF trough levels above the median had significantly lower Inflammatory Bowel Disease Questionnaire (IBDQ) scores and lower (non-significant) 36-item QoL short form scores than patients with lower trough levels.

Data to inform decisions about anti-TNF dosing interval and treatment cessation are also limited. In a retrospective study of IBD patients in long-term remission who discontinued anti-TNF therapy, two factors significantly associated with a lower risk of relapse during follow-up were identified: undetectable anti-TNF levels when stopping therapy ($p = 0.002$), and normal levels of inflammatory biomarkers (CRP and faecal calprotectin) ($p = 0.004$) [22].

Assessment of secondary loss of response

A multicentre RCT investigated 69 CD patients who had lost response to infliximab treatment and were randomised to receive routine dose-escalated infliximab or to be treated using an algorithm based on serum infliximab concentrations using a lower threshold of 5 µg/mL and ADAb levels. Most patients (70%) with secondary loss of response had normal therapeutic drug levels and no detectable ADAbs, with 20% of patients having a loss of response due to ADAbs. Clinical response in the two treatment groups was similar, but the TDM-based approach produced a significant cost saving [23].

American Gastroenterological Association and Gastroenterological Society of Australia (GESA) guidelines on TDM in IBD have recently been published [24,25], both of which are much more detailed than previous guidelines based on the presence or absence of ADAbs [26]. In the TDM-based algorithms developed by GESA for IBD patients with bowel symptoms or in clinical remission options for TDM include adding immunosuppressants, dose escalation of the anti-TNF, and change of drug either within or out of class [25]. While in IBD patients in clinical remission, options for TDM include dose reduction, dose escalation, and repeat testing for ADAbs to identify whether antibodies to the anti-TNF are transient or persistent [25].

TDM alone is insufficient for effective decision making in IBD. A recent study of CD patients in clinical remission treated with infliximab showed that a combination of TDM (infliximab trough level < 2 µg/mL) with the inflammatory biomarker faecal calprotectin (> 250 µg/g of stools) were the most effective parameters for predicting loss of response [27].

CONCLUSIONS

Inflammatory burden in IBD results in increased drug clearance of anti-TNF, producing lower circulating levels. The cut-off values for a therapeutic range of serum trough levels of anti-TNFs remain to be determined, and values may differ between induction and maintenance therapy. Development of ADAbs can also produce a secondary loss of response to TNF inhibitors. ADAbs which are clinically relevant need to be more clearly defined in terms of titre and whether they are transient or persistent. RCTs have failed to show the benefit of TDM alone for achieving clinical remission in IBD. As inflammatory burden appears to be critical for the efficacy of anti-TNFs, a tool which combines anti-TNF drug levels and inflammatory biomarkers may have clinical benefit.

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ES-CEN-GF-51919-PP

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