PERSPECTIVES ON TDM IN RHEUMATOLOGY

ISSUE 1

INTRODUCTION

Therapeutic Drug Monitoring (TDM) can assist Rheumatologists in their clinical practice to enhance decision making and safety in patients with inflammatory rheumatic diseases such as Rheumatoid Arthritis, Spondyloarthropaties or Ankylosing Spondylitis, 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® can provide traceable results as well as precision in the detection of trough drug levels (TDL) 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 or adverse effects.

In this first issue of Perspectives on Therapeutic Drug monitoring (TDM) in Rheumatology, Jose Rosas and Francesca R Spinelli from Hospital Marina Baixa and Universita degli Studi di Roma La Sapienza, respectively, describe the scientific evidences about the benefits of TDM in both supporting clinical decisions and improving cost-effectiveness and safety, in rheumatic patients treated with biologic therapies.

In his article Dr. Rosas addresses the importance of tapering drug dosage by reducing the dose or decreasing dose frequency in patients in remission or in low clinical activity, using decision-making algorithms based on trough drug serum levels and ADA titers when necessary. For this purpose, Dr. Rosas cites clinical studies that evaluate the costs or the savings of tapering dosage. In addition, the author shares his experience in the Rheumatology Unit of Hospital Marina Baixa with patients being managed with TDM. In addition, an overview is given of the main concepts of TDM and the decision-making algorithms that have been published. Finally, the prevalence of immunogenicity of anti-TNF drugs and the effects of DMARDs (Disease-modifying antirheumatic Drugs) on ADA appearance is described. The benefits of TDM shown in Dr. Rosas' review underscore the importance of maintaining a smooth communication between the hospital laboratory performing the tests and the rheumatology unit that will receive the results for interpretation.

In the second article of this issue, Dr. Spinelli shares a review about the impact of immunogenicity on the clinical outcomes in rheumatic patients treated with biologic drugs. Dr. Spinelli

first describes the main concepts of primary non-response and secondary loss of response and immunogenicity as an underlying factor of secondary loss of response. Then Dr. Spinelli explains the differences in immunogenicity between the different anti-TNF drugs in the market, and the effects of anti-drug antibodies on the efficacy of treatments and on the pharmacokinetics of biologic drugs. The importance of monitoring drug levels and its correlation with the disease activity and the cut-off levels associated with low disease activity in patients with rheumatoid arthritis is also described. Moreover, the author reviews several publications showing an inverse correlation between ADA and drug levels, demonstrating the utility of measuring ADA to unravel the etiology of loss of efficacy in treatments with biologic drugs.

Articles

CLINICAL UTILITY AND ECONOMIC IMPACT OF ANTI-TNF DRUG MONITORING

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Rheumatoid arthritis (RA) and inflammatory spondyloarthritis (SpA), which includes psoriatic arthritis and ankylosing spondylitis, are chronic inflammatory diseases, of universal distribution, with a prevalence of around 0.5% to 1% among the adult population[1]. If the inflammation is not adequately controlled it produces irreversible damage, deterioration of functional capacity, a reduction in quality of life, and even a shortened lifespan. However, in the last two decades, with the introduction of biologics, particularly the anti-TNFs, the prognosis has improved measurably for a large portion of the patient population. Nonetheless, a loss of clinical effectiveness occurs in around 30% of patients, either from the beginning of treatment (primary failure) or, more commonly, over time after a positive initial response (secondary failure)[2-5]. The objective is to try to achieve disease remission as quickly as possible, using "treat to target" treatment adjustments[6-7].

ANTI-TNF DRUG MONITORING

For the last several years it has been possible to measure and monitor the serum level of anti-TNF drugs such as infliximab (INF)[8], adalimumab (ADL)[9], etanercept (ETN)[10] and golimumab (GLM)[11], as well as detect the presence of antibodies to these drugs (anti-TNF Abs)[12]. ELISA is the most commonly used technique, both for measuring drug levels and for detecting anti-TNF Abs[13, 14], and is available at all hospital centers. However, it is only able to detect free anti-TNF Abs, not those bound to the drug. For correct monitoring, the sample should be collected the day of treatment +/– 24 hours (trough level), but before its administration, and can be stored frozen until its analysis. Nonetheless, the monitoring of anti-TNF drug levels has complicating factors, such as the clinical activity of the disease (high levels of activity require a larger quantity of drug to block TNF, and the level reached at the beginning of treatment can be lower) or pharmacokinetic variation[8, 15, 16]. Moreover, unlike radioimmunoassay, which is more precise, ELISA is not capable of detecting IgG4 antibodies; drug levels are capable of interfering with the technique; and a standardized cut-off does not exist between the different types and commercial suppliers[17, 18].

Numerous studies have demonstrated the relationship between anti-TNF drug levels and clinical effectiveness (Figure 1)[9-11]. The appearance of anti-TNF Abs is associated with loss of response[9, 11, 19, 20], and, in the case of INF, with the appearance of infusion reactions[21].

Algorithms have been published over the last several years that use anti-TNF serum levels to determine whether to maintain (normal or therapeutic drug levels) or to withdraw (sub-therapeutic level) the anti-TNF, and even to optimize treatment (high or supra-therapeutic levels), reducing the dosage or increasing the time between doses, which indicate that monitoring is useful in clinical practice but also is cost-effective[9, 22] (Figure 2).

FACTORS THAT INFLUENCE THE LEVELS OF ANTI-TNF DRUGS

Various factors can negatively impact the level of anti-TNF, and therefore the effectiveness of the treatment:

1. Adherence to the treatment. In patients treated with subcutaneous drugs, irregular or improper adherence should be the first cause investigated[9, 22].
2. Immunogenicity. The appearance of antibodies that neutralize anti-TNF drugs is correlated with a loss of effectiveness[8, 9, 11, 19-21].
3. Anti-TNF treatment without concomitant therapy. The treatment, when combined with DMARDs, particularly methotrexate, is correlated with lower immunogenicity, above all in patients treated with INF or ADL[23, 24].
4. Obesity. Obese patients achieve lower anti-TNF blood levels[25, 26].
5. Inflammatory activity. Where there is more inflammatory activity there is more TNF, thus requiring a larger quantity of anti-TNF drugs.
6. The pharmacokinetics of the drug and the patient[27].
7. The underlying disease.
8. The measurement technique employed[12-14].

THE PREVALENCE OF IMMUNOGENICITY

The prevalence of immunogenicity depends on the anti-TNF drug, the underlying disease, and on factors such as concomitant treatment with DMARDs:

1. Immunogenicity can prevail in up to 40% of patients treated with INF[20].
2. In patients treated with ADL, the immunogenicity depends in large part on whether the drug is combined with DMARDs, particularly methotrexate[23, 24]. In one study of patients with RA, in which 40% did not receive DMARDs, up to 28% developed anti-ADL Abs[28]. However, in another study, in which all patients concomitantly received DMARDs, the immunogenicity was less than 10%[8]. On the other hand, in ankylosing spondylitis, where monotherapy predominates, immunogenicity can reach up to 30%.
3. In GLM, the prevalence of immunogenicity is less than 10%[11].
4. The case of ETN is different because the antibodies that appear are non-neutralizing. These cannot be detected with the aforementioned ELISA techniques and are not associated with a loss of response, though their appearance in large numbers can affect response by provoking a quick elimination of the drug from the body[10].

BENEFITS OF ANTI-TNF DRUG MONITORING

The benefits of anti-TNF drug monitoring can be numerous and of assistance in clinical practice.

1. Evaluate the adherence to treatment. It should be considered in patients with low drug levels.
2. Distinguish primary failure (adequate drug without clinical response), which implies that blocking TNF is not the appropriate target. And secondary failure, when the patient responds initially to treatment but the treatment subsequently loses effectiveness. In this case, if the presence of anti-TNF Abs is demonstrated, the patient can continue treatment with a different anti-TNF.
3. Select the patients who could benefit from dosage optimization (Figure 2).
   - Among patients in clinical remission, patients with high drug levels could benefit from a dose reduction or a decrease in the frequency of drug administration. Thus overtreatment would be avoided and possible side effects and unnecessary costs could be reduced.
   - Avoid a dose reduction or a decrease in the frequency of drug administration in patients in remission with levels in the lower range of therapeutic drug levels, given that by reducing the dosage drug levels would fall into sub-therapeutic levels, risking reactivation of the disease.
4. In patients experiencing a loss of effectiveness and undetectable drug levels, looking for anti-TNF Abs is recommended.
5. In patients with an infratherapeutic level of anti-TNF without anti-TNF Abs, acid dissociation can be performed (figure 2), and if there are anti-TNF Abs bound to the drug, they will be released and will potentially become detectable with ELISA.
6. In the case of INF, detecting Abs would avoid the appearance of infusion reactions in a subsequent administration.

ECONOMIC IMPACT

One of the problems of biologics therapy is the cost of treatment. Both RA and SpA are chronic incurable diseases that primarily affect young or middle-aged patients, and therefore productive adults. This will result in an increase in the direct health costs related to prevention, diagnostics and treatment (medication, specialized clinical monitoring, possible hospitalization, comorbidities, etc.), as well as indirect costs relating to decreases in family income and work productivity, and intangible costs relating to decreased quality of life or lifespan[29]. However, anti-TNF drugs are effective in a high percentage of patients, which may help to reduce these direct and indirect costs[30]. It is projected that the use and thereby the spending on this type of drug will gradually but considerably increase.

With the exception of INF, which is administered intravenously, adjusting the dosage to the weight of the patient, the majority of anti-TNF drugs are administered subcutaneously with a fixed dosage and frequency. However, this rigidity may result in some patients receiving a larger dosage than necessary. A variety of previously mentioned factors may influence the cost of treatment: 1) In patients that do not respond to treatment, the clinician evaluates whether to increase the dosage of the drug, with the corresponding increase in costs, or to change the drug or even the therapeutic target. 2) In patients that respond and achieve clinical remission, some propose reducing the drug dosage in accordance with their experience and others add drug level monitoring to guide their decisions[9, 22].

Some recent studies have analyzed the economic impact of these drugs. In the study by Curtis et al, which looked at 15,000 American RA patients from the database of a medical insurance company, the cost effectiveness per patient in the first year was lower for the subcutaneous anti-TNF drugs (ADL, ETN and GLM) than in patients undergoing intravenous biological treatment (abatacept, INF)[31]. Román et al demonstrate that the weight of a patient and the possibility of optimizing vials by treating patients together are important factors in the cost of patients being treated with drugs administered intravenously[32].

Krieckaert et al[33] compared, in 272 RA patients beginning treatment with ADL, the economic impact on a group in which an algorithm based on the clinical activity and level of ADL was followed, versus another group treated according to normal clinical practice. The impact of the mean total savings per patient was greater (€2,500,000) when the algorithm that included drug levels was used, in a simulation carried out using the Markov method.

Several other studies have recently been published evaluating the cost or the savings incurred by reducing the dosage or the frequency of treatment administration of anti-TNF drugs. De la Torre et al[34], in a study with 195 RA patients undergoing treatment with ADL, ETN or INF, including patients with reduced treatment dosage, noted that only those patients treated with ADL or ETN achieved relevant economic savings per patient and year. Similar results were obtained by Escudero et al[35] in a study conducted in 119 patients with ankylosing spondylitis, also including patients with dose reduction. In the study of Rosas et al[36], 45 RA patients in clinical remission (DAS28<2.6) being treated with optimized doses for an average of 1.2 years with ADL (with a frequency of every 18, 21 or 28 days) or ETN (with a frequency of every 10 days or 14 days), were included under clinical management. DAS28 and blood drug levels were measured every 3 months. Over the course of the study 260 doses of ADL and 548 doses of ETN were avoided, with approximate savings of €130,000 and €137,000 respectively, which equals the yearly treatment of 22 patients.

In summary, RA and SpA are chronic incurable diseases. Given that anti-TNF drugs are effective in a high percentage of patients, it is expected that a large number of patients will likely undergo these therapies, resulting in increasing costs. It would be interesting to have strategies for the individualization of the dosages of these drugs because a significant percentage of patients could benefit from a dose reduction without losing therapeutic effectiveness, and simultaneously reducing costs. Monitoring anti-TNF drug levels has proven to be cost effective, and it can be very helpful in this regard.

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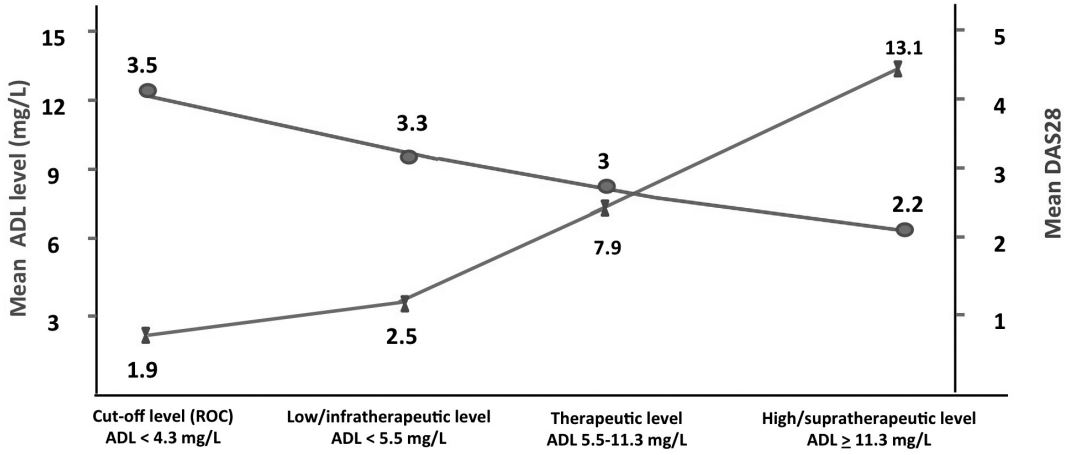

Figure 1. Relationship between the DAS28 result and the ADL level groups: ROC cut-off point and terciles (ADL: adalimumab) Adapted from Rosas J et al (9).

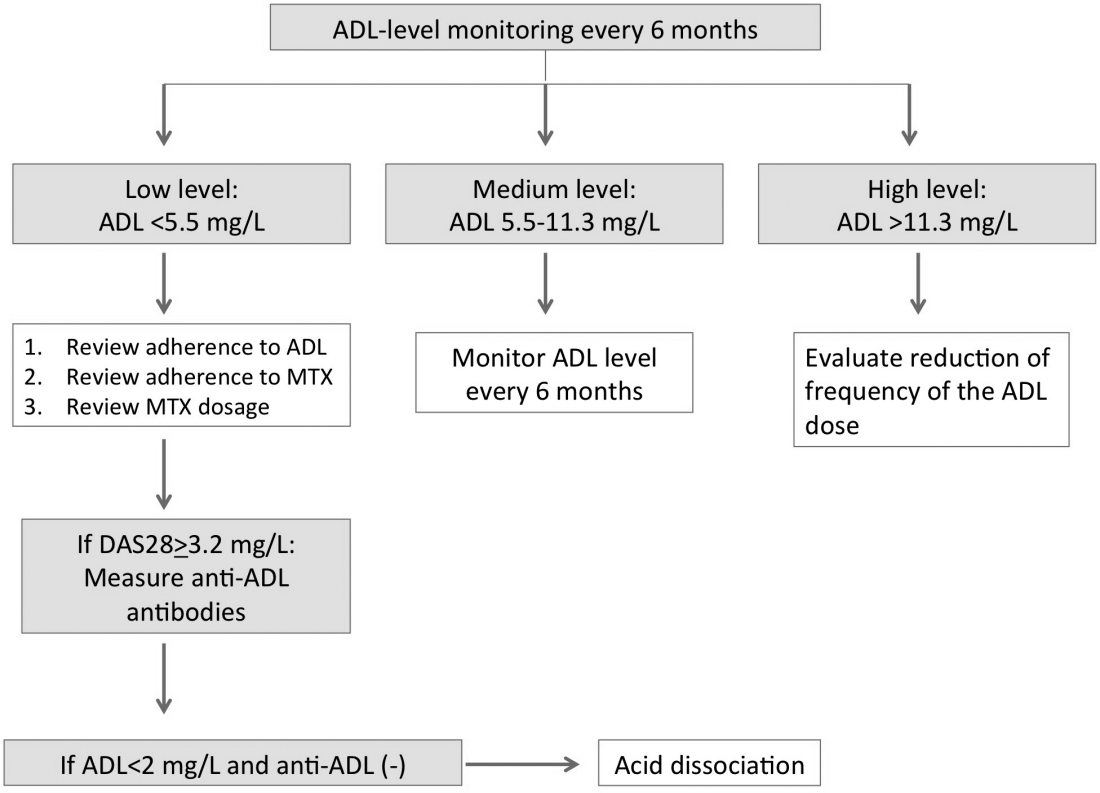

Figure 2. Decision algorithm for the monitoring of RA patients in treatment with ADL in clinical practice (ADL: adalimumab. Anti-ADL: anti-adalimumab antibodies. MTX: methotrexate). Adapted from Rosas J et al (9).

Articles

IMPORTANCE OF IMMUNOGENICITY IN THE MANAGEMENT OF PATIENTS WITH RHEUMATIC DISEASES TREATED WITH ANTI-TNF BIOLOGIC DRUGS

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In the last two decades, biological drugs have transformed the treatment of many chronic inflammatory conditions and by now are a therapeutic cornerstone of diseases such as Rheumatoid Arthritis (RA) and Spondyloarthropaties (SpA). After 15 years of experience, the overall effectiveness of the biological drugs is undeniable; however, about one third of patients fail to respond at all to biological Disease Modifying Anti-Rheumatic Drugs (bDMARDs) (primary failure) and one third lose effect over time (secondary failure).

Among the different factors responsible for secondary loss of response, immunogenicity – i.e. the development of antibodies to the biological drug – may be an underlying factor, by altering the clearance and/or neutralizing the biological effect of the bDMARDs.

Immunogenicity is the ability of a particular "antigen" to elicit an immune response; all biotherapeutics currently used are engineered proteins exogenous to human immune system and given their special nature they can induce the emergence of anti-drug antibodies (ADA). Besides the randomized clinical trials, most of the data available on bDMARDs immunogenicity in rheumatic diseases concern the Tumor Necrosis Factor inhibitors (TNFi).

Infliximab is a chimeric monoclonal anti-TNF antibody, considered the most immunogenic TNFi for its murine component: anti-infliximab antibodies have been reported in 19-50% of patients with RA and SpA with a cumulative incidence of 25%[1,2]. Similar data have been reported with adalimumab, a fully human anti-TNF antibody, which is associated in the development of ADA in 5-54% of patients with rheumatic diseases (with the exception of a small study on 15 RA patients reporting anti-drug antibodies in up to 87% of patients) and a lower cumulative incidence (14.1%)[1,2]. The other fully human anti-TNF antibody, go-

limumab, is associated to the emergence of ADA in up to 15% of patients[3]; the cumulative incidence of anti-golimumab is 3.8%[2].

The incidence of anti-etanercept is 1.2%, with ADA reported in a small percentage of patients (0-6%) with RA and SpA[1,2]; the molecular structure of etanercept – i.e. the p75 TNF receptor fusion protein – seems to render the drug less accessible and less immunogenic compared to the full antibodies infliximab, adalimumab and golimumab. Data on certolizumab pegol, the PEGylated anti-TNF Fab' fragment, are limited to randomized clinical trials: antibodies to certolizumab pegol have been reported in up to 6.4% of patients with a cumulative incidence of 6.9%[2,4]. A recent meta-analysis, evaluating observational studies and randomized clinical trials, showed a statistically significantly higher percentage of patients becoming ADA positive among infliximab-treated subjects compared to adalimumab ($p=0.029$), golimumab, etanercept and certolizumab pegol ($p<0.001$ for all); moreover, a significantly higher prevalence of ADA was found in patients treated with adalimumab compared to golimumab and etanercept ($p<0.001$) but not certolizumab pegol (this latter result should be considered with caution because immunogenicity of certolizumab was investigated in a smaller number of patients)[2].

Antibodies to biotherapeutic can bind drug's epitopes that lie within regions that do not participate in the interaction with the target molecule (anti-allotype "binding" antibodies) (Figure 1). Otherwise, ADA can interact with the drug by binding to epitopes that are functionally relevant for the interaction with the target; in this latter case ADA are directed to idiotype and are defined neutralizing (Figure 1).

A recent study investigated the extent of neutralizing capacity of anti-infliximab, anti-adalimumab, anti-golimumab and anti-certolizumab pegol demonstrating a high percentage of neutralizing antibodies (ranging from 90 to 97%) with all the anti-TNF drugs; interestingly, infliximab showed a broad response, not limited to the murine component of Fab', with a slightly lower percentage of neutralizing ADA[5].

Whether only neutralizing antibodies can affect the efficacy of the biotherapeutic is questionable: anti-allotype antibodies may form large immuno-complexes and reduce circulating levels of drugs by binding it and altering its pharmacokinetics[6].

EFFECT OF IMMUNOGENICITY ON DRUG EFFICACY

The effect of ADA emergence on TNFi efficacy was recently investigated in 2 systematic reviews of the literature with meta-analysis evaluating observation cohort studies and randomized clinical trials[2,7]. Overall, detectable ADA in RA and SpA reduced the odds of response to TNFi - infliximab, adalimumab and golimumab - by 67-68%[2,7]. The majority of the data on the relation between immunogenicity and drug efficacy derives from studies involving infliximab and adalimumab and indicates a reduced likelihood to respond to adalimumab by 87% and to infliximab by 58%; the few data on golimumab suggest a 58% reduction while data on etanercept and certolizumab pegol are scant and not conclusive[2].

The production of ADA seems to be relevant for long-term outcomes such as treatment discontinuation and reduction of disease activity during follow-up. In their long-term, prospec-

tive observational study, Bartelds et al detected anti-adalimumab antibodies in 28% of RA patients followed-up for a median time of 156 weeks; two third of the patients became positive as early as 28 weeks after the initiation of the TNFi[8]. ADA positive patients discontinued their treatment - because of treatment failure or adverse events - earlier and more often compared to ADA negative patients (63% compared to 39%); moreover, the authors observed higher DAS28 scores in ADA positive patients as well as lower incidence of low disease activity or remission[8].

Many studies support the hypothesis that co-administration of DMARDs – in particular methotrexate – can reduce the impact of ADA on clinical response. Overall, immunosuppressant drugs decrease the likelihood of ADA formation by 74%[2]. Vogelzang et al observed that serum trough levels of adalimumab were highest in patients co-treated with methotrexate plus other immunosuppressant and higher in patients taking immunosuppressive drugs other than methotrexate compared to adalimumab monotherapy[9]. Furthermore, in RA patients treated with adalimumab, methotrexate seems to reduce the emergence of ADA in a dose-dependent manner[10]. Chen at al demonstrated a positive correlation between golimumab levels and MTX dosages, supporting the pharmacokinetic findings previously described in adalimumab-treated patients[3,10].

In their meta-analysis, Garces et al showed a greater effect size of ADA on drug response in studies where methotrexate was less used compared to studies in which the percentage of patients treated with methotrexate was greater (77% reduction in clinical response compared to 68%)[7]. Therefore, if we assume that concomitant immunosuppressant reduce ADA formation and that ADA can affect clinical response to bDMARDs, the use of immunosuppressant should be encouraged in patients due to start a TNFi - unless contraindicated or not tolerated.

The studies included in the systematic reviews with meta-analysis are heterogeneous in terms of methodology used to investigate immunogenicity, sampling timing and clinical outcome; moreover, according to the Effective Public Health Practice Project quality assessment tool only less than a half of the papers considered were of good quality[11]. Therefore, a conclusive consideration on how much ADA actually contributes to loss of response to biotherapeutics is difficult to draw.

A recent cross-sectional study was specifically designed to investigate the correlation between a secondary failure to TNFi – defined as an increase of disease activity after having responded to adalimumab or etanercept – and the emergence of ADA[12]. The authors measured both drug and ADA concentration at the time of loss of response in 36 patients with inflammatory arthropathies (RA and SpA) and found subtherapeutic drug levels correlating with the emergence of ADA in 5 out of 21 adalimumab-treated patients (23.8%); none of the etanercept-treated patients showed ADA nor subtherapeutic drug concentrations[12].

A larger prospective observational cohort study investigated whether ADA and/or drug levels might predict treatment response to adalimumab or etanercept in 311 RA patients[13]. Disease activity and immunogenicity were assessed at the same time at baseline and after 3, 6 and 12 months of treatment. European League Against Rheumatism

(EULAR) response at 12 months was significantly positively associated with adalimumab serum levels and negatively associated to anti-adalimumab status; even etanercept levels were significantly associated to EULAR response, but none of the patients developed anti-etanercept antibodies[13].

EFFECT OF DRUG LEVELS ON DRUG EFFICACY

The response to TNFi parallels the drug trough levels. Secondary failure can be related to individual differences in drug bioavailability and pharmacokinetic affecting circulating drug levels. Some studies clearly demonstrated how infliximab bioactivity disappears from the circulation as soon as anti-infliximab antibodies appear[14-16]. Several other investigators demonstrated an association between low levels of TNFi (infliximab, adalimumab and golimumab) and ADA detection[3,4]. Besides immunogenicity, pharmacodynamic issues, mechanisms underlying inflammation, as well as infections and modification of concomitant therapies, may be involved in the decrease of drug levels.

In the study by Jani et al, other factors that are known to influence the pharmacokinetic (i.e. sex, body mass index, disease activity and adherence) were investigated, but only immunogenicity to adalimumab was confirmed to be significantly associated to circulating drug levels[13]. Etanercept levels seems to be significantly higher in good responders compared with moderate and EULAR non-responders even in absence of ADA[17]; however, etanercept serum levels have a wider variation over time, maybe attributable to the shorter half-life, and seem to be less useful to predict the clinical response[13].

The recent availability of validated commercialised immunoassays able to measure drug levels and anti-drug antibodies levels has attracted the interest of scientists and clinicians on the therapeutic drug monitoring. Rosas et al studied 57 RA patients treated with adalimumab and observed that patients with positive ADA (7%) had significantly lower adalimumab levels and higher DAS28 scores compared to ADA negative patients[18]. The authors identified a cut-off value of serum adalimumab associated with a low disease activity (DAS28 < 3.2) with 88% sensitivity and 60% specificity[18].

However, there is still no agreement on the ideal cut-off values to reach in order to guarantee the clinical efficacy of TNF inhibitors adalimumab and etanercept. In a recent study, Chen et al identified 1.274 µg/ml as the optimal cut-off level of adalimumab for a good EULAR response at 6 months, with 90% sensitivity and 100% specificity; the optimal etanercept cut-off level was 1.242 µg/mL with 80.8% sensitivity and 100% specificity[19]. Anti-drug antibodies were detected in up to one third of patients treated with adalimumab – but none of those treated with etanercept – and were associated with a reduced therapeutic response after 6 and 12 months[19].

To establish a concentration–effect curve, Pouw et al followed up 193 RA patients treated with adalimumab and investigated the relationship between drug trough levels and clinical response after 28 weeks; concentrations around 3 µg/ml was sufficient to reach a DAS28 improvement of at least 1.2 and serum levels up to 8 µg/ml showed a positive association with ΔDAS28 whereas levels above 8 µg/ml did not further improve clinical efficacy[20]. This latter observation suggests that therapeutic drug monitoring could avoid overtreatment (and

possibly resulting side effects) and reduce drug-related costs without affecting treatment efficacy.

MONITORING IMMUNOGENICITY IN THE CLINICAL PRACTICE: TESTING DRUG AND ANTI-DRUG ANTIBODIES

Immunogenicity is one of the open issues included in the research agenda of the updated EULAR recommendations for RA management: "*is measurement of serum drug and/or drug antibody levels useful in clinical practice?*"[21].

The actual impact of drug immunogenicity on circulating drug levels and drug efficacy can be better realized only if patients are monitored both for drug levels and ADA routinely or, at least, in the case of treatment failure.

Therapeutic drug monitoring - i.e. monitoring circulating levels of drug and ADA – seems to warrant cost-effective interventions and would allow clinicians to optimize the treatment of autoimmune rheumatic diseases, tailoring therapy according to individual needs rather than generically treating the disease.

Drug and anti-drug should be monitored simultaneously to better define the strategy to adopt in each different situation.

The proof of an inverse correlation between ADA and drug levels suggests that assessing immunogenicity may be useful to determine the etiology of low drug levels thus facilitating the choice of the alternative therapeutic option.

Figure 2 shows a real case of a patient in which the determination of drug levels and ADA in research setting guided the therapeutic choice.

Different authors have proposed therapeutic algorithms based on therapeutic drug monitoring. Trough drug serum level can be considered a surrogate pharmacokinetic marker and monitoring drug levels and ADA in patients who lost response to the bDMARDs would allow adjusting treatment on the basis of pharmaceutical evidence.

In patients experiencing a secondary failure we are faced with 4 different situations (Figure 3).

In patients who are inadequate responders to TNFi, optimal concentration of the drug and absence of ADA suggest that TNF is not the main pathogenic pathway indeed not the best therapeutic targets; such cases would benefit more from a drug with a different mechanism of action. On the contrary, subtherapeutic drug concentration and ADA positivity suggest that TNF is the right target but immunogenicity may have reduced drug's effect; since immunogenicity of a TNFi does not affect the effectiveness of a different drug of the same class, those patients experiencing a loss of response due to ADA formation can take advantage from a new TNFi. Moreover, the addition of an immunosuppressant should be considered in non-responder patients treated with TNFi monotherapy In case of optimal drug concentration and ADA positivity, the therapeutic choice could be either a bDMARD with a different mode of action or a new TNFi. Finally, in patients with subtherapeutic drug levels

without ADA, treatment adherence and pharmacokinetic issues other than immunogenicity should be evaluated. Figure 4 proposes a therapeutic algorithm that integrates drug levels and ADA evaluation in clinical decision both in responder and non-responder patients. Indeed, therapeutic drug monitoring could be useful also in patients who are responding to the dDMARDs: optimal drug levels in absence of ADA may suggest to consider dose reduction or interval prolongation to avoid over-therapeutic, unnecessary high levels of circulating drug; moreover, in patients responding to the TNFi, monitoring of ADA should be considered since certain side effects can be related to the production of immune-complexes between circulating drug and anti-drug antibodies.

In conclusion, it is clear that the response to a bDMARDs parallels the drug trough levels. In case of secondary loss of response, besides treatment adherence ("*drugs don't work in patients who don't take them*" C. Everett Koop), immunogenicity should be always kept in mind as a mechanism altering the clearance and/or neutralizing the biological effect of the drugs.

Determining optimal treatment in patients failing a biological drug is challenging. The empirical increase of dosage may be ineffective and carry a high cost; moreover, the availability of bDMARDs with different mechanism of action call for markers pointing to clinicians the choice of the right drug for each patient. Monitoring both circulating levels of drug and ADA – mimicking the *in vivo* situation – seems to provide essential information for such a demanding choice.

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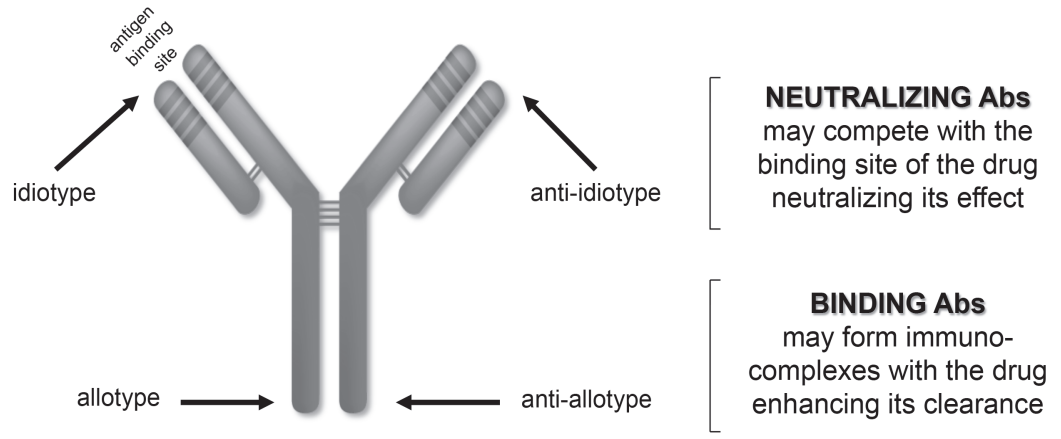


Figure 1. Sites of anti-drug antibodies binding and implications in drug effect.

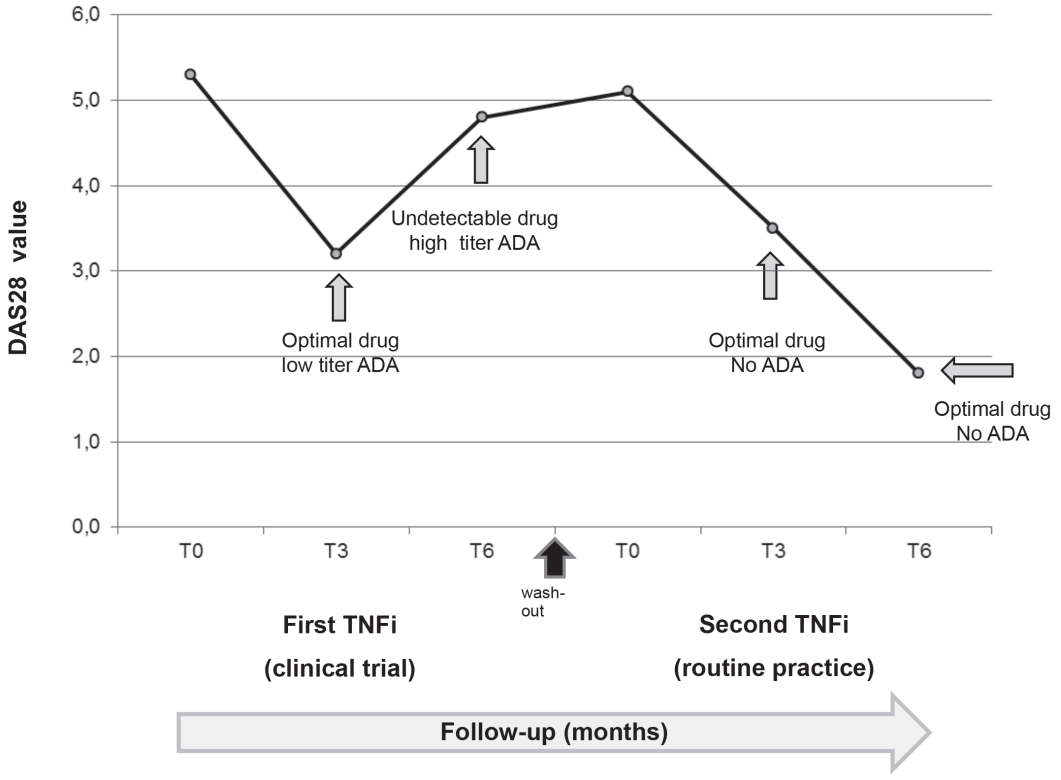
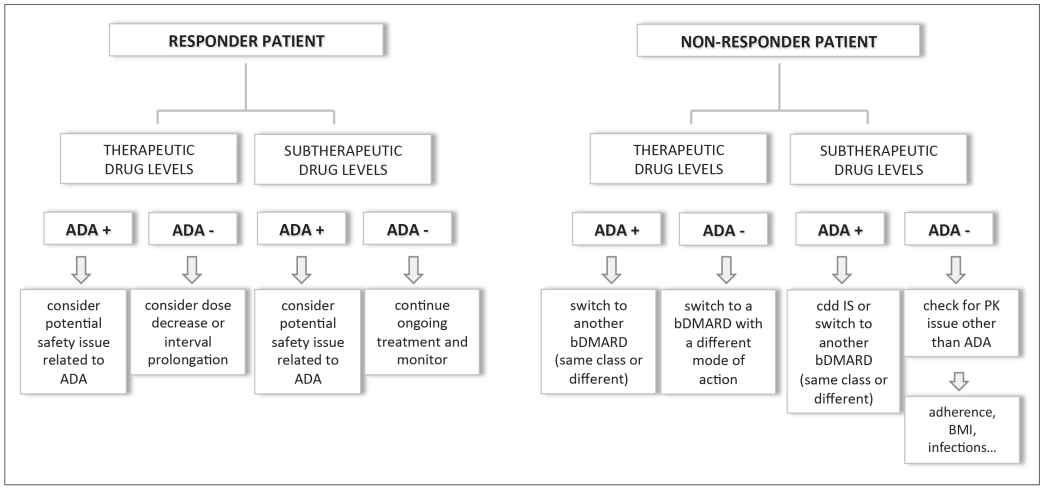


Figure 2. Clinical application of therapeutic drug monitoring: the exemplifying case of a rheumatoid arthritis patient enrolled in a clinical trial.

SUBTHERAPEUTIC DRUG ADA +	**SUBTHERAPEUTIC DRUG ADA -**
OPTIMAL DRUG ADA +	**OPTIMAL DRUG ADA -**

ADA = anti-drug antibodies.

Figure 3. Possible scenarios encountered in patients with inadequate clinical response.



ADA=anti-drug antibodies, bDMARD = biological Disease Modifying Anti-Rheumatic Drug, IS = immunosuppressant, PK = pharmacokinetic, BMI = body mass index

Figure 4. Algorithm for therapeutic strategies based on therapeutic drug monitoring.

TRENDING TOPICS

COST-EFFECTIVENESS OF MONITORING BIOLOGICAL THERAPIES

PERSONALISED TREATMENT USING SERUM DRUG LEVELS OF ADALIMUMAB IN PATIENTS WITH RHEUMATOID ARTHRITIS: AN EVALUATION OF COSTS AND EFFECTS

Krieckaert CL, Nair SC, Nurmohamed MT, van Dongen CJ, Lems WF, Lafeber FP, Bijlsma JW, Koffijberg H, Wolbink G, Welsing PM.
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ECONOMIC IMPACT OF DECREASING ADALIMUMAB AND ETANERCEPT DOSES AND DRUG MONITORING IN PATIENTS WITH RHEUMATOID ARTHRITIS IN CLINICAL REMISSION: PRELIMINARY STUDY FROM A LOCAL BIOLOGICS UNIT [ABSTRACT]

Rosas J, Llinares-Tello F, Senabre JM, Santos-Soler G, Salas-Heredia E, Barber X, Pons A, Cano C, Lorente M, Molina.
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A TEST-BASED STRATEGY IS MORE COST EFFECTIVE THAN EMPIRIC DOSE ESCALATION FOR PATIENTS WITH CROHN'S DISEASE WHO LOSE RESPONSIVENESS TO INFLIXIMAB

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CLINICAL BENEFITS OF MONITORING DRUG LEVELS AND IMMUNOGENICITY

DRUG TROUGH LEVELS PREDICT THERAPEUTIC RESPONSES TO DOSE REDUCTION OF ADALIMUMAB FOR RHEUMATOID ARTHRITIS PATIENTS DURING 24 WEEKS OF FOLLOW-UP

Chen DY, Chen YM, Hsieh TY, Hung W3, Hsieh CW, Chen HH, Tang KT, Lan JL.
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THE CLINICAL RELEVANCE OF EARLY ANTI-ADALIMUMAB ANTIBODIES DETECTION IN RHEUMATOID ARTHRITIS, ANKYLOSING SPONDYLITIS AND PSORIATIC ARTHRITIS: A PROSPECTIVE MULTICENTRE STUDY

Hoxha A, Calligaro A, Tonello M, Ramonda R, Carletto A, Paolazzi G, Bortolotti R, Del Ross T, Grava C, Boaretto M, Favaro M, Teghil V, Ruffatti A, Punzi L.
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INFLUENCE OF IMMUNOGENICITY ON THE EFFICACY OF LONG-TERM TREATMENT WITH TNFA BLOCKERS IN RHEUMATOID ARTHRITIS AND SPONDYLOARTHRITIS PATIENTS

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SIGNIFICANT ASSOCIATIONS OF ANTIDRUG ANTIBODY LEVELS WITH SERUM DRUG TROUGH LEVELS AND THERAPEUTIC RESPONSE OF ADALIMUMAB AND ETANERCEPT TREATMENT IN RHEUMATOID ARTHRITIS
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CLINICAL UTILITY OF RANDOM ANTI-TUMOR NECROSIS FACTOR DRUG-LEVEL TESTING AND MEASUREMENT OF ANTIDRUG ANTIBODIES ON THE LONG-TERM TREATMENT RESPONSE IN RHEUMATOID ARTHRITIS
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ANALYTICAL AND CLINICAL EVALUATION OF A NEW IMMUNOASSAY FOR THERAPEUTIC DRUG MONITORING OF ETANERCEPT
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PREDICTIVE VALUE OF THERAPEUTIC DRUG MONITORING IN RHEUMATOLOGY

DRUG TROUGH LEVELS PREDICT THERAPEUTIC RESPONSES TO DOSE REDUCTION OF ADALIMUMAB FOR RHEUMATOID ARTHRITIS PATIENTS DURING 24 WEEKS OF FOLLOW-UP
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BIOSIMILARS

COMPARABLE LONG-TERM EFFICACY, AS ASSESSED BY PATIENT-REPORTED OUTCOMES, SAFETY AND PHARMACOKINETICS, OF CT-P13 AND REFERENCE INFLIXIMAB IN PATIENTS WITH ANKYLOSING SPONDYLITIS: 54-WEEK RESULTS FROM THE RANDOMIZED, PARALLEL-GROUP PLANETAS STUDY

Park W, Yoo DH, Jaworski J, Brzezicki J, Gnylorybov A, Kadinov V, Sariego IG, Abud-Mendoza C, Escalante W, Kang SW, Andersone D, Blanco F, Hong SS, Lee SH, Braun J.

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ANTIBODIES TO INFLIXIMAB IN REMICADE-TREATED RHEUMATIC PATIENTS SHOW IDENTICAL REACTIVITY TOWARDS BIOSIMILARS

Ruiz-Argüello MB, Maguregui A, Ruiz Del Agua A, Pascual-Salcedo D, Martínez-Feito A, Jurado T, Plasencia C, Balsa A, Llinares-Tello F, Rosas J, Torres N, Martínez A, Nagore D.

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EFFICACY AND SAFETY OF CT-P13 (BIOSIMILAR INFLIXIMAB) IN PATIENTS WITH RHEUMATOID ARTHRITIS: COMPARISON BETWEEN SWITCHING FROM REFERENCE INFLIXIMAB TO CT-P13 AND CONTINUING CT-P13 IN THE PLANETRA EXTENSION STUDY

Yoo DH, Prodanovic N, Jaworski J, Miranda P, Ramiterre E, Lanzon A, Baranauskaite A, Wiland P, Abud-Mendoza C, Oparanov B, Smiyan S, Kim H, Lee SJ, Kim S, Park W.

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A RANDOMISED, DOUBLE-BLIND, PARALLEL-GROUP STUDY TO DEMONSTRATE EQUIVALENCE IN EFFICACY AND SAFETY OF CT-P13 COMPARED WITH INNOVATOR INFLIXIMAB WHEN COADMINISTERED WITH METHOTREXATE IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS: THE PLANETRA STUDY

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IMMUNOGENICITY OF TNF INHIBITORS

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 OTHER ELISA ASSAYS

THE DETECTION OF ANTI-ADALIMUMAB ANTIBODIES IN A SERIES OF INFLAMMATORY POLYARTHRITIS: THREE ELISA METHODS COMPARED

Fabris M, Pistis C, Zabotti A, Picco L, Curcio F, Tonutti E, Vita SD.

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ACID-DISSOCIATION

PRACTICAL APPLICATION OF ACID DISSOCIATION IN MONITORING PATIENTS TREATED WITH ADALIMUMAB

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