Pharmacogenetics of methotrexate in patients with rheumatoid arthritis

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General introduction

Rheumatoid arthritis (RA) is the most common chronic inflammatory joint syndrome affecting approximately 1% of the population, with higher prevalence in females [1]. Remarkably, the occurrence of RA is not the same throughout the world which may be explained by either genetic or environmental factors [1,2]. Although many studies revealed that aberrant inflammatory and immunomodulatory components such as tumour necrosis factor (TNFα) and interleukin-1 (IL-1) are involved in RA, the etiology and pathogenesis of the disease remains largely unknown [3].

RA has a broad spectrum of clinical manifestations including joint swelling and tenderness, morning stiffness and impairment of movement. Even though the features of RA are predominantly found in the joints, the disease may have a detrimental effect on the blood vessels, lungs and the heart contributing to an increased morbidity and mortality in RA-patients [4].

Continuous disease activity in RA leads to progressive joint and cartilage destruction resulting in declining functionality and disability within a few years of disease onset [5–7]. No treatment cures RA; therefore, reducing disease activity with early therapeutic intervention is key in the disease process to minimize the joint damage and functional decline [7,8]. Indeed, a delay of three months in the introduction of medication has been shown to result in substantially more radiographic joint damage at five years [5–7].

Treatment of RA usually follows a stepwise approach with monotherapy methotrexate (MTX)-administered weekly in low doses – being the most commonly used drug [8–10]. If there is insufficient response and/or adverse drug events, MTX may be switched for another disease modifying anti-rheumatic drug (DMARD), a second DMARD may be added to the MTX monotherapy, or therapy is changed to a newer subgroup of DMARDs, so-called biological agents, either alone or in combination with other DMARDs [11].

Despite the fact that different treatment options and strategies for RA patients are available, the response to treatment with DMARDs is suboptimal. For example, only 45–65%

of the patients show a good clinical response with MTX monotherapy and 30% discontinue treatment due to toxicity [10,12–17]. Remarkably, studies in the field of identifying determinants for effective and safe treatment for individual RA patients are still scarce. As a result, drug choices and the course of therapy are currently made empirically in the field of rheumatology.

Personalized medicine aims at the identification of prognostic indicators relevant to clinical response to treatment. Since treatment is an important factor which influences RA outcome, the research emphasis has been shifted from the comparison of effective treatments towards studies aiming at the detection of prognostic indicators relevant to clinical response [2,8,18,19]. Thus, the challenge is to improve RA therapy by targeting DMARDs only to those patients who are most likely to respond and thereby predicting the individual response with maximum efficacy and avoiding toxicity. In this context, pharmacogenetic research may be an approach to tailor therapy for RA patients. Pharmacogenetics is the field that studies the influence of variations of DNA sequence on drug response with single nucleotide polymorphisms (SNPs) representing the most abundant source of genetic variation in humans [20].

MTX may be considered as the first candidate drug in the step toward individualized therapy in RA. First, MTX is the anchor drug in the treatment of RA either as monotherapy or in combination with other DMARDs [21]. Although MTX has proven to reduce disease activity and delay or stabilize the development of bone erosions, individual good clinical response rates for MTX treatment vary between 45–46% whereas adequate suppression of RA disease activity is essential [7,13–15,17]. Next, there is no alternative DMARD monotherapy with a more favourable therapeutic profile and price. Moreover, to date there are no useful and reliable clinical or molecular markers to predict MTX treatment outcome. Importantly, the influence of SNPs on the response to MTX as a cytotoxic drug in bone marrow transplant patients and acute lymphoblastic leukemia patients has been shown [22,23]. These findings indicate that genetic variations may contribute to MTX treatment outcome. In addition, nongenetic factors such as age and sex and factors such as disease duration, prior DMARD use, and folic acid supplementation have been studied to predict MTX treatment outcome, but results regarding both efficacy and toxicity are conflicting [10,24–27].

Therefore, this thesis aims to determine whether SNPs are associated with MTX treatment outcome in patients with RA. In the context of personalized treatment, we hope that the pharmacogenetic approach will lead to better-tailored initial treatment decisions in RA-patients.

Scope of this thesis

As a first step, we will focus on the potential pharmacological mechanisms of action of MTX next to the genetic variants that have been studied in relation to response to DMARDs. The aim of these chapters is to identify (molecular) targets as potential indicators relevant for MTX treatment outcome (Chapter 2–3).

The current strategies used in pharmacogenetic studies include association studies of drug response with SNPs in 'candidate genes' which are genes selected on the basis of the pharmacokinetic and pharmacodynamic properties of the drug under study. Although

MTX affects various target pathways, which probably account for its in vivo anti-proliferative and immunosuppressive effects in RA, there are many reports showing that MTX inhibits or interferes with the activity of folate pathway enzymes and directly or indirectly releases endogenous anti-inflammatory adenosine.

Given these potential mechanisms of action of MTX in RA, the second part of this thesis addresses the genetic association of SNPs in candidate genes coding for folate pathway enzymes and genes related to the release of endogenous adenosine with MTX efficacy and toxicity in newly-diagnosed RA-patients (Chapter 4–6).

The subsequent chapter (Chapter 7) provides a framework of how pharmacogenetic results, combined with clinical factors and nongenetic determinants, can be used in a model to predict individual MTX efficacy in RA. Because MTX toxicity is an important reason for treatment discontinuation in RA patients, chapter 8 aims at the identification of SNPs via genome-wide analysis as markers for MTX induced liver toxicity. In contrast to the candidate gene approach, this latter approach intends to associate SNPs across the human genome in (or in linkage with) candidate genes with response, without using any a priori knowledge about the pharmacology of a drug.

Finally, the theme of this thesis is summarized and the potential of pharmacogenetics in inflammatory arthritis are discussed in the last two chapters (Chapter 9–10).

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