Pharmocogenetics in the future treatment of rheumatology

> 'Pharmacogenetics … holds the promise not only to explain interindividual variability in drug response, but also to predict efficacy and adverse drug events in individual patients.'

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Even though the armamentarium of drugs available for the treatment of rheumatoid arthritis (RA) is ever expanding, the treatment of this disease is still suboptimal. In addition, clinicians are familiar with the inability to predict the response to drug therapy in the individual patient, both with respect to efficacy and side effects. For example, with the most commonly used DMARD, methotrexate (MTX), only 45–65% of the patients show a good clinical response with MTX monotherapy and 30% discontinue treatment for reasons of toxicity [1–7]. While achieving good response early in the disease process is key to minimizing the joint damage and functional decline characteristic of RA [8–11], it is not yet possible to predict which patients will respond to MTX therapy. As a result, drug choices and the course of therapy are currently made empirically in the field of rheumatology [12], as it is in most fields of drug therapy.

Pharmacogenetics, the inheritance of drug response, holds the promise not only to explain interindividual variability in drug response, but also to predict efficacy and adverse drug events in individual patients. This so-called personalized medicine or tailored therapy aims at the identification of prognostic factors, based upon genetic variations, relevant to clinical response to drug treatment [13–15]. Since treatment is an important factor that influences RA outcome, the current research emphasis has been shifted from the comparison of effective treatment towards studies identifying prognostic indicators for treatment response [9,16–18]. Thus, the challenge now is to improve RA therapy by targeting drugs only to those patients most likely to respond with maximal efficacy and avoiding toxicity.

Pharmacogenetics associates differences in drug response to genetic variation. While two unrelated individuals share more than 99.9% of the DNA sequence, the 0.1% variation is considered a source for differences in phenotypes. Allelic variants, especially single nucleotide polymorphisms (SNPs), represent the most abundant source of genetic variation in humans. SNPs occur every few hundred bases in promoter regions and coding and noncoding sequences.

Most of the allelic variations are located in the intergenic segments of the genome and are thought to be harmless to the organism. However, functional SNPs can alter promoter activity (regulatory SNPs), DNA, pre-mRNA conformation or mature RNA (alternative splicing), and can influence the function or expression of the gene product – the protein. As a consequence, SNPs may play a direct or indirect role in the demonstration of the therapeutic phenotype. Studies of other complex diseases have already indicated the relevance of SNPs in drug-metabolizing enzymes, transporters, receptors and signaling pathways to alter drug response. Genetic factors are thought to be responsible for up to 30% of differences in drug metabolism and drug response [13–15].

Pharmacogenetic studies in RA remain relatively scarce and are only beginning to provide results. Recent reviews have summarized studies addressing genetic variability in genes contributing to outcome with nonbiologic DMARDs (MTX, sulfalazine, azathioprine and hydroxychloroquine) and with biological DMARDs (infliximab, adalimumab and etanercept) [19–23].

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Studies show that MTX, sulfalazine and azathioprine are the nonbiologic DMARDs with the potential for tailoring drug therapy by applying pharmacogenetics. For MTX, associations are thought to exist between the C677T and A1298C polymorphisms in the methylenetetrahydrofolate reductase gene and MTX efficacy and adverse drug events. More recently, polymorphisms in genes (adenosine monophosphate deaminase, aminoimidazole carboxamide ribonucleotide transformylase and inosine triphosphate pyrophosphatase) contributing to the

release of anti-inflammatory adenosine were found to be associated with MTX treatment outcome. An increased incidence of gastrointestinal side effects and hepatotoxicity with sulfalazine use is associated with the slow acetylators phenotype due to the *N*-acetyltransferase-2 polymorphism.

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Genetic polymorphism of the gene encoding thiopurine methyltransferase (*TPMT*), the enzyme involved in the metabolism of azathioprine, leading to a *TPMT*-deficient phenotype is related to bone marrow toxicity in patients using this drug. There is a growing body of evidence that efficacy of the anti-TNF drugs may be associated with TNF-promoter polymorphisms and the HLA–DRB1 shared epitope.

Unfortunately, the currently available pharmacogenetic investigations in RA, especially with regard to very expensive therapies with biologicals, do not yield unanimous results that allow us to draw clear-cut conclusions regarding the relationship between genotype and treatment outcome. Therefore, in general it is too early to advocate the clinical use of genotyping RA patients before initiation of drug treatment. However, a possible example is the individualization of the response on MTX. To predict the response to this drug, prediction models that include pharmacogenetic tools have been developed and replicated [24], but it remains to be seen whether these tests will be implemented in clinical practice.

Moreover, most of the association studies warrant replication and prospective validation in independent patient cohorts. Indeed, the pharmacogenetic studies demonstrating an association between a genetic variant and treatment outcome do not reveal which alternative intervention (such as dose adjustment or choosing an alternative drug) may be more successful, and therefore these studies are of limited value for clinical practice. Studies aiming at developing a predictive decision-making model, such as recently published by our group for predicting the efficacy of MTX in early RA patients and taking into account both genetic and nongenetic determinants, may be easier to implement in clinical practice [24].

In addition, there is a need for better designed pharmacogenetic studies. Most pharmacogenetic studies performed so far have insufficient sample size (power) to detect expected differences in genotype frequencies between responders and nonresponders. Furthermore, the definition and assessment of a clear-cut phenotype (responder, toxicity and drug dose) is essential for performing associations studies. Another problem that arises is that for several drugs used in RA, the precise mechanism of action is as yet unknown, making it impossible to select candidate genes for pharmacodynamic studies. For example, pharmacogenetic studies with sulfalazine are limited to genetic differences in metabolizing phenotype (due to variable *N*-acetyltransferase-2) since the specific cellular site of action is as yet unknown. A genome-wide approach with dense SNP-arrays, which have become affordable in recent years, may theoretically overcome this problem. However, due to multiple testing this approach may lead to a high number of false-positive selected genetic variants of interest and are found hard to replicate.

Other difficulties may exist in interpreting results in pharmacogenetic studies. When genetic variations are known to be disease related, such as the *HLA–DRB1* shared-epitope gene, mutations in these genes are likely to be related to a more severe disease state and, thus, a higher disease activity at baseline, as compared with patients lacking such mutations. Owing to regression to the mean, patients with high disease activity, in contrast to those with lower disease activity, might show a higher response.

Predicting a positive or negative treatment outcome is then hampered by higher disease activity at baseline, rather than referring to an effect of variance in genotype. Despite the difficulties in distinguishing factors relevant for disease progression or severity from factors important for treatment response, it is likely that different prognostic sets, including clinical and genetic factors, may cover an identical group of RA patients with a favorable response profile.

The proof-of-concept of pharmacogenetics, specifically the study of inherited differences in interindividual drug response, is without doubt. Its implementation into clinical practice as personalized medicine is as yet developing but has the potential to be of great benefit to patients with RA.

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