Predictors of Response to TNF Inhibitors in Rheumatoid Arthritis
Do We Have New Tools for Personalized Medicine?

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Abstract
The use of biological agents in the treatment of rheumatoid arthritis (RA) has grown constantly since the approval of the first therapeutic monoclonal antibody against tumor necrosis factor-alpha (TNF) in 1996. While these agents transformed RA treatment, not all patients respond to these agents. Moreover, the cost of these agents is high, and some patients may suffer from adverse events. Thus, the prediction of individual response to biological treatment has become a major clinical challenge in RA. Recent studies have provided evidence that biomarkers may be identified predictive of the response to therapy with these agents. This article will review some of the recent advances in the biomarkers and therapeutic drug monitoring as predictors of response to TNF inhibitor therapies in patients with RA.

We now achieved a state of relative comfort with the results of randomized controlled trials of the last decade, convincing us that tumor necrosis factor-alpha inhibitors (TNFi) are effective therapeutic modalities in patients with rheumatoid arthritis (RA). While TNFi therapies revolutionized the treatment for many patients, a substantial percentage of patients (40% to 60%) do not respond to either DMARD or biologic therapies. Thus, what we are trying to figure out now is a way to predict those patients who are likely to respond to these therapies. Identifying the characteristics of RA patients that are able to predict a beneficial response to these agents before the start of treatment is important, especially in view of the high costs and potential side effects of these agents. Moreover, instituting the most effective treatment early in the disease course could have considerable impact on long-term outcome. Last year witnessed numerous studies addressing this problem with different approaches, which can be categorized under several subheadings. The focus of this review is limited only to those studies published last year and investigating biomarkers and therapeutic drug monitoring (immunogenicity) as predictors of response to TNFi therapies. While several studies have investigated the role of genetic biomarkers, the genetic indicators of drug response will not be discussed in this review.

Biologic Markers
Several studies, mostly with small sample sizes, have studied the influence of baseline TNF levels to the treatment response in RA patients treated with various TNFi and failed to demonstrate robust results regarding the value of TNF levels as predictive of treatment response. On the other hand, it is appealing to speculate that production and consequential plasma levels of TNF, the target molecule of TNFi, exceeds the neutralizing capacity of these agents in insufficient responders who are unable to maintain threshold serum levels of these agents. If this is the case in at least some of the patients, then escalating the dose of the TNFi would be a logical approach in those who had high baseline levels of TNF and unresponsive to standard dosing regimen. Takeuchi and associates investigated whether baseline TNF levels determine who would benefit from dose escalation in RA patients who participated in a randomized controlled trial (RISING study) of infliximab (IFX). The RISING study consisted of 327 patients with active RA who had inadequate response to methotrexate (MTX), and randomly assigned to three different doses of IFX (3, 6, or 10 mg/kg, every 8 weeks, from weeks 14 to 46) based on the response obtained during the open-label period of study (weeks 0 to 14, patients...
were administered 3mg/kg IFX at 0, 2, and 6 weeks). This study has shown that clinical response to IFX at a dose of 10 mg/kg is significantly higher as compared to 3 mg/kg IFX, while the measurable differences among the different doses of IFX were quite small. Since plasma samples for the evaluation of baseline TNF were collected before the first infusion of IFX, they were able to analyze the influence of baseline TNF levels on the clinical response at week 54. To analyze this, patients were stratified into three groups (TNF-low, TNF-intermediate, and TNF-high) according to their baseline TNF levels. It was found that in patients with high TNF production at baseline, clinical response and disease activity were significantly better at 10 mg/kg as compared to 3 mg/kg and 6 mg/kg, while dose escalation was not provide any benefit in low and intermediate producers of TNF. In contrast to the studies showing no benefit of higher doses of IFX on clinical responses than standard doses, this study shows us that there exist subgroups of patients who may gain some benefit from dose escalation that can be identified by baseline plasma TNF measurements.

As in the case of baseline TNF levels, the pattern and amount of other proinflammatory cytokines might have a value in determining the response to TNFi. A small study of DMARD-IR patients treated with three different TNFi and followed for 24 weeks found that IL-1β production of lipopolysaccharide-stimulated whole blood cultures was significantly lower in non-responders (EULAR response criteria) compared to responders. Moreover, the sensitivity and specificity of IL-1β for predicting response to TNFi were found as 78.1% and 77.8%, respectively. However, the researchers were not able to explain why IL-1β is more suppressed in non-responders.

Chen and colleagues suggested the potential usefulness of circulating Th17 cells and IL-17 as a biomarker to monitor response to TNFi therapy. In a study with 48 active RA patients who were followed up for 6 months, the frequencies of circulating Th17 cells and serum levels of Th17 related cytokines were determined both before and after TNFi therapy. Increased pre-treatment serum IL-17 levels were detected in patients categorized as non-responders compared to those achieving EULAR good and moderate response at week 24. While groups (responders vs. non-responders) are different with regard to their baseline IL-17 levels, multiple logistic regression analysis demonstrated that only a high baseline IL-17 level could be a significant predictor of poor therapeutic response (sensitivity 66.7%, and specificity 83.3%). In addition to their finding regarding the predictive role of IL-17, the results of this study may also suggest that, at least in a subset of RA patients with poor response to TNFi, Th17 dependent inflammatory mechanism could be in charge.

Therapeutic Drug Monitoring (Immunogenicity)

Therapeutic drug and antibody monitoring is increasingly recognized as an important new concept in the treatment of RA patients given TNFi. Previous studies showed that the presence of neutralizing anti-drug antibodies is associated with the drug levels below the therapeutic range, and thus the suboptimal clinical outcome, particularly when there is no detectable drug in the serum. Last year several studies reported important data regarding the potential value of therapeutic drug and anti-drug antibody monitoring as a predictor of response to TNFi.

In their retrospective observational study, Pascual-Salcedo and coworkers analyzed the clinical consequences of the production of anti-infliximab antibodies (anti-IFX Abs) and serum trough concentrations of IFX in a cohort of 85 RA patients undergoing IFX treatment over a prolonged period of time. They found that almost one-third of the patients developed anti-IFX Abs, which appeared mostly following the forth infusion. According to the EULAR response criteria, 100% of non-respondent patients at any time point showed anti-IFX Abs, while only 24% of responders had such antibodies. Serum trough concentration were also in support of this finding as showing inverse correlation with the presence of anti-IFX Abs and with the loss of clinical efficacy in time. While this study did not add much to our knowledge obtained from previous work, it differs from the preceding studies with respect to longer time of follow-up. With the extension of the analysis over more than 4 years, the researchers had a chance to examine survival of IFX treatment, which disclosed an increased median survival time on IFX treatment in patients without antibodies as compared to those having antibodies (8.89 years vs. 4.15 years). An interesting finding of this study was the duality of the dynamics of anti-IFX Abs levels in response to drug dose escalation. Two kinds of response on dose escalation were observed; in some patients, it resulted in the loss of anti-IFX Abs coinciding with an improvement in clinical outcomes, while in another group of patients, escalation in the dose of IFX did neither influence the level of anti-IFX Abs nor clinical response. Moreover, those patients who had not showed any response to dose escalation were found to have a higher rate of infusion related reactions.

Last year, another study with different TNFi, adalimumab, investigating the influence of immunogenicity on the long-term clinical outcomes of RA patients was published. The study cohort consisted of 272 RA patients who started treatment with adalimumab and were followed for up to 3 years at Jan van Breemen Institute with serial drug and anti-drug antibody measurements. As similar to the findings of IFX study, after 3 years 28% of the patients developed anti-adalimumab antibodies, and two-thirds of the antibody positive patients developed these antibodies in the first 28 weeks of treatment. Serum adalimumab levels were inversely correlated with the anti-adalimumab antibody concentrations, as also expected. Presence of anti-adalimumab antibodies strongly predicts the poor clinical outcome in this cohort of patients, as 48% of patients without anti-adalimumab antibodies had minimal disease.
activity (DAS28 < 3.2), while such a state was achieved in only 13% of patients having these antibodies (HR, 3.6, 95% CI, 1.8-7.2; p < 0.001). As in support of this finding, patients with anti-adalimumab antibodies more often discontinued the drug because of treatment failure (38%) compared with those who had no antibodies detected (14%), (HR, 3.0, 95% CI, 1.6-5.5; p < 0.001). It is not known whether increasing the dosing of biologic helps to overcome immunogenicity and hence improve the clinical outcome of the patients. While patient numbers in this study were too small to conduct statistical analysis, data shows that none of the patients in whom anti-adalimumab antibodies became undetectable after increased dosing, reached minimal disease activity in due course.

The use concomitant immunosuppressant (mostly MTX) has been shown to be associated with decreased likelihood of anti-drug antibody development, while the dosing of MTX required is largely unknown. Using the same cohort of RA patients followed at Jan van Breemen Institute, Krieckaert and coworkers stratified those patients according to the baseline MTX dose as no concomitant MTX, low dose (5 to 10 mg/week), intermediate dose (12.5 to 20 mg/week), or high dose MTX (22.5 mg/week). Analysis of the data disclosed that MTX is effective in the prevention of anti-adalimumab antibody development (all patients using MTX vs. no MTX users, OR, 0.20, 95% CI, 0.12 to 0.34; p < 0.001). Moreover, it was also shown that its action works in a dose-dependent manner, with an OR of 0.14 for high dose MTX and OR of 0.36 for low dose MTX groups (compared MTX non-users). An interesting point to note is that all patients using MTX in this study had been on treatment with MTX before the start of adalimumab therapy. Indeed, as also suggested by previous observations, it may not be possible to abolish antibody response once it has started.

While all these studies related with immunogenicity helped us to gain some insight about why some of our patients do not respond to TNFi, we need something more practical that can help us while guiding our treatments in daily practice. Today several therapeutic strategies are available for a patient not responding to a TNFi, and among them switching from one TNFi to another has become the most common approach. However, our current use of this strategy is based on the clinical data instead of any known biologic marker. It would have been desirable to use anti-drug antibody measurement while deciding whether to switch another TNFi or switching to a biologic with a different mechanism of action. In a cohort of 292 etanercept treated RA patients, Jamnistki and coworkers studied the question of whether the reason for non-response to a first TNFi has implications for treatment response to the next TNFi. Eighty-nine out of 292 of these patients were switchers and had previously been treated with either IFX (N = 30) or adalimumab (N = 59). Among the switchers, 53% of them had anti-drug antibodies that were measured at baseline. They found that clinical improvement by means of DAS28 was significantly larger in patients who were TNF naïve as compared to switchers without antibodies after 16 weeks of etanercept treatment. On the other hand, switchers with antibodies did not differ from the patients who were TNF naïve with regard to DAS28 improvement. Taken together, this data suggests that in switchers without antibodies, mechanisms other than TNF could be operating; thus, switching to another class of biologics, such as rituximab, abatacept, or tocilizumab, would be a better option.

Finally, despite the abundance of studies showing an association between low circulating drug levels and poor clinical response for IFX and adalimumab, there are only a few studies addressing this issue for etanercept. This is partly due to the fact that antibodies to etanercept are mostly non-neutralizing and detected in less than 2% of the patients. Recently, a study investigating the association between circulating etanercept levels and clinical response in a cohort of 292 etanercept-treated patients with RA has been published. The study showed that, after 6 months of therapy, etanercept levels were significantly higher in EULAR good responders compared to those patients categorized as moderate and non-responders. Furthermore, when patients were grouped into quartiles according to the height of serum etanercept levels, the lowest quartile covered 40% of all non-responders. Interestingly, none of the patients were found to have anti-etanercept antibodies in their sera. Despite the lack of clear explanation for the lower etanercept levels in some of the patients in the absence of immunogenicity, this study demonstrates that therapeutic drug monitoring should not be limited only to those agents having a potential to develop anti-drug antibodies.

**Conclusion**

In patients with RA, personalized treatment aims at choosing the best treatment to achieve the most applicable goal (remission or low disease activity) for the individual patient. Since RA is a syndrome rather than a disease comprising subsets with different pathogenesis, it is no surprise that a specific therapeutic intervention, such as TNFi, may work better in some patients than in others. Thus, in order to achieve our goal of personalized treatment in RA, we need to identify predictors of response to targeted therapies. Despite some promising markers (anti-drug antibodies, drug trough levels, and other biomarkers) identified to fulfill this role, currently the predictive value of single markers seems not strong enough to predict treatment response in the individual RA patient. Therefore, future studies should focus not only the identification of novel biomarkers but also the development of prediction models using the combination of several parameters to improve the performance of a biomarker-guided approach. Reaching the state of personalized medicine with the help of biomarkers...
has the potential of improving disease outcomes as well as lessening the economic burden of the disease.

Disclosure Statement
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References