Prediction of Response to Targeted Treatment in Rheumatoid Arthritis

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Learning Objectives: On completion of this article, you should be able to (1) recognize that rheumatoid arthritis is a heterogeneous disease and the implications for the response to treatment; (2) distinguish between primary and secondary nonresponders to anti–tumor necrosis factor therapy and integrate this knowledge in treatment decisions for patients with rheumatoid arthritis who are inadequate responders to tumor necrosis factor inhibition; and (3) assess baseline characteristics of patients with rheumatoid arthritis that may be predictive of the response to biologic treatment and formulate the implications for a stratified medicine approach.

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Abstract

Rheumatoid arthritis is an autoimmune syndrome presenting with chronic inflammation of the joints. Patients with the same diagnosis can present with different phenotypes. In some patients severe joint inflammation and early joint destruction are observed, whereas a milder phenotype can be seen in others. Conversely, patients with the same signs and symptoms may exhibit different immunological and molecular abnormalities. Since the introduction of early treatment in clinical practice, the treat to target principle, and new medicines such as biologic disease-modifying antirheumatic drugs, clinical remission can be achieved early in the disease course, albeit not in all patients. The clinical response and efficacy of biologic disease-modifying antirheumatic drugs vary among different individuals. Therefore, there is a need to develop a more personalized approach toward treatment to achieve rapid remission in every patient to prevent disability and restore and maintain quality of life, without unnecessary adverse effects, in a cost-effective manner. The latest data from explorative studies of predictive markers of response are discussed here, together with a preliminary treatment algorithm based on currently available knowledge.

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Rheumatoid arthritis (RA) is a chronic systemic immune–mediated inflammatory disease affecting synovial tissue in multiple joints. The diagnosis is made by a combination of clinical signs and symptoms of arthritis together with autoantibody profiling and measurement of the acute phase response. The 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria have been developed for the identification of patients with RA earlier in the disease course, hereby facilitating early initiation of treatment and clinical trials in early RA.[1] It is important to note that patients with the same diagnosis can present with different signs and symptoms. Patients with rapid radiographic progression characterized by loss of cartilage and bone erosions will experience loss of function in early disease. Extra-articular manifestations such as pleuritis, pericarditis, and formation of rheumatoid nodules can be found in some patients. These extra-articular manifestations have become rare since the introduction of biologic disease-modifying antirheumatic drugs (bDMARDs). There are different immunological and molecular mechanisms involved in different subsets of RA. For instance, patients can be either positive or negative for autoantibodies such as anti-citrullinated protein antibody (ACPA) and rheumatoid factor (RF). The presence of ACPA is associated with more rapid joint destruction[2,3] and the presence of genotypes encoding the shared epitope,[4,5] smoking,[4,6] and periodontitis.[7] Heterogeneity has also been shown by studies of the major target of the disease, the synovium. Patients with RA with the same clinical symptoms may have different patterns of synovial cell infiltration,[8,9] cytokine expression,[10,11] activation of genes associated with inflammation,[12,13] and gene expression in fibroblast-like synoviocytes.[14,15]

The notion that RA is a heterogeneous syndrome rather than a disease entity is also supported by the variability in clinical response to treatment. Biologic disease-modifying antirheumatic drugs that are used in daily clinical practice have diverse modes of action that either inhibit the effects of tumor necrosis factor (TNF; infliximab, adalimumab, etanercept, golimumab, and certolizumab), block the anti-interleukin 6 (IL-6) receptor (tocilizumab), deplete B cells (rituximab), or interfere with T-cell costimulatory signaling (abatacept). In addition to bDMARDs, there are targeted synthetic DMARDs. The first approved targeted synthetic DMARD is the Janus kinase inhibitor tofacitinib. A variable response to targeted treatment has been shown for TNF blocker,[16-20] rituximab,[21] abatacept,[22] tocilizumab,[23] and tofacitinib.[24] On the group level, comparable clinical responses have been observed among different mechanisms of action, but patients who respond to a specific bDMARD are not necessarily the same as those who respond to another.[25] It will be important to become better at predicting which patients are more likely to respond to a specific mechanism to improve the risk-benefit ratio and cost-effectiveness in individual patients as well as the overall treatment success on the population level (Figure 1).[25]

PREDICTORS OF RESPONSE TO ANTI-TNF TREATMENT

Clinical improvement after TNF inhibition is observed in approximately 60% to 70% of patients who previously failed conventional synthetic DMARD (csDMARD) treatment such as methotrexate (MTX). This means that 30% to 40% of patients do not respond. At present, no factors have been identified that fully explain or predict response to anti-TNF therapy, but pretreatment differences at baseline between patient groups have been identified.

POTENTIAL SYNOVIAL AND PERIPHERAL BLOOD BIOMARKERS PREDICTIVE OF CLINICAL RESPONSE TO ANTI-TNF TREATMENT

A small study (n=8) has suggested that pretreatment increased synovial synthesis of TNF might be related to clinical efficacy.[26] A study of 143 patients with active RA found increased synovial tissue TNF expression in patients who subsequently exhibited clinical improvement (change in disease activity score in 28 joints [ΔDAS28] $\geq$1.2 at week 16) after initiation of infliximab treatment compared with those who did not (ΔDAS28 $<$1.2 at week 16).[27] In addition, an increased number of synovial macrophages, including $CD163^+$ resident macrophages and myeloid-related protein 8^+ (MRP8) and $MRP14^+$ infiltrating macrophages, as well as an increased number

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