Netherlands
The Journal of Medicine

EDITORIAL

Personalised treatment of arthritis in the next eRA

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Rheumatoid arthritis (RA) is the most predominant chronic inflammatory joint disease affecting approximately 1% of the population. Over the last 20 years great progress has been made in the treatment of this immune-mediated inflammatory disease. Current practice consists of early goal-directed therapy with disease modifying antirheumatic drugs such as methotrexate aiming at significant reduction of inflammation and ultimately remission.[1] However, this certainly has its cost for society as many patients need expensive new treatments with biologic agents such as monoclonal antibodies targeting TNF alpha or anti-B cell therapy to achieve remission. To date no therapy has been proven to be effective in all patients. Consequently, patients can be classified as responder or non-responder. It would be ideal if response to treatment could be predicted prior to starting a new therapy in order to optimise patient care, reduce the risk of adverse effects and last but not least substantially reduce costs.

RA is nowadays thought to consist of different pathogenic subsets leading to common signs and symptoms, clinically defined as RA.[2] It is likely that gaining more insight into the underlying mechanism(s) that cause inflammation in an individual patient will lead to a more rational choice of treatment with a better response rate. Therefore, there is a continuous search for the best biomarkers in combination with clinical variables to predict clinical course and response to therapy.

At present clinicians are only able to make a crude clinical discrimination between early arthritis patients based on the presence or absence of autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) in combination with the presence or absence of bone erosions on X-rays of hands and feet. This classification in RF or ACPA negative vs. positive, and erosive vs. nonerosive disease is important in predicting which early arthritis patients will ultimately develop RA and at least in part influences treatment algorithms. For example, if an RF/ACPA positive RA patient primarily fails to respond to anti-TNF treatment there are some indications that it may be more beneficial to treat this patient with anti-B cell therapy (rituximab) rather than to try another TNF blocker, T cell co-stimulation blockade (abatacept) or anti-IL-6 monoclonal antibodies (tocilizumab), whereas a RF/ACPA negative patient is likely to benefit more from the latter types of therapies.[3] However, more extensive studies are required to decide if this should be common practice.

Immunohistochemical analysis of synovial tissue and molecular biology have defined further subtypes of synovial inflammation that could be associated with a different pathogenesis or response to treatment, whereas the clinical features are identical: pattern of lymphocyte infiltration (diffuse *vs* organisation in perivascular aggregates with features of germinal centres as seen in lymphoid tissue),[4-6] high *vs* low inflammation associated with genes indicative of an activated type I interferon/STAT-1 signal transduction pathway,[7,8] and heterogeneity in synovial macrophage populations (reviewed by Hamilton and Tak)[9] or expression of cytokines.[10]

Furthermore, a number of studies have been performed to determine whether response to treatment could be predicted by composition of synovial inflammation prior to treatment. One of these studies investigated the response to anti-TNF therapy in relation to baseline TNF expression and the number of macrophages in the synovium, but this could only explain about 10 to 15% of the variance in response to therapy.[11] With the advent of DNA microarray technology, transcriptome analysis has become feasible and is increasingly applied in RA research. One of these studies has demonstrated that almost all patients with a high transcript level of inflammation-related genes responded to anti-TNF therapy.[12] Until now, these approaches are only applicable at the group level and unless a golden

synovial biomarker is found, taking synovial biopsies is a rather invasive procedure for routine patient care.[13] For that reason, finding good predictive biomarkers in blood samples would obviously be a lot easier. However, the peripheral blood is not the site of inflammation in RA and may therefore be less informative in terms of disease pathogenesis. Nevertheless, a lot of effort has been put into this technique that is thought to be especially suitable for discovery of clinically relevant biomarkers in large cohorts of patients.

In this issue of the *Netherlands Journal of Medicine*, Professor Cor Verweij discusses the heterogeneity of RA and explains the (molecular) subtypes of inflammation that have arisen from genomics research in more detail.[14] In addition, recent progress in predicting the response to therapy and personalised medicine using gene expression profiling will be described. These studies are clinically extremely relevant as they may define new biomarkers/disease entities and predict response to treatment. Although DNA microarray technology is suited for picking up signatures of genes associated with RA subsets or response to therapy, this technique also has some pitfalls. Because of its high costs usually only one or two measurements are done per patient. This raises the issue whether the specific molecular profile is stable over time and, in the case of synovial tissue analysis, whether the profile from one biopsy is representative for other sites of synovial inflammation. In addition, this technique does not take into account regulatory mechanisms such as inhibitory micro RNAs[15,16] or posttranslational modification of proteins. Therefore, to gain more insight into the pathogenesis of this complex multifactorial disease, it is necessary to take it to the next level and perform functional studies on the genes/pathways that emerge from microarray data or genome-wide association studies. This is also crucial in light of the development of new treatments for this disease in order to achieve the ultimate goal of personalised medicine.

It is anticipated that great progress will be made in this field over the next few years, because large clinical datasets of early arthritis and arthralgia patients are currently generated. Genomics research will subsequently identify biomarkers for diagnosis and response to treatment. This will allow early recognition of patients who will develop (chronic) arthritis, and if so, to which therapy they are likely to respond. Therefore, the next era of translational RA research promises to be just as fascinating as it has been in the past 20 years.

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