

Personalized medicine in rheumatoid arthritis: rationale and clinical evidence

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The treatment of rheumatoid arthritis is challenging because of the diversity of disease courses (from mild to aggressive) and because of the large varying response to treatment. At present, the individual patient is treated in accordance to international guidelines based on findings from randomized controlled trials and large study cohorts. As a consequence, each patient does not get the optimal treatment from his/her individual perspective. In this article the currently available ways that could optimize the treatment in the individual patient are addressed.

Keywords: biological • disease-modifying antirheumatic drugs
• personalized medicine • rheumatoid arthritis • treatment

Rheumatoid arthritis (RA) is a chronic inflammatory disease that can lead to serious joint damage and joint deformity if untreated. Extra-articular manifestations can occur and include serositis, scleritis, intrapulmonary noduli and vasculitis. First symptoms present most frequently between the ages of 40–60 years. The disease affects females more frequently and the male to female ratio is 1:3. Etiology is not exactly understood; it is probable that multiple factors (ranging from genetic to environmental) play a role.

For the benefit of clinical trials, classification criteria for the diagnosis of RA were defined in 1987 [1]. With these criteria, patients with early RA are classified in general practice as not having the disease. However, recent studies showed that starting treatment at an earlier phase gives a better outcome [2]. Therefore, in favor of quicker diagnosis and treatment, the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) formulated new criteria in 2010 [3].

RA is a heterogeneous disease that can be mild in individual cases with low levels of inflammation and hardly any joint damage, or can show an aggressive course with high levels of inflammation leading to joint damage and deformity. In addition, progressive damage in individuals with low levels of inflammation can be seen [4]. Factors predicting an unfavorable course are thought to be the presence of autoantibodies (rheumatoid factor [RF] and anticitrullinated protein antibodies [ACPA]), high disease activity (high disease activity score, raised erythrocyte sedimentation rate and/or CRP and multiple swollen joints) and early erosions. Studies in early RA and in established disease showed that positivity for RF is of prognostic significance regarding eventual joint damage and functional outcome [5]. Also of prognostic value for outcome (radiological damage and grade of activity) are a positive ACPA and the presence of the shared epitope, a highly similar amino acid sequence shared by all of the RA-associated alleles (*HLA-DRB1*) [6].

Treatment of RA

The medications used in the treatment of RA can be subdivided into nonbiologic

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disease-modifying antirheumatic drugs (DMARDs) and biological DMARDs (biologics).

The clinical effect of nonbiologic DMARDs sets in several weeks to months after the start of treatment. The most frequently used nonbiologic DMARD is methotrexate; it is taken once weekly either orally or subcutaneously. Sulfasalazine, hydroxychloroquine and leflunomide are also frequently used. Azathioprine and ciclosporin are applied less often in the treatment of RA.

Biologics are monoclonal antibodies targeted against a specific part of the immune system. Most of them show a clinical effect within several weeks of the start of treatment. The most frequently used biologics are the TNF inhibitors, which block the proinflammatory cytokine TNF- α . Other targets for biologics are the B-cell receptor CD20 (rituximab), IL-6 (tocilizumab) and T cells via the blockade of the CD80/86 receptor on antigen-presenting cells (abatacept).

In both the ACR and EULAR recommendations, methotrexate is the primary treatment of choice for RA [7,8]. When there are contraindications, another nonbiologic DMARD can be started. In the case of treatment failure of the primary DMARD, the options are substitution by another nonbiologic DMARD, addition of a second nonbiologic DMARD, or the start of a biological (the first choice is a TNF inhibitor).

Predictors of response to nonbiologic DMARDs

At present, the effect of a nonbiologic DMARD in the individual patient with RA cannot be predicted. Factors that are thought to be associated with a decreased response to treatment are previous failure of DMARDs, female gender, poor patient global assessment, longer disease duration, disability, higher baseline RF, swollen joints and a higher pain score [9].

In the SWEFOT trial, a number of characteristics were found that were associated with an insufficient response to treatment with methotrexate in DMARD-naïve patients. Smoking status, female gender, longer duration of symptoms and younger age were associated with a lower response [10]. In a study of 42 patients, Maillefert *et al.* showed that in longer existing RA, a higher baseline serum level of TNF- α predicts a better response to a traditional DMARD [11]. In this study the DMARD was mostly methotrexate.

The disease activity after 12 weeks of treatment with a nonbiologic DMARD is associated with the long-term outcome as well. A higher activity at the 12-week mark is associated with more radiological damage after 2 years [12]. Failure of methotrexate treatment seems to be a negative prognostic marker regarding response to a second nonbiologic DMARD

[13]. It is argued that in these cases, a biological can be considered a better option for secondary treatment.

Regarding the prediction of the efficacy of methotrexate, Wessels *et al.* made a pharmacogenetic model, based on gender, presence of RF, smoking status, disease activity score and four polymorphisms in genes (related to the action of methotrexate and to the synthesis of purine/pyrimidine) [14]. A total of 205 patients with newly diagnosed RA were treated with methotrexate. A score of ≤ 3.5 (out of 11.5) gave a positive response rate of 95% and a score of ≥ 6 (out of 11.5) gave a negative response rate of 86%. In an attempt to optimize the model regarding patients with an intermediate probability of response to methotrexate (scores < 6 and > 3), the same authors subsequently incorporated another biomarker (number of alleles of *MTHFR* 1298A and 677C) [15]. This adjustment, however, did not lead to a better classification of these patients.

Predictors of response to TNF inhibitors

Presently there are no valid or useful biomarkers to predict the response to TNF inhibitors. The studies regarding biomarkers in the treatment with TNF inhibitors are currently only exploratory and too small to make predictions possible. It is suggested that the level of TNF- α in the synovium is a possible predictor, but further research is needed. In eight patients with RA, Ulfgrén *et al.* found a correlation between a higher baseline level of TNF- α in the synovium and a 50% ACR improvement (ACR50) response at 2 weeks after a single infliximab infusion [16]. In a study by Julià *et al.*, a higher number of circulating regulatory T cells (CD4⁺CD25⁺) seemed to be associated with a higher response rate to treatment with infliximab ($p = 0.0009$) [17]. Further, González-Alvaro *et al.* suggested in their study with 75 RA patients that lower serum levels of RANKL and a lower RANKL:OPG ratio at baseline are associated with a better response to treatment with a TNF inhibitor (the TNF inhibitors used in the study were infliximab and adalimumab) [18]. Serum level of RANKL was also associated with remission ($p = 0.037$). In a cohort of 190 RA patients treated with a TNF inhibitor (infliximab, etanercept or adalimumab) the presence of anti-Ro was associated with less response at 24 weeks, in particular infliximab showed this correlation [19]. A moderate or good EULAR response at the 24-week mark was significantly lower in anti-Ro-positive patients ($p = 0.006$) and at 56 weeks the discontinuation rate of the TNF inhibitor was also higher in the case of anti-Ro positivity ($p = 0.0005$).

In addition, at present there is insufficient evidence to use pharmacogenomics in the prediction of response to anti-TNF therapy in RA [20]. Multiple

articles about the use of transcriptome analysis in the prediction of response to TNF inhibitors have been published in the past few years, but the consistency between the studies is low. Regarding treatment with infliximab, Lindberg *et al.* found differences for 38 transcripts (associated with a higher level of metabolism) in synovial tissue samples between responders and nonresponders, although this was only significant in patients with synovial lymphoid aggregates [21]. Liu *et al.* provided a reference list of single-nucleotide polymorphisms (SNPs) possibly related to response to anti-TNF therapy, and these should be further studied [22].

A successful approach to individualized use of biologicals in RA could be blood-level testing. This concept was shown to be a possibility for TNF inhibitors by Bendtzen *et al.* [23]. This option is especially interesting since it harbors the possibility to anticipate the effects of anti-TNF-inhibitor antibodies. The latter are formed as an immune response to the immunogenic compounds of TNF inhibitors (especially the murine and chimeric ones). The effect is the removal of the effective TNF inhibitor from the blood. Unfortunately, the methodology is not uniform and the cut-off thresholds are not established yet [24]; therefore, this approach is not used widely in daily clinical practice. More research is needed to address and overcome the problems encountered with this approach.

■ Predictors of response to abatacept

In a cohort of 32 patients treated with abatacept, Scarsi *et al.* found that low levels of circulating CD28⁺ T cells were associated with a higher rate of remission after 6 months of treatment [25]. Other predictors of outcome with the use of abatacept are not yet available, so further research is needed.

■ Predictors of response to tocilizumab

At present there are no known biomarkers that can predict the response to treatment with tocilizumab.

Rituximab

Rituximab (RTX) is a chimeric monoclonal antibody directed against CD20⁺ B cells [101]. After binding, the mechanisms of action comprise complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity and apoptosis. The result is deletion of B cells from the peripheral blood. RTX is registered for use in RA. The registration label states that the patient needs to have moderate disease activity despite methotrexate and one TNF blocker shown to be ineffective or contraindicated. The effect of RTX in the individual patient is hard to predict. Fortunately, recent research brought evidence that

may help to predict the response to RTX in RA [26].

Genetics may help in predicting the effect of RTX. Daïen *et al.* studied nine genes (13 SNPs), including ones that code for cytokines involved in RA, in 63 RA patients on RTX therapy [27]. In 44 responders and 19 nonresponders they found two SNPs associated with clinical response. Presence of the TGFβ1 codon 10 and TGFβ1 codon 25 showed a good probability to respond to RTX treatment (overall response [OR]: 1.6; $p = 0.002$ and OR: 1.6; $p = 0.025$, respectively). If both codons were present, the probability to respond to treatment was doubled (OR: 2.6; $p = 0.008$). It should be noted that the odds are small given the small sample with a wide range. How these results can be applied to daily clinical practice needs to be subjected to new studies.

Sellam *et al.* studied B-cell subsets in RA patients with regard to their role as predictors for RTX treatment success [28]. They found that both CD27⁻ and CD27⁺ memory B cells were decreased in RA patients ($p = 0.001$). Furthermore, low CD27⁺ memory B-cell counts before RTX treatment were associated with a better clinical response to RTX treatment (OR: 0.97; 95% CI: 0.95–0.99). Since flow cytometry is an expensive method and may not be commonly available, the benefit of these results for daily clinical practice remains to be seen.

In contrast to the two aforementioned predictors, previous number of DMARDs used, RF positivity and anti-CCP positivity appear to be clinically useful and applicable markers to predict response to RTX therapy. Narvaez *et al.* demonstrated that the presence of RF and/or anti-CCP added to the chance of RTX success [29]. In their publication, they reported that after multivariate analysis the best method to predict RTX success was to consider both anti-CCP antibody positivity (cut-off level 300 U/ml) and the number of previous DMARDs used. Anti-CCP-positive patients had an OR of 3.4 (95% CI: 1.03–11.2) of achieving a major EULAR response. Patients with failure to two or more TNF blockers had an OR of 0.275 (95% CI: 0.087–0.871) of achieving a moderate-to-good EULAR response. Lal *et al.* looked at the results from the SERENE and REFLEX studies (a total of 1026 patients) and found similar results [30]. Their study showed that the presence of RF positivity and/or anti-CCP autoantibodies, together with an elevated CRP level, could be markers to predict enhanced RTX effect. The problem, however, was that in the prospective study only one subgroup (CRP >2.9 mg/dl and IgA RF >25 units/ml) demonstrated a statistically significant effect. A study by Haraoui *et al.* with 112 patients confirmed the findings that RF-positive patients who failed to respond to a single TNF blocker, show an increased effect to RTX compared with RF- patients [31]. ACR50 scores at

week 12 ($p = 0.036$) and week 24 ($p < 0.001$) improved for RF-positive patients. No amelioration of ACR50 scores at 4, 12 and 24 weeks was seen for RF-negative patients. More comparisons of scores in favor of success in RF-positive patients were made. It is unclear whether these results have sufficient power to declare a difference in RF-positive and -negative status. The British Society for Rheumatology Biologics Register involving 646 patients, starting with RTX after TNF- α -blocker failure, further supports the assumption that RF-positive patients respond better to RTX [32]. At 6 months following initial therapy in patients who failed one TNF blocker, RF-positive status proved to be a predictor of an improvement in the disease activity score in RA (DAS28) of -0.30 (-0.57 – 0.03).

The possibility of selecting the best candidates for RTX therapy, partly based on RF and anti-CCP status, seems a promising step towards individualized treatment. Unfortunately, at the moment the statistics are not very convincing. Moreover, the results of the different studies are not always easy to compare because of the difference in study groups. One of the important issues to be dealt with in the future, as can be deduced from the papers from Lal *et al.* [30] and Narvaez *et al.* [29], is establishing an exact autoantibody titer above which RTX is the therapy of choice.

Which biological to use?

At the moment the algorithm posted by Tak can be used to decide which biological to use [33]. A TNF inhibitor is the primary choice for patients failing on methotrexate. However, tocilizumab and abatacept can also be considered in these cases. In case of primary failure (no response) to a first TNF inhibitor, the

treatment options are tocilizumab or abatacept and in RF-/ACPA-positive patients, also RTX. In the case of secondary failure (loss of initial response) to a first TNF inhibitor, a switch can be made to a second TNF inhibitor, abatacept or tocilizumab and RTX can be used in patients positive for RF and/or ACPA.

Future perspective

There is a florid search for specific biomarkers. Recently it was found that a high baseline serum-soluble IL-15 in patients with early RA is associated with a more aggressive course [34]. There is no question that other biomarkers can be expected in the future.

Patients with RA could possibly be subdivided on the basis of gene-expression profiling conducted on synovial biopsy specimens and this in turn could aid in a more individualized treatment plan. At present, however, there is no solid evidence regarding the use of gene-expression profiling for such a subclassification.

The ultimate goal in the future is to start the most optimal DMARD therapy (nonbiologic and/or biologic) in an RA patient based on the patient's individual biomarkers. This could possibly be achieved through the construction of new models using more than one biomarker.

Conclusion

Defining the possibility of a worse outcome (radiological damage and less functionality) in a patient with RA is an important issue to be dealt with at present.

With respect to predicting the effect of nonbiologic DMARDs on the disease course, there are at present no unique specific biomarkers that can accurately predict the response to treatment with a nonbiologic

Executive summary

- Rheumatoid arthritis (RA) is a chronic inflammatory disease with a heterogenous course between individuals. Some factors are thought to be associated with a worse outcome (e.g., the presence of autoantibodies, high disease activity and early erosions).
- At present, the first choice in the treatment of RA is methotrexate. When there are contraindications, another nonbiologic disease-modifying antirheumatic drug (DMARD) can be started, and in the case of treatment failure, a biologic DMARD (the primary choice is a TNF inhibitor) can be considered.
- Some characteristics (e.g., smoking status, female gender, longer duration of symptoms and younger age) seem to be associated with insufficient response to methotrexate and the failure of methotrexate seems to be a negative prognostic predictor regarding the response to a second nonbiologic DMARD.
- Several possible predictors of a better response to treatment with TNF inhibitors have been mentioned in recent years: higher baseline TNF α levels in the synovium, higher baseline circulating regulatory T cells, lower baseline serum levels of RANKL, anti-Ro negativity and absence of antibodies to TNF inhibitors.
- Regarding abatacept, an association between low levels of circulating CD28⁺ T cells and a higher rate of remission after 6 months is mentioned.
- At present, there are no possible biomarkers mentioned regarding the treatment with tocilizumab.
- Positivity for rheumatoid factor and/or anti-CCP are associated with a better response to treatment with rituximab.
- The algorithm posted by Tak can be used to decide which biological to use after failure to a first TNF inhibitor, the choice depends on the sort of failure (primary or secondary) and the rheumatoid factor/anti-CCP status.
- The ultimate goal in the future is to start the most optimal DMARD therapy in an RA patient based on the patient's individual biomarkers.

DMARD on an individual level in clinical practice.

Regarding biologicals, there is some evidence that RF positivity and anti-CCP status can predict the response to treatment with anti-CD20. The nature of failure to a first TNF inhibitor (primary or secondary failure) predicts the success of treatment with a second or third TNF inhibitor.

Despite all the hard work and promising results, more research is needed to determine predictable and practical biomarkers.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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