

Tailor-Made Therapy in Rheumatoid Arthritis: Fact or Fiction?

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Abstract

There has been a paradigm shift in the treatment of rheumatoid arthritis in recent years. Early and aggressive treatment with good control of disease activity has improved the prognosis of the disease, however, there is significant variability in the response of patients to different therapeutic agents. Hence it is essential to find the predictors of response to a drug at baseline so that we can avoid the delay in achieving remission and improve the outcome. Here we review the literature on available predictors for treatment response in general and specifically for methotrexate and biological agents. We also look at specific scores or indices that can help predict the response in individual patients.

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There has been a paradigm shift in the treatment of rheumatoid arthritis in the last decade. The current emphasis is on early and aggressive management. Combination therapy with other disease-modifying anti-rheumatic drugs, early aggressive followed by step-down therapy and tight control of disease activity have been successfully employed in reducing disease activity in RA. The addition of biological agents in the form of anti-tumor necrosis factor therapy, B cell depletion and co-stimulatory blockade has increased the proportion of patients achieving remission.

Radiographic damage, which predicts the outcome of RA, progresses maximally in the initial years and effective control of disease activity can slow the rate of progression of erosions [1]. A trial of sequential monotherapy results in delayed control of disease activity and ongoing destruction of joints. Empirical combination therapy, analogous to the treatment of malignancies, exposes patients to significant toxicity. Tailor-made therapy involves identifying patients with aggressive disease as well as the likely response to individual pharmacological agents. The two may not be mutually exclusive and ultimately results in poor outcome. Therapeutic decisions can be based on this information if available at baseline. Here we review the available literature on predictors of aggressive disease and treatment response in RA.

General predictors of aggressive disease and treatment response

Many factors have been associated with poor treatment response in RA [Table 1]. The strongest indicator of poor prognosis is

a history of previous DMARD failure. Additional indicators of aggressive disease and likely poor response to therapy are higher inflammatory parameters like erythrocyte sedimentation rate and C-reactive protein, rheumatoid factor, anti-cyclic citrullinated peptide antibodies, early erosive disease, and presence of subcutaneous nodules [2,3].

Genetic factors and prognosis of RA

HLA-DRB1 0401 and DRB1 0404 have been associated with progressive erosive disease and poor prognosis in studies across different ethnic groups and races. Shared epitope-positive patients are less likely to respond to methotrexate alone and are best treated with combination DMARD *de novo* [4]. Methotrexate alone resulted in good response in 83% and 32% of patients respectively without and with shared epitope. Combination with hydroxychloroquine and sulfasalazine, on the other hand, resulted in 94% response in the shared epitope-positive group.

HLA-DM, HLA-DQ, and certain TNF α haplotypes have been associated with severe disease and these patients might require aggressive management [3]. Lack of response to hydroxychloroquine at 24 months of therapy was successfully predicted by HLA C7xx (odds ratio 3.38, 95% confidence interval 1.22–9.35) [5]. Patients with HLA B8 and DR3 have excellent response to gold while those with HLA DR7 have poor response [6]. Other genetic markers specifically associated with methotrexate and anti-TNF response will be discussed below.

Composite scores for prediction

Composite scores involving HLA DRB1 04, erythrocyte sedimentation rate, rheumatoid factor, disease activity score, joint counts, hemoglobin, platelet counts and health assessment questionnaire

Table 1. Factors associated with poor treatment response in rheumatoid arthritis [2,3]

Previous DMARD failure
Longer disease duration
Disability
Female gender
Baseline RF > 1:40
Swollen joints
Pain score
Poor patient global assessment

RA = rheumatoid arthritis

DMARD = disease-modifying anti-rheumatic drugs

TNF α = tumor necrosis factor-alpha

have been proposed in different permutations and combinations [3]. However, these scores have not been validated in a different cohort, severely limiting their clinical applicability.

Prediction of methotrexate response

Methotrexate is the anchor drug in the management of RA. There have been several directed attempts to identify indicators of good response MTX therapy.

Metabolism and effects of methotrexate

Despite almost 95% of the MTX dose being metabolized in a day, once weekly low dose MTX is effective in RA. MTX is taken up by cells using the reduced folate carrier followed by polyglutamation via folate polyglutamate synthase. MTX polyglutamates have a prolonged half-life intracellularly and are thought to be primarily responsible for the therapeutic effects of MTX. The intracellular MTXPG is hydrolyzed by gamma glutamyl hydrolase resulting in efflux of MTX. Accelerated efflux of MTX is mediated by the family of multidrug-resistant proteins [7].

A pharmacogenetic index comprising enzymes of the folate pathway identified patients with good response to methotrexate

MTX inhibits the enzymes in the folate pathway including dihydrofolate reductase, thymidilate synthase and aminoimidazole carboxamide ribonucleotide transformylase. A lower pharmacogenetic index (comprising polymorphisms in RFC, ATIC and TS) was associated with poor response to MTX [8]. Patients with the RFC 80AA genotype compared to those with the 80GG genotype were 3.4-fold more likely to have elevated MTXPG levels and 3.32-fold more likely to attain remission [9,10]. However, this has not been corroborated in all studies and higher influence of multidrug-resistant proteins was seen [11].

There have been several studies on FPGS and GGH activity and their relation to efficacy and toxicity of MTX. Stranzl et al. [12] reported better response to MTX in those patients who did not have FPGS mRNA expression. This was contrary to expectation as higher FPGS should result in higher MTXPG and an increase in efficacy. It was thought that this could be due to production of FPGS from activated cells and that the reduction in response might actually reflect higher activity in those patients [13]. This is unlikely since FPGS mRNA expression did not correlate with either clinical or laboratory markers of disease activity

MTX = methotrexate
 MTXPG = MTX polyglutamates
 RFC = reduced folate carrier
 ATIC = aminoimidazole carboxamide ribonucleotide transformylase
 TS = thymidilate synthase
 FPGS = folate polyglutamate synthase
 GGH = gamma glutamyl hydrolase

[12]. Patients with the GGH-401TT genotype compared to those with the 401CC genotype were 4.8-fold more likely to have lower MTXPG levels [9]. Patients with higher RBC MTXPG at 3 months were likely to respond to MTX at 6 months [14].

Folic acid is taken up by cells and it undergoes polyglutamation like MTX. Higher RBC folic acid polyglutamate levels are associated with poor response to MTX [8]. Recently it was shown that patients who show a reduction in the RBC folic acid polyglutamate level at 4 months of therapy were more likely (OR 8.4, 95%CI 1.4–52.3) to respond to MTX [14].

Effect of MTHFR gene mutations in clinical response to MTX

Ethnic and racial differences in methylene tetrahydrofoalte reductase gene are well known. Those with the MTHFR 1298 A and the rs4846051 C alleles were more likely to have MTX toxicity but no effect on MTX response. We did not find any relation of C677T polymorphism to toxicity or efficacy of MTX in 150 patients with RA [15]. Dervieux and co-workers [14] reported that patients with the MTHFR 677TT and serine hydroxyl methyl transferase-1 (SHMT-1) 1420CT/TT genotypes were likely to have a poor response to MTX. The prediction was better with MTHFR (OR 22.2, 95%CI 1.2–42.2) than with SHMT-1 polymorphism (OR 7.4, 95%CI 1.0–56.4).

Cytokine suppression and MTX response prediction

Methotrexate has been shown to cause suppression of T cell cytokine production. However, different individuals require different dose for suppression [16]. Similarly, there is variability in the clinical response to MTX. The differential sensitivity to cytokine suppression could mirror the differential clinical response to MTX in patients with RA. There was significant correlation between the dose of MTX required to suppress TNF α and interferon-gamma production by 50% (inhibitory dose 50) with the clinical response at 4 months [17]. We could also identify a cutoff ID50 which could predict ACR20 and EULAR response to MTX with excellent sensitivity and specificity. This assay is being tried in a larger cohort to validate it for clinical use.

Prediction of response to biological agents

Despite the good results achieved with biological agents, a significant proportion of patients with RA continue to have active disease. Data from the British Society for Rheumatology Biologics Registry throw light on some of the baseline characteristics predictive of response or remission with etanercept and infliximab [18]. Patients with higher disability and those not on concomitant MTX were less likely to respond to biological agents. Females are less likely to achieve remission than males with infliximab (OR 0.6, 95%CI 0.4–0.89) and etanercept (0.61, 0.38–0.94). Concomitant use of non-steroidal anti-inflammatory drugs and a lower baseline

OR = odds ratio
 CI = confidence interval
 MTHFR = methylene tetrahydrofoalte reductase
 ID50 = 50% inhibitory dose
 EULAR = European League Against Rheumatism

health assessment questionnaire score were indicative of better chance of remission.

Lequerré et al. [19] recently reported a positive predictive value of 100% and negative predictive value of 83% for predicting treatment response to infliximab using a set of eight transcripts by microarray. The sensitivity and specificity were 80% and 100% respectively. In the same study, when a set of 20 genes were used, the positive and negative predictive values were 75% and 87.5% respectively.

It is logical to think that TNF α polymorphisms might be responsible for the variability in response to anti-TNF therapy. In a study from Korea, patients with the TNF α 857 T allele were more likely to respond to etanercept [20]. Patients with the interleukin-10 promoter microsatellite allele IL10.R3 (OR 5.5, 95%CI 1.6–18) and the haplotype R3-G9 (5.1, 1.5–18) were more likely to have good response by EULAR criteria [21]. However, the association of TNF α polymorphisms with the efficacy of infliximab in RA has not been well documented.

Conclusion

With the expanding armamentarium against RA, the choice of drugs should be based on sound scientific grounds. A good predictive scoring system using pharmacogenomics, novel biomarkers and specific cutoff values like the ID₅₀ can help formulate tailor-made therapies for patients with RA.

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The thing I hate about an argument is that it always interrupts a discussion

C.K. Chesterton (1874-1936), British essayist, novelist and poet.