DMARD use in rheumatoid arthritis: can we predict treatment response?

Genga EK[1, 2] , Moots RJ[3], Oyoo GO[1, 2]

[1]Department of Clinical Medicine and Therapeutics, College of Health Sciences, University of Nairobi, PO Box 19676-00202, Nairobi, Kenya
[2]Nairobi Arthritis Clinic, Kenya
[3]University of Liverpool, Clinical Sciences Centre, Aintree University Hospital, Longmoor Lane Liverpool, L97 AL, United Kingdom.

Corresponding author:
Dr EK Genga.
Email: eugenekalman@gmail. com

Abstract

Objective: To review the current and emerging predictors of treatment response by DMARDS in Rheumatoid Arthritis (RA) patients.
Data source: Published original research work and reviews were searched in English related to determinants of treatment response in rheumatoid arthritis on DMARDS
Study design: Only articles that emphasis on determinants of rheumatoid arthritis treatment response with DMARDS
Data extraction: Online and library searches done.
Data synthesis: Data added and summarized
Conclusions: Treatment of RA has been based on the use of a group of Disease-Modifying Antirheumatic Drugs (DMARDs), of which methotrexate is the most widely used. Although comprehensive clinical experience exists for MTX and synthetic DMARDs, to date it has not been possible to preview correctly whether or not a patient will respond to treatment with these drugs. Predicting response to MTX and other DMARDs would allow the selection of patients based on their likelihood of response, thus enabling individualized therapy and avoiding unnecessary adverse effects and elevated costs. Distinguishing responders from non-responders at treatment start as studies have failed to consistently reproduce similar determinants. Variables possibly influencing drug effectiveness may be related to disease, patient, treatment, clinical or biological (genetic and non-genetic) factors. This study seeks to review the current data regarding biomarkers of treatment response to DMARDS.

Key words: Rheumatoid arthritis, DMARDS, Determinants of treatment response

Introduction

Current rheumatoid arthritis management emphasises the benefits of early Disease-Modifying Anti-Rheumatic Drugs (DMARDs). These agents are characterised by their ability to reduce or reverse signs and symptoms, disability, impairment of quality of life, inability to work, and progression of joint damage and thus to interfere with the entire disease process. DMARDs form two major classes: synthetic chemical compounds and biological agents. Examples of synthetic DMARDs include methotrexate, hydroxychloroquine, leflunomide, sulphasalazine and azathioprine. Rheumatoid Arthritis (RA) treatment has changed dramatically during the last decade after the introduction of biologic DMARDs that target important mediators of the immunological mechanisms in RA. Examples of biologic DMARDS include Tumour Necrosis Factor (TNF) inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), the T cell co-stimulation inhibitor, abatacept, the anti-B cell agent, rituximab, the interleukin (IL)-6 receptor (IL-6R)-blocking monoclonal antibody, tocilizumab and the oral Janus Kinase inhibitor molecule tofacitinib. The benefits from using DMARDs extensively must be balanced against patients' wishes to minimise drug use, potential toxicities, and costs of long-term DMARDs. One of the main challenges in RA management for over two decades has been the ability to predict treatment response to DMARDs.

This would be of benefit in several ways. Identifying patients less likely to respond will avoid needless exposure to potentially toxic drugs and the waste of precious time to achieve disease control, a crucial endpoint to prevent development of structural damage[1]. Likely responders would be maintained with the most appropriate DMARD with more certainty, avoiding an early or possibly unnecessary, switch to other potentially less effective DMARDs or to more costly biologicals. This will lead to having a more personalized tailor made therapy for each patient. While predictors of poor RA prognosis are well established[2, 3], they do not accurately correlate with response to treatment. This is because a heterogeneous response is most likely the result of multi-

factor interactions and cannot be explained by a single cause-effect mechanism. Factors that possibly influence drug effectiveness can be divided into patient-related (age, gender, ethnicity, comorbidities), disease-related (duration, activity, disability, biomarkers), treatment-related (compliance, dose, previous drugs) and genetic factors[4]. We conducted a literature review on current available data on predictors of response to DMARDs (clinical factors, non-genetic biomarkers and genetic biomarkers), discuss and analyse the possible translation into clinical practice.

How to assess for treatment response

The goals in treating patients with rheumatoid arthritis are managing the symptoms of disease, preserving joint structure and achieving disease remission. Studies have shown that treatment decisions driven by quantitative rather than subjective monitoring of disease activity result in significantly improved patient outcomes. Various assessment tools are available that measure both clinical and patient-reported outcomes. Some measurement tools may be more appropriate for use in clinical trials, several have been developed that are simple and practical to use, even in a busy clinic. They are many tools, the most common being the CDAI, DAS28 (ESR or CRP), PAS, PAS-II, RAPID-3, and SDAI. These six produce a single continuous index and have defined ranges for indicating low, moderate, or high disease activity or clinical remission. These clinical assessment tools are indices that measure different aspects of RA and have their pros and cons. Tools such as the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI) were designed for use in clinical practice. They are both derived from the DAS28 and have high correlations to DAS28 scores[5]. However, both the SDAI and CDAI are simpler to use and easier to calculate than the DAS28[5]. The SDAI and CDAI include 28-joint counts, patient global assessment of disease activity, and physician global assessment of disease activity. Unlike SDAI, CDAI does not require a blood test for evaluation of an acute phase reactant; therefore, complete results can be obtained and used to drive treatment decisions at the same time as the patient's visit.

Clinical, radiographic, and biochemical markers of DMARD response

Several clinical, radiological and biochemical factors have been studied. It has been difficult to reach a consensus on which factors can predict the response to treatment with DMARDs. Most studies have evaluated responsiveness to methotrexate.

Gender

A systematic review by Drouin *et al*[6] found that male gender was associated with a better clinical response to MTX both in early and established RA. Similar conclusions were reached in a large meta-analysis of Randomized Controlled Trials (RCTs) by Anderson et al n 1,435 patients, in terms of achieving American College of Rheumatology (ACR) 20 responses. Saevarsdottir *et al*[8], in a population of early RA patients (SWEFOT trial) also reported a worse European League Against Rheumatism (EULAR) response in women (odds ratio (OR) = 0.50, 95% confidence interval (CI) 0.31 to 0.81). Stranzl *et al*[9] also found female sex to be an independent predictor of poor response to MTX (OR = 3.3, P = 0.009). Vázquez *et al*[10],reported in early RA patients, male gender was associated with remission after two years of MTX ± gold treatment in the univariate analysis but not in the multivariate analysis. Hider *et al*[11] found no differences between men and women in response rates to MTX in a prospective study of an early inflammatory polyarthritis cohort and there are also other studies that were not able to identify an influence of gender on MTX response. In spite of some conflicting results, it seems that most of the evidence points in the direction of male gender being a predictor of good response to MTX in both early and established RA. A predictive model for 24-month remission was developed for patients with early RA treated in a RCT with MTX ± corticosteroids ± cyclosporine; it was validated in an early RA cohort (ERAN) of patients treated with MTX or other conventional DMARDs[12]. The authors concluded that one of the three variables that predicted remission at 24 months was male gender (OR = 3.14, P <0.001). As in this latter study, most of the analyses of response to other DMARDs have been done together with MTX, so their individual effect is difficult to predict. A meta-analysis and an observational study from the 1990's, comprising a significant number of patients, demonstrated that gender did not influence the response to treatment with sulphasalazine, gold and penicillamine[13]. Another open label trial showed no influence of gender on whether patients with early RA started on hydroxychloroquine would have to step up therapy to MTX. Other studies have also failed to detect a significant effect of gender on treatment response to DMARDs, other than MTX[14, 15]. Overall, it seems that under the light of current evidence it is not possible to generalize the better response to MTX treatment seen in men to other conventional DMARDs. Hider *et al*[4] postulated that gender influence on MTX responsiveness, is due to hormonal factors influencing the pharmacokinetics and pharmacodynamics of each drug thus contributing to a better or worse response. This may explain the apparent discrepancy in the influence of this factor on different DMARDs.

Most research has found that male patients are more likely to respond or achieve remission with TNFi. This was reported by Kleinert *et al*[16] who evaluated adalimumab in 2,625 RA patients[15], the Research in Active RA trial (ReAct), a 12-week study open label on adalimumab that enrolled 6,610 RA patients and the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO) that had 682 patients receiving ETN[17]. In the 540 RTX-treated patients included in British society of

rheumatology biologics register who had at least one TNFi failure, female sex was significantly associated with lower odds of disease remission[18].

Age

Age seems to be a predictive factor of response to biologics unlike MTX or other DMARDs. Most studies showed a lack of effect of baseline age on clinical response to MTX therapy, including two large meta-analyses[6]. Some studies have contradicting results, such as the SWEFOT trial[10] which showed that older age was associated with a higher likelihood of both EULAR and the Clinical Disease Activity Index (CDAI) response to MTX treatment at three to four months. Another study by Ma *et al*[12] showed older patients (>50 years old), on the contrary, were less likely to be in remission at 24 months after the start of MTX ± cyclosporine. Thus, despite these two early RA studies, where age seemed to influence response to MTX treatment, although in opposite directions, most studies, including large meta-analyses, showed that age is not a predictor of response to MTX. There is limited literature on other conventional DMARDs. One study showed that younger patients respond better to SSZ , with no effect of age on the response to penicillamine and gold[13]. All other publications excluded age as an independent predictive marker of response to conventional DMARDs[10, 19, 20].

Data on biologics favours age as a predictive factor. Kleinert's et al and the ReAct study found younger patients had better clinical outcomes[21]. Tocilizumab in the Japanese multi-centre retrospective study (REACTION) revealed that younger age was independently associated with a good EULAR response and remission at 24 weeks[22]. No association between clinical response and gender or age were found in the South Swedish Arthritis Treatment Group Register, the Orencia and Rheumatoid Arthritis and British Society for Rheumatology Biologics Register (BSRBR) between EULAR responders and non-responders[23-25].

Smoking

Smoking has a negative impact on disease outcomes and is associated with higher disease activity[26]. In early RA, current smokers respond worse to MTX treatment. Wessels *et al*[27] showed that early RA patients have a worse response to MTX monotherapy were associated with smoking and positive rheumatoid factor. In an early RA cohort, where 873 patients started MTX monotherapy at inclusion, current smoking was independently associated with significantly worse early and late EULAR, Disease Activity Score (DAS) 28 and joint count responses, when adjusted for other clinical, serologic and genetic factors (OR = 0.60, 95% CI 0.39 to 0.94)[8]. SWEFOT trial done on a similar population showed that current smoking was the strongest predictor of achieving a poor response[8]. Studies have shown that smokers tend to consume a higher number of conventional DMARDs over time, suggesting that smoking can reduce therapeutic efficacy and that non-smokers are more likely to achieve an ACR response than smokers[28]. Saevarsdottir *et al*[8] proposed that smoking may interfere with the pharmacodynamics and pharmacokinetic properties of the drugs, thus altering responsiveness. Stamp *et al*[29] showed that smokers have reduced intracellular levels of some MTX polyglutamates, suggesting that MTX metabolism is altered which leads to a poor response. Whatever the mechanism, active smoking is an important modifiable factor that seems to be associated with a poor response to MTX. Tobacco discontinuation should be encouraged and considered an important part of the therapeutic approach.

BSRBR patients who smoke cigarettes have a lower treatment response to infliximab[23]. This result was duplicated in other studies such as a retrospective case control study of 395 RA, in a prospective cohort of 617 Portuguese and in a Swedish register that included 1,998 early RA (Epidemiological Investigation of Rheumatoid Arthritis EIRA) [8, 30-31]. However, smoking cessation has not been associated with increasing the chance of response to therapies. A Swedish study on 1,460 RA patients with early disease and had patients who had quit smoking found no difference in treatment response between the smokers and those who quit (BARFOT (better anti-rheumatic pharmacotherapy) [32]. No data is currently available on the influence of smoking on response to TCZ, ABA, or RTX.

Disease activity and severity

Data on disease activity at baseline as a potential marker of response have yielded inconsistent results. This can be related to the different clinical instruments and response criteria used in the studies. Disease activity can be assessed using clinical-laboratory variables (CRP), Erythrocyte Sedimentation Rate (ESR), Tender Joint Count (TJC), Swollen Joint Count (SJC), global assessment of disease activity on a Visual Analogue Scale (VAS) or by composite scores (DAS, DAS28, CDAI, Simplified Disease Activity Index (SDAI) and different criteria are used to define response (EULAR, ACR, DAS/SDAI remission). It is thus important to consider this information when interpreting literature data. A meta-analysis by Drouin *et al*[6] identified high disease activity at baseline as measured by DAS or SDAI as a predictor of a weak response to MTX monotherapy. Wessels *et al*[27] also found poor response to MTX monotherapy in an early RA population was associated with high DAS and high SJC were associated with a poor response to MTX monotherapy as defined as achieving a DAS ≤2.4 at 6 months. Other factors such as VAS, ESR and CRP had no effect on response. In established RA, higher disease activity defined by DAS has been associated with decreased likelihood of response to MTX[33]. Studies by Aletaha *et al*[34] and Saevarsdottir *et al*[8] showed that early RA patients with higher baseline SDAI (but also CDAI and DAS28) were less likely to achieve remission or low disease activity on MTX monotherapy. Vázquez *et a*[10] demonstrated that in early RA, patients with low

to moderate disease activity at baseline were four times more likely to be in remission after two years of MTX ± gold therapy. Two other studies also demonstrated that in patients with recent onset RA treated with MTX, SSZ or both, a lower baseline DAS was predictive of remission at two, three and five years[35-36]

The literature seems to show that when disease activity is assessed by composite measures, lower activity at baseline predicts better responses to MTX. When disease activity is determined by isolated laboratory and clinical variables, evidence is inconsistent. Anderson *et al*[7] found lower patient, but not physician, global assessment at baseline to be predictive of worse response to MTX and other DMARDs. This contradicts with the above and other studies. High SJC has been found to predict poor response to MTX in early RA by Wessels *et al*[27]. This was not confirmed in established RA[27, 37]. Ma *et al*[12] showed that a TJC higher than 5 at baseline decreased the likelihood of achieving DAS remission at 24 months. This was independent of effect for SJC. Verstappen *et al*[38] determined a lower Thompson joint score at baseline as predictive of remission patients treated with MTX, gold or HCQ. Majority of the data where SJC and TJC as isolated variables have been identified not to be predictors of response to treatment with MTX and other DMARDs [36, 39-40]. As a whole, these data suggest that low disease activity defined by isolated clinical variables is probably associated with a better response to treatment as part of composite measures. Composite scores such as DAS or SDAI, are better predictive tools.

Similarly, role of inflammatory markers to assess disease activity is also far from being in consensus. Meta-analysis by Drouin *et al*[6] determined neither CRP nor ESR were predictors of response to MTX monotherapy. Other studies regarding therapy with MTX ± other DMARDs have shown no effect of ESR and/or CRP on treatment response[9-12, 36, 38]. One study by Combe *et al*[18] identified ESR and CRP as two of the five independent predictive factors of disability at five years in early RA patients treated mainly with MTX and SSZ. Data on other DMARDs is also inconsistent. A low baseline CRP was the only predictor of a favourable response to HCQ monotherapy in early RA patients which contradicts Matteson *et al*[40] found that ESR had no influence. Van Roon *et al*[15] identified that the lower the ESR (<35 mm.h-1) at initial treatment Initiation was able to predict better response to leflunomide. Contrary to these findings, Capell *et al*[41] observed that a lower ESR was associated with a worse response to gold, penicillamine or SSZ. As a whole, these results are not sufficient to state whether ESR or CRP alone are predictive factors of response to MTX and other DMARDs. While some studies showed a significant association between inflammatory markers and response, usually with higher baseline values associated with weaker treatment responses, others, including large meta-analyses, do not find these variables to be good predictive markers, at least when considered independently. In the light of current evidence, for the purpose of predicting DMARD response, it is probably better to integrate ESR and CRP components as part of disease activity scores and not judge them individually. Disease severity and disability at baseline have been proposed as being predictive of treatment response. Using the Steinbrocker criteria to identify a lower functional status, Anderson *et al*[7] found it to be associated with a weak response to MTX and other DMARDs. Other RA studies found that patients with low baseline Health Assessment Questionnaire (HAQ) score treated with MTX, SSZ,HCQ or in combination were more likely to be in remission (DAS < 1.6) at two or three years [8,27,36,43].

However, several studies showed contradictory results, with baseline HAQ not being an independent predictor of responsiveness to MTX and other DMARDs[11,12,20,37, 41]. While some studies seem to suggest that a higher HAQ predicts a weaker response to MTX and other DMARDs, several other studies with similar populations did not confirm this association.

Most studies on TNF inhibitors, patients with higher baseline HAQ scores are less likely to respond or to achieve remission[16-18, 23,31]. Studies have also shown that higher baseline DAS28 scores are a good predictor of DAS28 decrease[16,17,21,23,24]. Similar finding were found for other therapies. In the 97 patients treated with TCZ registered in the nationwide Danish DANBIO registry, lower HAQ score at baseline was associated with EULAR response and higher DAS28 at baseline was significantly associated with achieving a low DAS28. The ORA registry identified higher initial DAS28 in ABA responders (5.4 (4.7–6.5)) than in non-responders (4.9 (4.0–6.0), $p < 0.0001$)[25]. Several studies on rituximab have also showed association between EULAR response and low HAQ, high DAS28 and low number of previous biological agents[18, 43-44].

Duration of disease

It has been widely shown that treatment of early RA yields better results than treatment of established disease[45-46]. This has led to the concept of 'window of opportunity'. Longer disease duration was identified by Anderson and colleagues[7] in a meta-analysis as the most important factor to predict worse response to MTX. Similar findings have been reported in other studies, regarding both MTX and other conventional DMARDs[4,8,13,15]. However Hoekstra *et al*[33] in a RCT on 411 patients treated with MTX did not find an association (although the mean disease duration was lower). Several other studies have found no association with MTX and other DMARDs[6, 10-12,27,47]. Discrepancies in these results may be due to evaluations performed mostly in established RA patients, who probably have a more uniform response to MTX, or in early RA populations that have short-term disease and a narrow disease-duration span making it harder to detect differences in response rates. In conclusion while it is likely that patients with early disease respond better than those with established RA, disease duration seems to lose its negative influence with long-term progression of disease and this might confound the results of studies addressing this factor.

RA drugs history: prior and current

Despite the existence of a few reports suggesting that previous DMARD use does not affect response to further treatments[47-48]. Most literature findings include references to a negative effect of previous DMARD use on the response to treatment with MTX and other DMARDs[7]. Lie *et al*[37] found that patients who had previously taken other DMARDs had significantly lower response rates to MTX monotherapy. Similar findings by Aletaha *et al*[5] in patients taking consecutive DMARD courses, with the first DMARDs obtained a greater decrease in C reactive protein (CRP) than subsequent ones. Based on these studies, the absence of any past DMARD therapy was identified as one of the predictive factors of a favourable response to MTX monotherapy[6]. Another study reported that the DMARD response was higher when started after non-steroidal anti-inflammatory drugs (NSAIDs) than following another DMARD[49]. One reason postulated was that patients who do not respond to a certain drug might have a globally more severe and less responsive disease, but other mechanisms might explain these observations. Hider *et al*[4] proposed that previous therapies may alter drug kinetics and influence metabolism in such a way that the effectiveness of subsequent drugs can be lowered. This hypothesis has not been adequately tested so far. Concomitant NSAIDs has been associated with an increased efficacy of MTX monotherapy in established RA and a similar but weak association was found in early RA (OR = 1.31, 95% CI 0.84 to 2.06)[8]. Further studies on effect of NSAIDS are needed to confirm this association, although a beneficial effect may be expected.

Data on use of concomitant corticosteroid therapy are more difficult to interpret because of different doses and timings for starting steroids (before DMARD therapy, during, or both). Saevarsdottir *et al*[8]found that RA patients who responded early were already on stable low-dose prednisolone at the start of MTX (OR = 2.84, 95% CI 1.43 to 5.63). Hider *et al*[11] identified that absence of steroid use predicted MTX inefficacy at two years, but not at one year. These results are in agreement with trials that showed that patients treated with combination therapies including steroids have better responses than those on DMARD monotherapy[50]. However, some studies have found no association between corticosteroid use and DMARD response[7,40]. Despite these latter findings, most literature supports that patients on corticosteroid concomitant treatment are more likely to respond to DMARD therapy. The concomitant use of MTX and biologics is associated with good clinical outcomes in many different studies including Kleinert's study, GISEA, BSRBR, and ReAct [16, 21, 24]. The concomitant use of MTX is thought to largely improve treatment response through synergic actions of the drugs on RA. It is also thought to probably impact on drug immunogenicity since the occurrence of antidrug antibodies is less frequent with MTX combined with biological therapies[51].

Ethnicity

Ethnicity may play a role in predicting DMARD response in RA. Genetic differences influences drug-metabolizing enzymes thus causing a different responses between ethnic groups[4]. This can limit the ability to generalize data from clinical trials to different population groups or choosing the best DMARD for a specific patient based on their ethnicity. This can be particularly relevant in some geographical areas for example North America, where patients' origins can be very heterogeneous. Some authors have found no association between ethnicity and likelihood of response. Majority of the studies have not analysed its predicting role[51]. Despite its favourable theoretical rationale, ethnicity is currently not a definite predictor of response to MTX and other DMARDs. More research with large populations are needed to clarify its influence on responsiveness.

Genetic biomarkers of response

Pharmacogenetics may provide an explanation to the discrepancies in treatment response to DMARDs among RA patients. Research has focused on polymorphisms and genetic patterns associated with increased or decreased drug response. The *HLA-DRB1* shared epitope (SE) has been associated with RA severity and disease progression[51]. Studies on its associated with treatment response to DMARDs have yielded conflicting results. A Japanese study found that carriers of SE positive 04 alleles were more likely to be resistant to DMARDs including MTX than non-carriers[52]. A Pakistani study on 91 RA patients found non-responders to have the SE allele HLA-DRB1*03. Another study showed that SE positive patients responded better to MTX, sulfasalazine, and hydroxychloroquine combination therapy compared to MTX alone, while SE-negative patients responded well irrespective of treatment[26]. Patients, who have previously failed one DMARD, O'Dell *et al*[47] showed that SE-positive patients are more likely to respond if put on combination treatment (MTX plus SSZ plus HCQ) compared to MTX monotherapy. There was no difference seen in patients who were SE negative[47]. In a study of 457 RA patients, the presence of two *HLA-DRB1* alleles encoding the SE were associated with good treatment response to etanercept as compared to MTX [26]. No effect was observed in other alleles, including DRB1*04 and DRB1*01[53]. Overall, SE seems to have an influence on response to DMARD treatment, with an apparent negative effect on MTX response. Further studies looking on this genetic marker are needed in order to clarify its true influence on drug effectiveness.

Another area of interest is the reduced folate carrier1 (RFC1) 80G>A (membrane transporter) which may influence influx of MTX into the cell. Its impact on drug responsiveness is still not established. Several studies have shown that patients with the RFC1 80A/A

genotype have a greater response to MTX than wild-type 80G/G patients. This was based on disease activity measurements[53]. It is thought that gene polymorphisms may affect the response to MTX as several other SNPs in the RFC1 gene have been associated with poor response to MTX. Further research is still needed in this area[53]. Targets for biologics have included SNPs related to TNFα or TNFα receptors (TNFR). A study on 59 patients IFX found that those with TNFA-308G/G responded better than those with A/A or A/G genotypes[54]. Some other studies have confirmed this data. However a meta-analysis of 11 studies did not find a significant association between TNFA- 308 and TNFi response. A multi variate analysis on 1,283 RA patients that looked into thirty-one SNPs associated with the risk of RA (i.e., TNFAIP3, STAT4, PTPN22, HLA class II, etc.) found that the SNP at the CD45 (also called PTPRC) gene locus (rs10919563) was associated with EULAR good response versus no response (OR = 0.55. Similar results were found in a study on 1,115 English patients[53-54].

Overall, studies evaluating the role of individual SNPs on response to DMARDs have been inconsistent and few. Majority of the data is on MTX. Inconsistencies may be related to different study designs, insufficient statistical power and several clinical and pharmacological confounders, such as ethnicity, outcome measures used, folate supplementation, drug dosing, duration and route of administration and concurrent therapies. While large prospective studies are missing, meta-analysis may overcome this problem, but because there are numerous pathways and a considerable number of targets that can be affected by DMARDS, an individual genetic variant within a single gene is unlikely to result in a significantly altered response, enough to be detected and replicated in different studies. It would probably be more advantageous to address gene polymorphism through polygenic analyses, haplotype analyses or gene-gene interactions rather than single genes.

Radiographic and biochemical correlates

RF and anti-citrullinated protein antibodies (ACPA) play important roles in diagnostic and prognostic of RA. The role of RF in treatment response has still not been established. Majority of studies have shown that RF factor has no influence on treatment response to DMARDs[8, 11, 12,14,15,16, 40, 47, 55]. Some studies for example Wessels' *et al*[27] found RF-positivity was associated with worse response to MTX monotherapy in early RA patients. Similarly, Morgan *et al*[56] found that RF positive patients were more resistance to three or more DMARDs. RF-negativity has been found by Verstappen *et al*[38] to be associated with four-year remission in early RA patients started on HCQ, MTX or gold. In a meta-analysis of 23 studies found an association between RF positivity and better treatment response in 14 studies with RTX and 6 studies with TCZ. Other studies with ABA found no association between response and RF[57]. Overall, most of the available evidence seems to show that baseline RF status does not influence the effectiveness of DMARDs

The role ACPA in RA has been associated with worse functional status higher disease activity severe radiographic progression and worse disease course[58]. Studies by Cao *et al*[61] Hodkinson *et al*[49], Verschueren at al [59] , Vázquez *et al*[9], Boire et al[60] , da Mota et al[55] and Gossec *et al*[34] have found no differences in DMARD response between ACPA-positive and ACPA-negative. However a Japanese study done on patients treated with MTX or SSZ within one year of disease onset found that ACPA positivity was strongly associated with resistance to treatment. Other studies have also found similar results of a lower response to treatment in ACPA-positive patients, in terms of decrease in DAS28, ESR, CRP and other clinical variables[61]. There is limited data on RF and Anti-Citrullinated Protein Antibodies (ACPA) role on predicting treatment response to biologics. Infliximab was investigated in the BeSt study and found that ACPA-positive patients responded as well as those who were ACPA-negative[62]. Treatment response was based on decreases in disease activity, remission rates and functional ability. Interestingly they found that these ACPA-positive patients had good treatment response but had worse radiographic progression and were less likely to maintain drug-free remission. Overall, research is scarce and it does not support the role of ACPA as predictive markers of response to MTX and other DMARDs. We need more studies to confirm its role as a treatment predictor in RA treatment. Cytokines play a key role in RA pathogenesis and has been an area of intense research looking into the ability of cytokines to predict treatment response. Several inflammatory cytokines have been evaluated as treatment response predictors. Some of the cytokines studied include IL-1ra/IL- 1beta and TNF-*α*. Lower levels of IL-1ra/IL- 1beta and TNF-*α* have been associated with good or excellent responses to MTX treatment[12].

Higher TNF-α production in an individual has been associated with a poorer response. In RISING study, the patients with high baseline TNF were found to have a higher disease activity as measured by DAS28, higher RF and anti-CCP levels. These patients were noted to have better clinical response but it was not statistically significant when compared to patients with low TNF-α levels.IL-7 has also been studied on RA patients on TNFi where it has been found to be significantly higher in non-responders[63].

Treatment response to TCZ it has been studied using IL-6. The studies showed that higher baseline serum IL-6 levels were significantly associated ($p < 0.0001$) with higher baseline disease activity using DAS28, erythrocyte sedimentation rate, C-reactive protein, and HAQ. Higher baseline serum IL-6 levels was associated with better clinical response to TCZ versus placebo in DMARD inadequate responders and in MTX-naive populations[64]. However, apart from those defined as TNFi inadequate responders its association with treatment response was found to be weak with threefold difference in baseline IL-6 level corresponded to a DAS28 change of 0.17-unit difference at week 16. This has limited its clinical usefulness of IL-6 in predicting treatment benefit.

Conclusions

One of the main challenges in RA management for over two decades has been the ability to predict response to first-line DMARDs. RA manifestations are complex and variable from patient-to-patient (age, sex, and comorbidities). The prediction of treatment response in individuals to ultimately allow selection of targeted, patient specific therapy will likely be based on novel and integrative biomarker approaches. This would be of benefit in several ways. Identifying patients less likely to respond will avoid needless exposure to potentially toxic drugs and the waste of precious time to achieve disease control, a crucial endpoint to prevent development of structural damage. We have identified clinical and biological factors that predict good response which are male gender, non-smoking, early disease stage, absence of previous DMARD use, lower baseline disease activity, concomitant corticosteroids, inflammatory biomarkers (TNF-α levels, ESR, CRP) and SE-negativity. There is still not enough literature to help determine the influence of factors such as age, genetics, RF, ACPA and inflammatory cytokines like IL-6, IL-7 etc. Another potential area of study is to come up with composite scores of various predictors that will help prognosticate and influence the choice of DMARDs. Further research is needed which will ultimately lead to the goal of a tailor made therapy for each patient.

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