

Factors Influencing Response to Disease Modifying Antirheumatic Drugs in Patients with Rheumatoid Arthritis

It is increasingly accepted that disease modifying anti-rheumatic drug (DMARD) therapy should be started early in patients with rheumatoid arthritis (RA) in order to achieve maximum benefit¹. It is clearly important not only to start DMARD therapy early but also to select a DMARD to which the patient is likely to respond. Although DMARD can retard disease progression, a significant proportion of patients have persistent joint inflammation and destruction². Even the biologics are not universally efficacious, with studies suggesting that up to one-third of patients do not respond to these treatments³. It is not known why some patients respond better to treatment than others, nor why some patients respond to one DMARD but not to another. This heterogeneity in drug response is likely to be a result of both individual patient factors (genetic and environmental) and disease-specific factors. We review the literature to identify the relative contributions of such factors in predicting drug response.

A systematic literature search using Medline identified 28 studies that had investigated possible predictors of response to DMARD therapy in RA⁴⁻³¹. These included results from observational studies⁴⁻¹³, single clinical trials¹⁴⁻²⁹, and metaanalysis of clinical trials^{30,31}. Studies varied in size from only 8²⁰ to nearly 3000 subjects⁴. It is difficult to judge the published evidence because both the definitions of response and the predictors studied varied. Elsewhere in this issue we discuss the relative merits of the differing approaches to assessing response³². Further, some studies examined individual DMARD whereas others combined all DMARD. Most studies did not distinguish between first and subsequent DMARD response. As might be expected from such a diverse set of approaches, the results were inconsistent. This is not surprising, since different factors may be important for response to different drugs. Equally, different factors may also exert an influence in early or late stages of disease. This report reviews the available evidence on individual predictors of response and

considers separately demographic, disease-specific, and patient-specific factors (Figure 1).

DEMOGRAPHIC FACTORS

Outcome studies in RA have suggested that female sex and young age at onset are associated with a worse prognosis in terms of radiographic damage and disability^{33,34}, which might relate to variation in drug response. Although there are well recognized age differences in drug handling, most studies have not found an association between age and DMARD efficacy. Responders to sulfasalazine in one observational study were significantly younger ($p < 0.05$) than nonresponders, although this effect was not seen for either gold or D-penicillamine in the same study⁹. There is also a consistent lack of effect of age on methotrexate (MTX) responsiveness^{7,31,35}. In a retrospective analysis of 265 patients with RA, Morgan, *et al*¹⁰ found that patients with a young age at RA onset were more likely to have multidrug resistance (defined in this study as failure to respond to ≥ 3 DMARD). However, in this study, multidrug resistant patients had a mean disease duration of 16.8 years, and hence younger patients would have a longer period in which to manifest their multidrug resistance. Once disease duration is adjusted for, age *per se* may be less important in predicting drug response.

In a metaanalysis of 14 randomized controlled trials (of which 13 studied MTX) including 1435 patients, Anderson, *et al*³⁰ found that female sex was associated with a poorer response rate [defined as the proportion of patients achieving American College of Rheumatology (ACR) 20% response³⁶]. A similar association was also found in a recent trial of 411 patients treated with MTX¹⁵. By contrast, neither a metaanalysis of 1140 patients with RA recruited to clinical trials³¹ nor an observational study of 681 patients treated with the gold, sulfasalazine, or D-penicillamine⁹ showed any effect of sex on drug response. The influence of sex may not be consistent for all agents and hormonal fac-

See Defining response to DMARD in RA, page 6

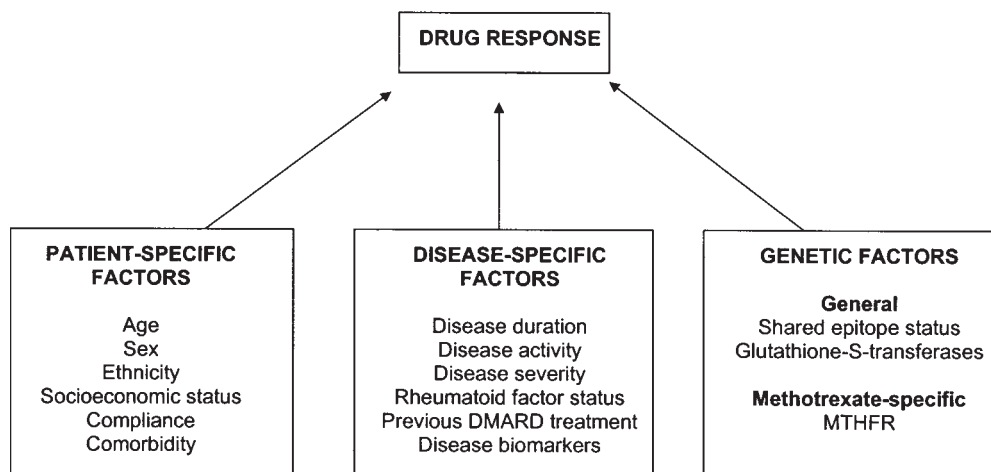


Figure 1. Factors influencing drug response in RA.

tors may contribute to differences in pharmacokinetics and drug responsiveness for particular DMARD.

Ethnicity may also be of relevance. Helliwell and Ibrahim¹² recently reported that people of South Asian origin were more likely to discontinue DMARD than North Europeans. Such ethnic differences in drug response may lead to problems with generalizability of randomized controlled trials if the majority of patients studied are of a single ethnic group. This observed ethnic difference may be due to biological mechanisms such as altered drug handling or genetic differences in drug-metabolizing enzymes. These potential biological mechanisms urgently require further study, as the choice of DMARD may be profoundly influenced by such information. Other factors such as access to healthcare, language issues, or cultural differences in perception and acceptability of dosing regimes or minor adverse events may also be partly responsible for these differences. Understanding these issues further may lead to more effective prescribing.

Studies from Glasgow have also shown that patients who live in socially deprived areas have poorer functional outcomes³⁷ and increased mortality³⁸. Although poor compliance with medication was not one of the factors associated with a worse functional outcome³⁷, this may be important in healthcare systems where patients have to purchase medication. Wolfe, *et al*⁵ noted that lower education levels were associated with reduced drug survival. Clearly, the explanations provided and adherence to treatment regimes by patients may significantly influence treatment outcome.

Therefore, although there is a suggestion that factors such as age, sex, and ethnicity may be important in drug response, the exact influence of these demographic factors is unclear. Nevertheless, plausible biological mechanisms have been identified that may explain sex and ethnic differences in drug response and further studies are required to examine these associations further.

DISEASE-SPECIFIC FACTORS

One goal is to identify those disease related factors that might predict poor response. Broadly, there are 2 groups of such factors. There are those markers that can be assessed at disease onset that might predict all future drug response and those factors present at the time of starting an individual DMARD that may predict subsequent response. To date, the majority of studies have examined predictors at *drug* onset rather than *disease* onset. In this first group, long disease duration^{9,30,31}, previous DMARD use^{4,6,11,30}, and poor functional status³⁰ appear to be the strongest predictors of poor response.

In their metaanalysis, Anderson, *et al*³⁰ found that the strongest predictor of overall response to treatment was disease duration, with a response rate of 53% for patients with less than one year of disease, compared to 35% for patients with over 10 years of disease. Other studies found similar results, specifically for gold³¹ and sulfasalazine⁹. Further, in the FIN-RACo trial of combination versus single DMARD therapy in newly diagnosed RA, delay to treatment of more than 4 months had a significant effect on remission rate at 2 years in the group treated with a single DMARD, although this effect was not seen in the group treated with combination therapy¹⁸. Not all studies have found such an effect. Hoekstra and colleagues¹⁵ found no association between disease duration and MTX response. In an observational study of 671 patients with RA, with 1017 new DMARD starts, Wolfe, *et al*⁵ used time on drug as a measure of drug efficacy and did not find that disease duration was a useful predictor of drug survival. O'Dell, *et al*^{16,39} in a study of 102 RA patients with a poor response to at least one DMARD, randomized to either MTX alone, sulfasalazine and hydroxychloroquine, or all 3 medications, also found that disease duration did not predict response to treatment¹⁶. Nevertheless, the majority of studies would seem to suggest that disease duration is important in determining drug

response. It is postulated that the biological process of RA changes early in the course of the disease⁴⁰ and so early aggressive drug intervention is important. Numerous studies support this hypothesis, showing that early treatment leads to improved outcome in terms of radiological damage and function³⁴.

There is a need, however, to disentangle whether long-standing disease *per se* is associated with a poor DMARD response or whether prior failure on a DMARD (which is more likely in patients with long-standing disease entered into clinical trials) predicts response to subsequent drugs. In an observational study of 593 Austrian RA patients receiving 1319 DMARD courses, Aletaha, *et al*⁶ reported that first DMARD courses were more effective than subsequent courses, with the greatest decline in C-reactive protein (CRP) occurring during the first DMARD prescribed. In addition, drug survival was greatest for the first drug course. Wijnands, *et al*¹¹ also noted that drug survival was shorter for drugs prescribed later in the disease course. In their metaanalysis of 14 clinical trials, Anderson, *et al*³⁰ also found that prior DMARD use was associated with a lower rate of response, independent of disease duration. However, O'Dell, *et al*^{16,39} reported that previous DMARD failure was not predictive of treatment response in a combination DMARD trial.

There are a number of mechanisms by which prior DMARD use could influence subsequent response to therapy. Previously-administered drugs may have effects on drug pharmacokinetics, such as induction of enzyme pathways, meaning that later treatments are more likely to fail (drug pressure effects). Fries, *et al*⁴ studied new starts of prednisolone, MTX, and hydroxychloroquine in 2898 patients from the ARAMIS dataset, and examined treatment effectiveness at 9 months using the Health Assessment Questionnaire (HAQ) disability score and a pain score using a visual analog scale as outcome measures. They found that the greatest effectiveness was seen with the first DMARD after nonsteroidal-only treatment. They concluded that treatment effectiveness was substantially influenced by prior treatment. It may be that there are alterations in drug kinetics over time, or the upregulation of enzyme pathways that mean that treatments prescribed later in the course of disease are less effective.

Studies examining disease activity as a predictor of treatment response are inconsistent, since most examined inflammatory markers at drug onset rather than at disease onset. In some studies inflammatory markers at treatment onset were not predictive of subsequent response^{6,9}. Others have suggested that patients with low disease activity are less likely to respond to treatment. Capell, *et al*³¹ noted that patients with a low erythrocyte sedimentation rate responded less well to sulfasalazine, gold, or D-penicillamine. Similarly, in a metaanalysis³⁰, patients with low disease activity (based on a patient global assessment < 5) were also

less likely to show a good response. Further, patients with low swollen joint counts before treatment have been found to be less likely to respond to biologics therapy⁴¹. All these observations could be based, however, on regression towards the mean, in that it is inevitably those with the more extreme values that will improve. Thus it is harder to detect a 20% response within subjects if the baseline disease activity is low. However, in the study by Hoekstra, *et al*¹⁵ patients with low disease activity at baseline were *more* likely to respond to treatment with MTX, a finding supported by others^{11,19}. In part, these inconsistent results may reflect different outcome measures used, and so it is important to use an outcome measure that retains consistency across the disease spectrum. It is likely that disease activity does influence response to treatment, although the effect may vary at different stages of disease and according to the measure of disease activity applied.

Other authors have suggested that patients with more severe disease may be less responsive to treatment, and Anderson, *et al*³⁰ highlighted that higher functional class (as measured by the Steinbrocker criteria) was associated with a poorer response. This effect may not be seen in early disease. In the FIN-RACo study¹⁸ of 195 patients with recent onset RA (median disease duration 6 mo), HAQ score at baseline did not predict remission. Clearly, there are issues in applying a disease severity measure that retains consistency at all stages of disease. It is well recognized, for example, that the HAQ is more closely associated with disease activity in early disease, while it has ceiling effects in established disease, reflecting underlying damage. Overall, the balance of published data would suggest that disease duration and drug order are important predictors of drug outcome, although whether these 2 factors are independent of each other is less clear. Certainly there are biological mechanisms to explain why these factors may be important in drug response.

There are, by contrast, relatively few data on what factors assessable at disease onset might predict poor response. Rheumatoid factor (RF) positivity is recognized to be predictive of both persistent disease and radiological progression^{33,42,43}, but whether RF status influences treatment response is less clear. Indeed, studies have suggested that RF status does not predict response to drug treatment^{6,16}. Morgan, *et al*¹⁰ did find, however, that patients who had failed 3 or more DMARD were more likely to be RF positive. One obvious explanation is that RF, as a marker of more severe disease, may influence treatment outcome. If this were the case it is surprising that Hall, *et al*²⁴ found rheumatoid nodules were not predictive of response to drug treatment.

GENETIC FACTORS INFLUENCING TREATMENT RESPONSE

Pharmacogenetics involves the study of genetic variation

underlying the differential response to drugs, and such polymorphisms may predict treatment response or toxicity by influencing drug pharmacokinetics, drug targets, or the disease pathway itself. This is a new and evolving area in RA investigation that seems to hold promise for a better understanding of some of the variability in treatment response.

The most frequently investigated genetic predictor of response has been the role of the HLA-DRB1 shared epitope (SE) alleles. Most studies have been of combination therapy or MTX and so are not necessarily generalizable to other DMARD. The data are summarized in Table 1. O'Dell, *et al*¹⁶ reanalyzed their combination DMARD study³⁹ and found that SE-positive patients treated with combination therapy did much better than if treated with MTX alone (ACR 50, 94% vs 32%; $p < 0.001$). SE-negative patients did equally well regardless of treatment allocation. Ferraccioli, *et al*¹⁷ found that MTX monotherapy gave poorer results in DR4/DR1-positive patients. By contrast, Criswell, *et al*⁴⁴ studied 148 patients taking MTX as part of a clinical trial and found that response (defined as proportion achieving ACR50) was significantly greater in patients with at least one copy of the SE compared to patients with no SE alleles (66% vs 45%; $p = 0.04$). In the FINRACo cohort⁴⁵, SE status did not predict induction of remission in either group. Although treatment outcome *per se* was not reported, secondary analysis of the COBRA study⁴⁶ showed that aggressive combination treatment attenuated the poor prognostic effect of DR4 positivity. In the sulfasalazine monotherapy arm, patients who were DR4-negative had a mean increase in Sharp score of 3 compared to 11 in the DR4-positive group ($p = 0.006$). However, in the combination arm there was no significant difference in radiological progression between the 2 groups, suggesting that aggres-

sive treatment improves the radiological prognosis for DR4-positive patients. O'Duffy, *et al*¹⁴ also examined the effect of HLA alleles on outcome with gold treatment and found that HLA-A3 positivity and HLA-DR4 negativity were the best predictors of response to gold.

In addition to SE status other pathways have been explored in the context of RA. First, there are key families of drug metabolizing enzymes, and polymorphisms in these enzymes may lead to clinically important differences in drug response. Glutathione-S-transferases (GST) are a family of enzymes involved in drug detoxification and metabolism. One study found that patients who had the GSTM1 null allele were significantly less likely to respond to D-penicillamine than patients who did not express the GSTM1 allele²⁵.

Second, there are polymorphisms within single drug pathways that may influence treatment outcome. MTX acts on a number of essential enzymes including thymidylate synthase, dihydrofolate reductase, and methylenetetrahydrofolate reductase (MTHFR)⁴⁷. Two polymorphisms within the MTHFR gene have been studied. In a retrospective study, Urano, *et al*²⁶ found that the A1298C polymorphism was associated with an improvement in inflammatory markers but not in joint counts in RA patients treated with MTX. Other polymorphisms may be associated with drug toxicity and hence treatment withdrawal. The C677T polymorphism has been shown to be associated with an increased risk of abnormal liver function tests^{26,27}. These early findings require confirmation, and further studies are required to examine polymorphisms in other enzymes involved in the metabolism of MTX and their effect on treatment outcome.

To date, 2 studies have examined the effect of polymorphisms in the tumor necrosis factor- α (TNF- α) gene on outcome of infliximab treatment. Mugnier, *et al*²⁹ genotyped 59 patients with established RA treated with infliximab and

Table 1. Effect of shared epitope (SE) status on response to treatment.

Study	No. of Patients	Inclusion Criteria	Treatment Studied	Primary Endpoint	Outcome
O'Dell ¹⁶	84	RA > 6 months Failed 1 DMARD Active disease (ESR > 28, \geq 8 tender joints \geq 3 swollen joints)	MTX vs HCQ + SSZ vs MTX + SSZ + HCQ	ACR 50	SE-positive patients much more likely to achieve a 50% response if treated with all 3 drugs than with MTX alone (94% responders vs 32%; $p < 0.001$). SE-negative patients did well regardless of treatment allocation (88% vs 83%; $p = 0.69$)
Ferraccioli ¹⁷	126	Early RA Erosive disease Only HCQ prior to inclusion	MTX + CyA* \pm SSZ** vs CyA + MTX* \pm SSZ** vs SSZ alone	ACR 50 at 6 months	HLA-DR 4/1-positive patients receiving MTX first did worse than HLA-DR 4/1-negative patients (29% responders vs 80%). Cyclosporine more efficacious in HLA-DR 4/1-positive patients (52% responders vs 5.8%). Little difference in SSZ group (41% responders vs 28%)
Mottonen ¹⁸	165	RA < 2 years DMARD naive Active disease	MTX + SSZ + HCQ \pm prednisolone vs single DMARD \pm prednisolone	Remission at 2 years	SE status did not predict remission

* 2nd drug added at 6/12 if ACR 50 not achieved. ** SSZ added at 12/12 if ACR 50 not achieved. HCQ: hydroxychloroquine, SSZ: sulfasalazine, MTX: methotrexate.

found that patients with the TNF α -308G/G genotype had a better response to infliximab at 22 weeks than patients carrying at least one copy of the TNF α -308A/G polymorphism. A second study⁴⁸ found a similar association between the TNF α -308G/G genotype and a good clinical response to etanercept. In addition, a combination of alleles influencing interleukin 1 receptor antagonist (IL-1ra) and transforming growth factor- β (TGF- β 1) production (A2 allele of the IL-1ra and TGF β 1 +915 G-C) was associated with a poor response to etanercept.

Other biological markers may also predict treatment outcome. For example, patients with high synovial tissue vascularity have a better response to DMARD²². Another small study²¹ found that patients who responded better to DMARD therapy (as measured by fall in CRP) had higher basal serum concentrations of soluble CD30 (a member of the tumor necrosis/nerve growth factor subfamily) than nonresponders. Other markers evaluated include serum matrix metalloproteinases-3²⁸, IL-1ra²³, IL-4, and IL-10²⁰. However, although many of these markers *correlate* with treatment outcome, larger studies are required to evaluate whether they are indeed *predictive* for treatment outcome.

CONCLUSION

It is not known why there is such heterogeneity in response to DMARD therapy. While factors have been identified that are associated with a poor longterm outcome, such as young age at onset, high disease activity at baseline, and RF positivity^{33,34}, these factors do not seem to predict response to DMARD therapy. It is likely that drug response is influenced by a combination of both patient-specific (including genetic) and disease-specific factors. To date the main predictors of poor response appear to be long disease duration and use of multiple previous DMARD. Genetic factors, including SE status, also seem to influence response to specific drugs, in particular MTX. It is likely, however, that other genes that control the metabolism and downstream effects of individual DMARD will be found that profoundly influence both response and adverse effects. Such knowledge would help to inform treatment choices in RA. Clearly, with the advent of effective (but expensive) biological agents it becomes ever more important to look for factors that predict response before starting treatment, and further studies are needed in this area.

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