Editorial

Predicting the future of anti-tumor necrosis factor therapy

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See related research by Hueber *et al*., http://arthritis-research.com/content/11/3/R76

Abstract

Tumor necrosis factor (TNF) antagonists are approved worldwide for the treatment of rheumatoid arthritis (RA). Clinical experience revealed that TNF-blocking therapy is effective for only approximately two thirds of patients, reflecting that there are 'responders' as well as 'nonresponders'. Given the destructive nature of RA, the risk of adverse effects, and considerable costs for therapy, there is a strong need to make predictions on success before the start of therapy. In the current issue of *Arthritis Research & Therapy*, Hueber and colleagues become the first to present a multiparameter serum protein biomarker set that has predictive value prior to the start of anti-TNF treatment. Ultimately, this finding may contribute to a personalized form of medicine, whereby a specific therapy will be applied that is best suited to an individual patient.

The concept of a personalized form of medicine has attracted interest in the search for molecular and clinical criteria to dissect anti-tumor necrosis factor (TNF) responders from non-responders in rheumatoid arthritis (RA). Essentially, two phases of unresponsiveness might be identified: a primary phase directly after the start of treatment and a secondary phase that develops in initial responders during the course of therapy. The latter is explained by the formation of anti-drug antibodies (anti-anti-TNF antibodies) in a subset of patients. Efforts to understand differential responsiveness have focused primarily on the mechanistic (that is, the primary) phase of unresponsiveness. However, due to the temporal aspects related to monitoring of the clinical response, research findings from studies on the primary phase of unresponsiveness might be intimately linked to processes that are (also) related to anti-drug development.

The value of biomarker strategies in guiding clinical management of monoclonal antibody (mAb) therapies has been highly appreciated in the field of oncology. The perceived importance and support for large-scale and well-powered studies, such as gene expression profiling studies, in oncology have been considerable and this may account for the success in this field. For example, trastuzumab (Herceptin), an anti-human epidermal growth factor receptor 2 (HER2) mAb, is approved along with a diagnostic assay to select breast cancer patients with a high likelihood to benefit from therapy. However, such approaches have lagged behind in the field of rheumatology.

It is to be expected that response prediction to TNF blockade is a multifactorial event that requires a multiparameter biomarker. Accordingly, the research focus is multidisciplinary, including clinometric, cytometric, metabonomic, genomic, proteomic, and imaging approaches. Ideally, a molecular biomarker signature as a predictor for anti-TNF responsiveness in RA should be obtained prior to the start of therapy in a readily available biosample, such as peripheral blood (DNA, RNA, protein, phenotypic cell markers, and/or metabolites), although this compartment may not have direct implications for our understanding of disease pathogenesis. In this issue of *Arthritis Research & Therapy*, Hueber and colleagues [1] report on a multiparameter serum protein biomarker set that has predictive value.

Initial biomarker discovery approaches aimed to understand the pharmacological effects of TNF blockade in the peripheral blood compartment by pharmacogenomics for a comprehensive understanding of the mode of action. These results suggest that all patients treated revealed an overall similar pharmacological response pattern, indicative of the presence of bioactive TNF in the circulation irrespective of clinical response [2,3]. Detailed analyses in search of (subtle) differences in the pharmacogenomic response profiles between responders and non-responders identified informative sets of genes whose expression changes during therapy

ABCoN = Autoimmune Biomarkers Collaborative Network; ACR = American College of Rheumatology; IL = interleukin; mAb = monoclonal antibody; RA = rheumatoid arthritis; TNF = tumor necrosis factor.

were associated with good clinical responses [4,5]. Moreover, baseline differences between responders and non-responders were found [6]. Pharmacogenetic studies have identified markers, including *TNFA* promoter polymorphisms, associated with treatment outcome, although the predicting capacity is weak and controversial findings were reported [7].

In the current issue of *Arthritis Research & Therapy*, Hueber and colleagues [1] describe a multistep proteomics approach to identify a serum protein biomarker set that has predictive value prior to the start of etanercept treatment in population-based RA patients. Their study is based on the premise of a role for differential autoantibody specificities and serum cytokine levels in guiding anti-TNF therapy. Therapy responsiveness was assessed 3 months after the start of therapy, based on the American College of Rheumatology (ACR) criteria for improvement (greater than or equal to ACR 50% improvement criteria response). An integrated analysis of a relevant set of 14 autoantibody specificities and a multiplex 12-cytokine Luminex data set in a combined set of 93 samples consisting of three independent cohorts (a US-based Autoimmune Biomarkers Collaborative Network [ABCoN] cohort [n = 29], a Swedish cohort [n = 43], and a Japanese cohort [n = 21]) showed superior differentiation of responders and non-responders. The autoantibodies were significantly elevated and the trends for all analyzed cytokines, such as TNF, interleukin-15 (IL-15), monocyte chemoattractant protein-1 (MCP-1), and IL-6, revealed higher baseline serum concentrations in responders, although the latter lacked predictive value in itself. These results partly corroborated findings reported by Fabre and colleagues [8]. Subsequent prediction analysis on the full sample set was applied to select an integrated biomarker signature comprising 13 autoantibody specificities and 11 cytokines that enabled pretreatment classification of response in the three ethnically diverse cohorts with a positive predictive value ranging from 58% (Japanese cohort) to 71% (ABCoN cohort). Although the overall prediction does not appear to be that strong, further optimization and preselection of patients on the basis of uniform disease-modifying anti-rheumatic drug (DMARD) treatment regimens are likely to yield stronger predictive values. These results suggest that patients with features of an activated immune status in the peripheral blood compartment are more likely to benefit from anti-TNF treatment. Similar findings were reported for baseline synovial tissue markers associated with responsiveness [9,10].

The identification of a proteomic biomarker in this work is an important further step in the direction of response prediction in RA and in the design of a multidisciplinary biomarker set that takes in account the multifactorial nature of the response prediction. The results of this and other biomarker studies look promising, but full confirmation of the biomarker profiles in independent uniform cohorts is of the utmost importance to guarantee their validity to create added value for prediction of the anti-TNF response in the general patient population. Moreover, the true value of independent and combinatorial biomarker sets can be tested in a prospective setting only. Therefore, combined efforts between different research groups and standardized clinical response measures and technological procedures to facilitate testing of multiple markers in huge well-characterized prospective and well-powered studies are essential and will bring the goal of personalized and optimized anti-TNF treatment in RA within reach.

Competing interests

The VU University Medical Center has filed a patent on research findings to predict the clinical response to anti-TNF (Patent file no. P086657EP00). CLV is listed as inventor and is a stakeholder in Preselect Diagnostics BV.

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