Potential role of pharmacogenetics for optimalization of drug therapy in rheumatoid arthritis

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Chapter 1:

General Introduction and Outline

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a prevalent autoimmune disease, which affects approximately one percent of all types of human populations (1;2). Generally, this immune-mediated disease is associated with symmetrically inflammation, destruction of the joints leading to overall functional impairment and (serious) comorbidity, like cardiovascular events (3-6).
Generally, the etiology of this inflammatory disease remains unclear due to the complexity of interacting factors representing a multifactor process. Still, important risk- and protective factors have been elucidated which are associated with development or severity of RA (7-11). These factors can be divided in two groups: environmental- and genetic factors. It has been demonstrated that these factors act synergistically in causing RA. Specifically, this phenomenon was highlighted by an interaction between smoking and HLA-DR risk alleles in RA patients (12;13). Likewise, it was observed that an environmental factor, like smoking, could increase the genetic risk course for RA. These interactions provide additional difficulties in clear understanding RA's etiology.
Similarly to etiology, the RA's pathophysiology is not fully understood. Hypothetically, after the stimulation of an environmental trigger, T-cells of the CD4+ type stimulate monocytes, macrophages and synovial fibroblasts to secrete three important pro-inflammatory mediators: Tumor Necrosis Factor alpha (TNFα), interleukin 1 (IL-1) and interleukin 6 (IL-6). It is thought that TNFα has a central place in the inflammatory cascade of RA leading to progression of inflammation and eventually erosion of bone and cartilage. Also, TNFα is recognized to be involved in stimulation of cytokine production (including its own), enhancing expression of adhesion molecules, neutrophil activation and it is also a co-stimulator for T-cell activation and antibody production by B-cells (14;15) (figure 1).

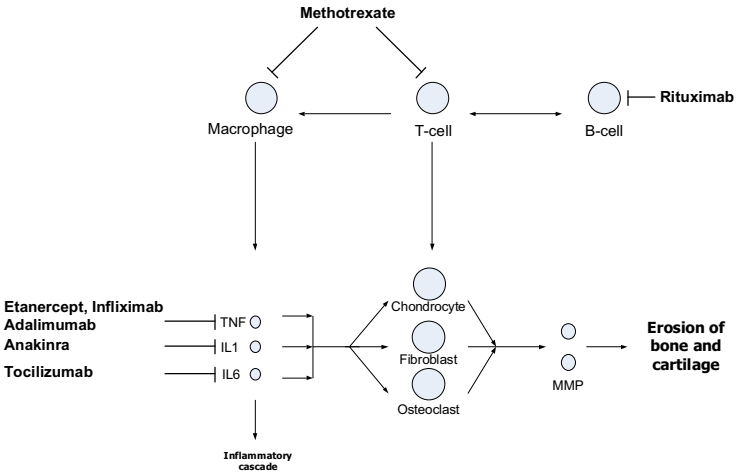

Figure 1. Pathophysiology and accessory therapeutic agents in rheumatoid arthritis

Abbreviation(s): IL1= interleukin 1, IL6= interleukin 6, MMP= matrix metalloproteinases, TNF= tumor necrosis factor.

Treatment of rheumatoid arthritis

In the last decades treatment outcome of RA has been successfully improved due to:
-1- the expanding knowledge of the disease's pathophysiology, which elucidated important key players in the inflammatory process as potential targets for therapy (14-16); -2- development of new

agents based on newly discovered targets leading to improved response percentages and facilitating a range of equivalent treatment modalities in drug therapy (e.g. for effectively switching to infliximab after failure of etanercept) (17;18); -3- the development of easy-to-use diagnostic tools to measure efficacy of therapy (19-22); -4- the recognition and acknowledgement that disability and joint damage occurs in an early state (6;23-25); -5- therapeutic strategy for RA patients that is focused on strictly- and early management of RA's disease course (26-28).
Despite an increasing knowledge on RA's etiology and pathogenesis, a therapy resulting in remedy of the disease is not achieved to date. Alternatively, treatment is aimed at remission of disease, by suppressing pro-inflammatory particles, like cytokines and lymphocytes (16;29). Notably, a widening arsenal of therapeutics has been developed, which have a general focus on modifying RA's disease course to alleviate pain, to suppress inflammation, to prevent joint damage and loss of function in order to postpone disability (Figure 1) (30). Hereby, an important role in modification of treatment outcome is being played by disease modifying antirheumatic drugs (DMARDs). Two types of DMARDs take a central place in the rheumatology clinics: methotrexate (MTX) and TNF inhibitors. Despite the fact that the mechanism of action of these drugs remains partially unclear, DMARDs have proven to be effective treatment modalities according to several disease activity measurements in clinical trials (26;31-36). For this reason, rheumatologists have increasingly prescribed both types of drugs. However, highly differential response rates in overall clinical efficacy and/or toxicity have been demonstrated in clinical trials with MTX and TNF inhibitors. Specifically, 40-70% and/or 15-30% in RA patients treated with MTX and TNF inhibitors fail to achieve a satisfactory response and/or develop adverse drug events, respectively (26;31-36). Because of the substantial differences in individual responses and also the knowledge that reduction of disease activity leads to less progression of RA, it is beneficial to predict which patients have a increased chance for responding to the different treatment modalities. Consequently, several studies have been performed considering an influence of demographic, clinical and immunological variables on treatment outcome to DMARDs (37-41). Similarly, genetic influences on response to DMARDs have also been explored (42-47). Generally, genetic factors are estimated to account for 15-30% of interindividual differences in drug metabolism and response. In this way, pharmacogenetics has the potential to increase drug efficacy and to ameliorate adverse drug events by applying genetic determinants of therapeutic response and is able to aid in predicting efficacy and toxicity of drug therapy in RA (48;49).

Pharmacogenetics

Pharmacogenetics is defined as the study of variability in drug responses attributed to genetic factors in different populations (48;49). In this context, the pharmacogenetics of most drugs is likely to be comparable to the genetics of complex diseases, like RA. In both cases numerous proteins are involved in complex pathways, and in this way one clear genetic explanation is not available (50).
The complete DNA sequence across the human genome, which consists of approximately 3.1 billion base pairs, has been determined. Approximately 99.9% of base pairs in the human genome are identical among individuals, whereas the remaining 0.1% reflects the individual differences in variants which may lead to differences in susceptibility to specific diseases and response to specific drugs. Single nucleotide polymorphisms (SNP) have been recognized as useful markers of genetic polymorphism. SNPs comprise genetic variation with a single-base difference between individuals resulting in due to alteration, deletion or insertion of the base (e.g. replacement of guanine by adenine). SNPs are widely distributed at a frequency of about one SNP in every 300–500 bases, which is approximately 1.5 million of this type of variants across the human genome. Hereby, SNPs are estimated to account for 90% of all genetic mutations (51;52).

Generally, in pharmacogenetics SNPs are involved in differences in drug response by affecting the expression of genes or by altering the types of amino acids and affecting their activities (49;53). In addition, as multiple SNPs exist within a single gene, several combinations of these polymorphisms (expressed by linkage disequilibrium- e.g. haplotypes) are important to consider in order to explain genetic variation as a whole in pharmacogenetic research (51).

Outline of this Thesis

The primary objective of this thesis is to assess the role of pharmacogenetics in the variation of treatment outcome in patients diagnosed with rheumatoid arthritis and treated with disease modifying antirheumatic drugs. Hereby, this thesis is divided in two parts: pharmacogenetics of methotrexate and of adalimumab in RA patients.

Part 1: Pharmacogenetics of methotrexate

In **Chapter 2** an overview is presented of the previously performed studies concerning genetic variability contributing to differences in response to MTX in RA treatment.

As it is generally accepted that MTX may act in RA through inhibition of folate pathway enzymes, other reports indicate that efficacy may also be related to the release of endogenous antiinflammatory adenosine. With this hypothesis, the relationship between SNPs in genes related to adenosine release and MTX treatment outcome in patients with recent-onset RA is explored in **chapter 3**.

So far, most genetic variants are selected for analysis based upon their hypothetical relation to the mechanism of MTX or inflammatory process in RA (**chapters 2**), such as genetic variants in the adenosine pathway (**chapter 3**). Ideally, functional genetic variants are chosen because the alteration in protein function is thought to influence drug action and thus may explain interindividual differences in drug response. **Chapter 4** assesses the role of SNPs with proven functional consequences. These SNPs are located in genes, which are thought to be related with the mechanism of action of MTX and/or immunopathogenesis of RA. In addition, replication analyses are performed in **chapter 4**, since previously applied endpoints for efficacy from other research reports are available. These replication analyses are important, since pharmacogenetic studies have the potential to result in reporting false positive findings.

Previously, a clinical pharmacogenetic predictive model was developed for predicting the efficacy of MTX monotherapy in patients with recent-onset RA comprising the Dutch BeSt Cohort. The model consists of non-genetic factors sex, rheumatoid factor and smoking status, Disease Activity Score (DAS) before starting MTX and 4 genetic polymorphisms (*MTHFD1* 1958G>A, *AMPD1* 34C>T, *ITPA* 94A>C and *ATIC* 347C>G). The performance of this model is validated in a second Dutch cohort (**chapter 5**) and in a Swedish cohort (**chapter 6**).

Chapter 7 evaluates the role of the haplotypes comprising the SNPs *MTHFR* 1298A>C and *MTHFR* 677C>T in treatment outcome to MTX in RA. Specifically, in this chapter optimalization of a previously designed pharmacogenetic model is aimed with addition of the number of haplotypes comprising *MTHFR* 1298A-677C alleles as additional criterion. Furthermore, the predictive value of the haplotype is compared with other genetic polymorphisms in predicting MTX efficacy.

Part 2: Pharmacogenetics of adalimumab

In **Chapter 8** an overview is given of the previously performed studies concerning genetic variability contributing to differences in response to TNF inhibitors in RA treatment.

In the next chapter, SNP selection for pharmacogenetic association studies is discussed. Additionally, a pharmacogenetic pathway approach is presented together with proposed criteria for systematic selection of SNPs. This method is applied for the selection of potential interesting SNPs within genes related involved in the mechanism of action of adalimumab and/or inflammatory process of RA (**chapter 9**).

Chapter 10 puts the presented systematically selection of SNPs in **chapter 9** into practice: efficacy of treatment with adalimumab is associated with genetic variants selected by a pharmacogenetic pathway approach using a custom made antiTNFα SNP array.
Furthermore, SNPs, which were previously associated with genetic susceptibility to RA and/or treatment outcome to TNF inhibitors, were examined for association with treatment outcome in **chapter 10**.

Chapters 11 and 12 provide a summary of this thesis (chapter 11) and present a general discussion including a perspective on future research (chapter 12).

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