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TRENDING TOPICS

PERSPECTIVES ON TDM IN GASTROENTEROLOGY

ISSUE 1

INTRODUCTION

Therapeutic Drug Monitoring (TDM) can assist Gastroenterologists in their clinical practice to enhance decision making and safety in patients with inflammatory bowel diseases (IBD) such as Crohn's Disease and Ulcerative Colitis, treated with biologic drugs. A higher awareness of both clinicians and laboratory managers on TDM could not only improve clinical outcomes, but would also have an impact in cost-savings and cost-effectiveness of biologic therapies with TNF inhibitors (or agents against other targets like CD20 …) and biosimilars.

Automated serology instruments for TDM such us Triturus® (Grifols) provide traceable results as well as precision in the detection of trough drug levels and anti-drug antibodies (ADA). In addition to the improvements resulting from measuring drug levels in patients treated with biologic drugs, safety can be increased by monitoring the appearance of ADA which can lead to infusion reactions and adverse effects.

In this first issue of Perspectives on TDM in Gastroenterology, coauthors Alberto Lué, and Fernando Gomollon from the Hospital Clínico Lozano Blesa (Zaragoza, Spain) and Daniela Gilardi and Silvio Danese from Humanitas Clinical Research Center and Humanitas University (Milan, Italy), respectively, describe the scientific evidences about the benefits of TDM in both supporting clinical decisions and improving cost-effectiveness and safety, in IBD patients treated with biologic therapies.

In their review article Dr. Lué and Dr. Gomollon address the importance of TDM in the management of IBD patients with loss of response. For this purpose, coauthors describe the problem of primary non response and secondary loss of response after an apparent initial response. Different strategies for recovering efficacy of treatment are described, and factors for loss of response are analyzed. Authors include an extensive review of the applications of measuring drug and anti-drug antibodies. Furthermore, authors describe the TAXIT study of Vande Casteele and coworkers (2013) and the studies of Steenholdt and coworkers (2014, 2015) comparing dose intensification with TDM based treatment strategy. Finally, authors conclude that TDM strategy may lead to a more cost-efficient use of anti-TNF drugs in patients with loss of response.

In the second article of this issue, Dr. Gilardi and Dr Danese share a review about the relevance of monitoring IBD patients treated with biologic agents, either with ref-

erence product or with biosimilar. Authors introduce a conceptual definition of biosimilar drugs, describe the first biosimilar (CT-P13) marketed in 2013, and a decision-making algorithm based on TDM is also described. Moreover, authors describe a study analyzing the cross-reactivity of ADA to the reference product Infliximab with the biosimilar CT-P13. These results suggest that ADA positive patients to the reference product should not be considered for switching to its biosimilar because the presence of ADA will interact with the biosimilar drug, potentially reducing the efficacy and increasing the risk of adverse effects. Finally, in the conclusions of this review article, authors confirm the utility of TDM for a better management in case of loss of response, and when considering a switch from a reference product to its biosimilar.

Articles

DRUGS AND ANTI-DRUG ANTIBODY LEVELS IN THE MANAGEMENT OF PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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INTRODUCTION

The inhibitors of tumor necrosis factor-α (antiTNF) have dramatically changed the management of patients with inflammatory bowel disease (IBD). It is well established that these drugs are useful for obtaining and maintaining clinical and endoscopic remission[1]. In patients with Crohn's Disease (CD) the available antiTNF drugs are: infliximab, adalimumab and certolizumab (not available in the EU; not approved by EMA)[2]. In ulcerative colitis (UC) infliximab, adalimumab and golimumab have been approved[3]. A variable number of patients do not respond to treatment since the beginning (primary nonresponders, may be around 15%); but a more significant clinical problem, perhaps affecting 10-15% percent of patients every year, is the loss of response after apparent initial success (secondary failures)[4]. When a loss of response occurs some strategies are available: switch antiTNF drug for another, change to a drug with different mechanism of action, combination with an immunosuppresor or intensify the antiTNF dose. We have not identified yet neither consistent clinical prognostic factors nor any biomarker useful for selecting patients with primary nonresponse. However, loss of response can be better classified evaluating pharmacokinetics and pharmacodynamics.

FACTORS INVOLVED IN LOSS OF CLINICAL RESPONSE

The main factors involved in the loss of response are the drug and/or patient-related: drug's factors as the structure and the route of administration, degradation and elimination; and patient's factors as sex, body mass index, albumin and C-reactive protein (CRP) levels, type of disease (CD or CU) and activity, cytokine and anti-drug antibodies (ADA) levels and concomitant treatment with immunomodulators could affect the antiTNF clearance and clinical response. The formation of ADA is related with lower levels of circulating antiTNF and a lower rate of response. The best characterized are the anti-infliximab antibody (ATI) but the

formation of ADA has also been described during treatment with adalimumab and certolizumab[5]. Most patients who develop persistent ATI do so in the first 12 months after the start of treatment. Often the start of loss of clinical response may be preceded by ATI formation. There are also other groups of patients who develop ADA only during a short time period, with a lower probability of loss of response[6].

CLINICAL APPLICATION OF DRUG AND DRUG-ANTIBODIES LEVELS IN THE MANAGEMENT OF PATIENTS WITH INFLAMMATORY BOWEL DISEASE

In those patients who develop neutralizing ADA, the intensification of the treatment would not be the ideal strategy. This hypothesis was confirmed in the landmark study of Afif et al. Studying 155 patients the authors observed that in those who developed ADA the change to other antiTNF lead to much better rate of clinical response compared to intensification (92% vs. 17%; P<0.004). Moreover in those patient with negative ADA but infra-therapeutic levels of antiTNF the optimization of drug doses lead to a better rate of clinical response (86% vs. 33%; P<0.016). These results suggested that in ADA positive patients the intensification of antiTNF doses should be avoided[7].

Other application of drug and drug-antibodies levels could be the tracing of levels to achieve an appropriate drug blood concentration that is related to higher rate of clinical remission and lower rate of ADA development. In the TAXIT study Vande Casteele et al. included 275 patients with CD and CU with clinical remission with infliximab treatment. Although primary endpoint was not reached, in the group treated following a strategy based on optimizing infliximab blood levels between 3 and 7 mcg/ml patients were more likely to remain in therapeutic range having lower CRP and ATI blood levels[8,9].

The individualization of treatment based on drug and drug-antibodies levels have been demonstrated to be also a cost-effective measure. In the works of Steenholdt et al. patients who have loss of response during treatment with infliximab where randomized to intensification or switch to another treatment according to the drug and ADA levels. There were no differences between booth groups in the rate of response or remission, but the costs were lower in the group where the decision has been realized according to the algorithm. The strategy continued to be cost-effective after one year of follow-up[10,11].

According to these results a possible strategy to manage a patient with a possible loss of response to the antiTNF drug should start from confirming that patient symptoms are related with the IBD activity. The second step should be the measurement of drug blood levels followed or not by ADA blood levels. According to the results we could meet these three situations[12]:

1. Normal or high blood levels of drug: it is possible that the inflammatory mediator could be different from TNF. The change to a drug with a different mechanism of action should be evaluated.
2. Low levels of drug and positive ADA: most of the patients probably would not respond to the treatment intensification. The most appropriate decision could be switch to another antiTNF.
3. Low levels of drug and negative ADA: in this case would be appropriate to assess the adherence to treatment. In case of high adherence to treatment, antiTNF drug should be intensified.

However, currently there remain many limitations. First the published studies are very heterogeneous, including different measurement techniques, different groups of patients and the criteria of loss of response are often not well defined. Moreover a clear cut-off value has not been established and is not well known when the best moment to realize the tests is. The standardization of the measurement methods will be a key point for the widespread use of these techniques. Furthermore in some studies has been observed that the presence of ADA is transient and could not be related with a clinical impairment, hence more data are needed before extending it to general practice. Nevertheless the results are encouraging they suggest that it is possible to optimize treatments, especially in patients with low probability of response.

CONCLUSIONS

Currently antiTNF drugs play a key role in IBD management particularly in the induction of clinical remission and its maintenance. The use of drug and drug-antibody levels in the clinical practice could be useful in those patients whom develop a loss of response to antiTNF. This strategy may lead to a more efficient use of antiTNF drug by lowering the costs avoiding unnecessary intensification of treatment. However more studies are required to validate a therapeutic flowchart that permits optimizing resources for all the antiTNF drugs and for all kinds of IBD patient.

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Articles

MONITORING DRUG LEVELS AND IMMUNOGENICITY IN IBD PATIENTS TREATED WITH BIOSIMILARS

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ANTI-TNF IN INFLAMMATORY BOWEL DISEASES AND BIOSIMILARS

Crohn's Disease (CD) and Ulcerative Colitis (UC), commonly known as Inflammatory Bowel Diseases (IBD), are characterized by chronic inflammation of the gastrointestinal (GI) tract.

The introduction of monoclonal antibodies, in particular anti-tumor necrosis factor agents (anti-TNF), led to dramatic changes in the management of several immune-inflammatory diseases, IBD included[1,2].

Biologics are characterized by a positive cost-effectiveness[3], even if long-term therapies can be very expensive[4,5]. The introduction of anti-TNF biosimilars, represents a chance of cost-reduction for National Healthcare Systems and a deep knowledge of these agents is deemed to optimize their use. Cost reduction can be currently quantified as 25-30% compared to the originator[6].

A biosimilar medicine is a biological medicinal product that was developed to be similar to a biological medicine already authorized (reference product, or originator).

The complexity of biologics molecules and the intrinsic characteristics of the manufacturing process lead to a certain degree in variability for these drugs. Variability can also be observed in originators, after changes in the manufacturing process[7,8]. Nevertheless, switching patients to different batches did not lead to any problem in clinical practice[9].

CT-P13, the first anti-TNF monoclonal biosimilar antibody, was approved by EMA in September 2013 for the same indications as reference product Infliximab (IFX).

CT-P13 has been marketed with two brand names: Inflectra® and Remsima®[10,11]. The European Medicines Agency (EMA) did consider data from Rheumatoid Arthritis (RA) and ankylosing spondylitis (AS) obtained in PLANET-RA[12] and PLANET-AS[13] trials strong enough to approve CT-P13 for all the approved indications of the originator, both for patients naïve to infliximab and for patients currently treated with scheduled maintenance treatment. Data on small cohorts of IBD patients shows that biosimilars have similar efficacy and safety profile than originator, even after switching[14-16].

The EMA has recently designated a biosimilar as automatically substitutable, although each country has defined different national guidelines.

Although PK parameters of the two drugs were found to be similar within a patient population, differences in the PK were observed across indications for patients treated with the originator. The clearance of infliximab is greater in adult patients with UC (0.38 L/day) or CD (0.38 L/day) compared to patients with AS (0.27 L/day) and RA (0.26 L/day[17-19] and this should be considered in evaluating the need of drug levels-measurement to optimize therapy.

MONITORING DRUG LEVELS AND IMMUNOGENICITY: RELEVANCE IN INFLIXIMAB TREATED PATIENTS

Infliximab is effective and safe in inducing and maintaining clinical and endoscopic remission in patients with inflammatory bowel disease (IBD)[1,20]. However, up to 50% of patients do not respond to the induction regimen (5 mg/kg i.v. at week 0, 2 and 6) and, moreover, treatment with infliximab is associated with a 10-13% risk per year of exposure of secondary loss of response overtime[21]. Lack or loss of response are mainly associated with low serum levels (trough levels, TL) or the presence of anti-drug antibodies (ADA)[21,22].

Immunogenicity is the ability of a substance to cause an immune response and it is one of the most important clinical issues associated with the use of biologics. The development of antidrug antibodies (ADAs) is influenced by patient characteristics and concomitant immunosuppressive therapy as well as product-related factors[9]. It is a multifocal phenomenon, influenced by the patient (genetic background, ethnicity), by the disease (type, activity), by the treatment (episodic vs. scheduled, co-administration of immunosuppressive agents) and/or by drug related factors (dosing, route of administration, product aggregation and denaturation), that can have a significant impact both on the efficacy and safety of biological therapies[23-25].

ADAs with neutralizing or binding properties can alter the pharmacokinetics and reduce the efficacy of biological drugs. The clearance of infliximab can be reduced up to 30% in patients with ADAs. The prevalence of loss of response to infliximab in patients with ADAs ranges from 40 to 100%, depending on schedule of administration and concomitant medications[26], with a 3-fold higher risk of loss of response in ADA positive patients[27]. The development of ADAs to adalimumab was associated with lower TLs and directly related to drug discontinuation[26].

To date, the prevailing body of evidence with both innovator biologics and biosimilars suggests that post-registration manufacturing changes do not alter their levels of immunogenicity[9].

Several factors influence drug levels and immunogenicity, for example signs of more intensive inflammation (high CRP and low serum albumin) increase IFX clearance, while scheduled maintenance therapy prevents ADA formation (5-10% of patients ADA positive vs. 61% of patients treated with episodic IFX administration)[26]. Another study confirmed a significantly lower incidence of ADAs with a regular maintenance treatment schedule when compared with an episodic strategy (8 vs 30)[28]. Concomitant immunomodulators reduce ADA formation: data from the SONIC trial, shows ADAs in 1% of patients receiving azathioprine and IFX vs. 15% of patients receiving IFX monotherapy[29]. In a post-hoc analysis of randomized controlled trials of IFX, ADAs were found in 10-20% of patients treated with IFX alone vs. 2-7% of patients receiving concomitant immunomodulators[30]. Moreover, IFX treatment in CD patients resulted in the formation of ADAs in 73% of patients who did not receive concomitant immunomodulators, compared with just 46% of patient who did[31].

It has been also observed that low drug levels during infliximab induction therapy (<2.5 l g/mL 4 weeks after the first infusion) have a positive predictive value of 86% for later development of ADAs (8 l g/ml)[31].

The cut-off levels of TL and ADA are still debated, mostly due to the laboratory kit used, although TL > 2 μg/ml seem to be associated with good clinical outcomes[27]. TL and ADA measurement can help the clinician in managing infliximab treatment to increase the probability to achieve and maintain clinical remission of IBD, with a significant impact on the cost of the long-term treatment, due to a tailored approach[32, 33].

An algorithm was proposed for a tailored treatment of patients losing response to anti-TNF, depending on ADAs concentration and TL. For patients with high drug levels, a change in therapeutic class should always be the best choice, without considering ADAs.

The combined evaluation of drug levels and ADAs is essential for patients with low drug levels: ADAs above threshold should lead to a change in anti-TNF and/or association with immunomodulators, while undetectable ADAs could lead to dose escalation.[26]. (Figure 1)

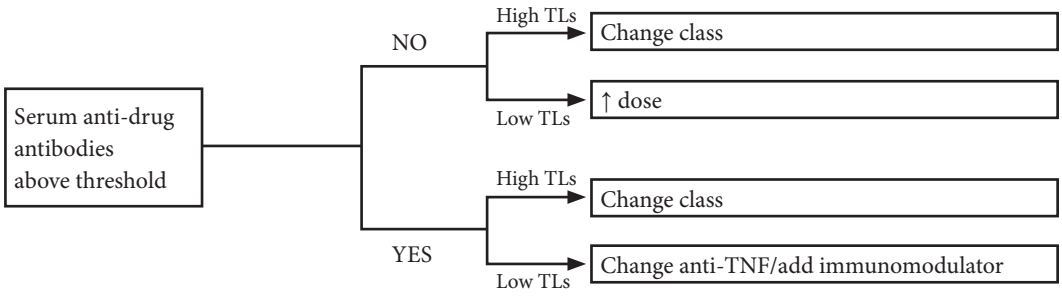

Figure 1. Algorithm for managing loss of response to anti-TNF in an IBD patient.

PHARMACOKINETICS AND IMMUNOGENICITY OF CT-P13

Proving pharmacokinetics and immunogenicity equivalence between the innovator and the biosimilar is essential to safely switch patients from innovator to biosimilar and to manage patients after starting therapy.

Pharmacokinetics was evaluated both in the PLANET-RA and in the PLANET-AS study, as a secondary and primary endpoint, respectively. CT-P13 and originator showed in both cases similar PK properties[12,13].

In a Japanese head to head comparison trial of CT-P13 or infliximab in combination with MTX in RA patients, C_{max} values were similar in the two groups at week 14 and at all the other time-points: authors also reported a lower proportion of patients with a trough concentration <1μg/ml in CT-P13 group compared with infliximab at week 53 (39.0% VS. 55.3%, p not shown)[34].

PK assessment was also evaluated in healthy volunteers in a Phase I study using CT-P13 and two reference IFX products (to evaluate also possible inter-batch variability). Two hundred and fourteen volunteers were randomly assigned 1:1:1 to receive 5 mg/kg of CT-P13, EU-reference IFX or US-reference IFX. C_{max} and AUC were within the predefined equivalence level (80-125%) for all comparisons[35].

The detection of anti-drug antibodies was similar in CT-P13 and infliximab innovator treatment groups both in RA and AS[12,13]. In the PLANET-RA study, the immunogenicity rates were 25.5% for CT-P13 and 25.6% for IFX at week 14 and 48.4% vs. 48.2 at week 30 and sera from ADA positive patients showed cross-reactivity of CT-P13 versus infliximab and vice-versa. In the same study, no cross-reactivity was seen between ADA to adalimumab, another anti-TNF drug, and CT-P13[12]. In the PLANET-AS trial immunogenicity rates for CT-P13 and IFX were, respectively 9.1 vs. 11% at week 14 and 27.4% vs. 22.5% at week 30[13].

Reactivity of antibodies to originator towards biosimilar was evaluated in 126 ADA positive sera obtained by patients treated with Remicade according to approved indications and never exposed to biosimilar. Sera from a balanced population of ADA negative patients were also analyzed (N=124). Sera were analyzed with three different ELISA assays: assay #1 used for detection of ADAs to infliximab originator, assay #2 for ADAs directed against Remsima assay #3 for ADAs against Inflectra. All antibodies developed in patients treated with originator did cross-react with both biosimilars and antibody concentrations detected were similar in all cases. These data suggests that the epitopes raising the immune response to the innovator drug are responsible for the same degree of reactivity when sera are confronted to the biosimilar molecules. As a consequence, ADA positive patients treated with originator should not be considered for switching to a biosimilar treatment, since pre-existing ADA will interact with the new drug, enhance clearance and potentially lead to loss of response and infusion-related reactions[36].

Cross-reactivity was confirmed in other studies[37-39].

Immunogenicity was also evaluated in RA patients treated with CT-P13 and IFX plus MTX: the proportion of ADA positive patients were similar in CT-P13 anf IFX group at each time-

point (19.6% vs. 15.1% at week 14, 25,5% vs. 26,6% at week 30 and 25.5% vs. 32.1% at week 54, respectively). All of the antibody-positive patients had neutralizing antibodies[34].

Efficacy, safety, pharmacokinetics and immunogenicity following an active switch from originator to CT-P13 in IBD patients was evaluated in an observational prospective study. Eighty-three patients (57 CD, 24 UC and 2 IBD-Undetermined) were switched from originator and TL evaluated at week 0 and 16. Clinical scores and biomarkers did not change after switching; TL increased significantly during follow-up (3.5 μg/ml at week 0; 4.2 μg/ml at week 16; p=0.010) and only 2 patients developed de novo ADAs. These data shows the feasibility of switching from originator to biosimilar[40].

A prospective evaluation was conducted in 184 CD and 107 UC patients treated with biosimilar. Only 24.5% of CD patients and 14% of UC patients were previously exposed to anti-TNF, but biologics were stopped more than 12 months before. Previous anti-TNF therapy lead to lower TLs at week 2 and 6 in previously treated patients, but not at later time-points, with consistent higher ADA levels; The association with immunosuppressive treatment was useful in preventing early ADA formation in anti-TNF naïve patients, but the effect did reduce over time (from week 14 to 30). Drugs levels and ADA levels were comparable with originator[41].

Some research groups have raised concerns about extrapolation of data from RA and AS to IBD. Discussion was focused primarily on the utilization of concomitant immunosuppressive therapy: this approach is more frequent in rheumatology than in gastroenterology and immunomodulators can differ, leading to differences in ADA formation in these populations. Moreover, patients with AS historically exhibit a lower incidence of ADAs to IFX than other patient population[38,42].

Furthermore, caution is deemed in merging immunogenicity data from different studies: they are highly dependent on the sensitivity of the assay used to measure the ADAs and on the timing of sampling. A recent study concerning temporal pattern of ADA formation in IBD patients showed that the evolution of ADA is gradual at first, but the majority of subjects form ADA within the first 12 months of infliximab therapy. Moreover, some ADAs can be transient and disappear upon subsequent sampling and continued drug administration. These data indicate that comparing immunogenicity rates between cross-sectional studies that sample ADAs at different and not standardized time-points is difficult[43-46].

In conclusion, monitoring drug levels and immunogenicity in patients treated with biosimilar could be a successful strategy for several reasons.

First of all, as for infliximab originator, a strict evaluation would allow a better management of therapy in case of loss of response, according to the cited algorithm (Figure 1) and could predict a poor response or immunogenicity onset in case of low drug levels during induction therapy[31].

ADAs levels are also relevant for considering switching from originator to CT-P13, due to the cross-reactivity of ADAs. Switching should be avoided in these patients.

Finally, due to the different PK characteristics of anti-TNF in IBD and rheumatologic patients, to the potential impact on immunogenicity caused by the different immunomodulators used in these populations, more data on IBD patients should be conducted to increase specific knowledge in this class of patients.

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TRENDING TOPICS

COST-EFFECTIVENESS OF MONITORING BIOLOGICAL THERAPIES

INDIVIDUALISED THERAPY IS MORE COST-EFFECTIVE THAN DOSE INTENSIFICATION IN PATIENTS WITH CROHN'S DISEASE WHO LOSE RESPONSE TO ANTI-TNF TREATMENT: A RANDOMISED, CONTROLLED TRIAL

Steenholdt C, Brynskov J, Thomsen OØ, Munck LK, Fallingborg J, Christensen LA, Pedersen G, Kjeldsen J, Jacobsen BA, Oxholm AS, Kjellberg J, Bendtzen K, Ainsworth MA.
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CLINICAL BENEFITS OF MONITORING DRUG LEVELS AND IMMUNOGENICITY

ADALIMUMAB TROUGH SERUM LEVELS AND ANTI-ADALIMUMAB ANTIBODIES IN THE LONG-TERM CLINICAL OUTCOME OF PATIENTS WITH CROHN'S DISEASE

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PREDICTIVE VALUE OF THERAPEUTIC DRUG MONITORING IN GASTROENTEROLOGY

SERUM INFLIXIMAB, ANTIDRUG ANTIBODIES, AND TUMOR NECROSIS FACTOR PREDICT SUSTAINED RESPONSE IN PEDIATRIC CROHN'S DISEASE

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BIOSIMILARS

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META-ANALYSIS

COMPARATIVE IMMUNOGENICITY OF TNF INHIBITORS: IMPACT ON CLINICAL EFFICACY AND TOLERABILITY IN THE MANAGEMENT OF AUTOIMMUNE DISEASES. A SYSTEMATIC REVIEW AND META-ANALYSIS

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COMPARATIVE STUDIES BETWEEN PROMONITOR AND COMPETITORS

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