Pharmacogenetics in the Rheumatic Diseases

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Abstract
Designing a therapeutic plan that involves the least risk of toxicity and the greatest chance of success is the goal of the modern physician. To better achieve this goal an understanding of the genetic basis for drug efficacy and toxicity is essential. Here we review the available information on the pharmacogenetics of drugs commonly used to treat rheumatic diseases in the hope that the application of this information to the patient will contribute to more effective and safer therapies for rheumatoid arthritis, systemic lupus erythematosus, and other inflammatory diseases.

In an ideal world, pharmacologic therapy of diseases such as rheumatoid arthritis would be designed for each individual patient depending upon that person’s genetic makeup and the severity of his or her disease. Although the genetic contribution to disease susceptibility and severity has been a subject of study in the rheumatic diseases for many years, studies on the role of genetics in response to the therapy of rheumatic diseases are more recent. As knowledge and understanding increases the interplay between an individual’s genetic composition and the therapeutic or toxic responses to specific drugs (pharmacogenetics), we will be better able to realize the goal of tailoring therapy to the individual.

A number of general considerations in the study of pharmacogenetics must be taken into account when examining the literature in this area. Single nucleotide polymorphisms (SNPs) occur at approximately every 1000 bases in the human genome, and the sum of these differences accounts for differences among individuals. However, any given SNP will occur with a different frequency in different populations, creating a greater or lesser likelihood of inheriting that specific genetic polymorphism in that group. It is increasingly clear that in the study of pharmacogenetics small studies can be and often are misleading; upon repetition pharmacogenetic associations made in small groups of individuals may not be reproducible or the magnitude of the association may shrink. Small groups are often susceptible to biases with respect to ethnic background, confounding diseases, or other causes. The best studies are those in which a genetic association is examined in multiple groups. When considering potential genetic determinants of response to a specific drug, it should be remembered that the genetic polymorphisms associated with poor/good efficacy may actually be associated with more severe/mild disease activity. Finally, detecting a SNP associated with toxicity is easier than finding a SNP associated with efficacy, since toxicity is a discrete event, but even a poorly efficacious drug may be effective in an individual with mild disease regardless of the genetic predisposition to respond to that agent.

Genetic factors most likely influence the response to all of the drugs used to treat rheumatic diseases. Multiple polymorphisms have been described in the glucocorticoid receptor that may affect sensitivity to corticosteroids, although the implications for response to glucocorticoids in the rheumatic diseases have not been well studied to date. Polymorphisms in the corticotrophin-releasing hormone receptor 1 have been assessed for an association with juvenile chronic arthritis, but no association has been observed.

Polymorphisms in the genes involved in metabolism of nonsteroidal anti-inflammatory drugs (NSAIDs) influence their pharmacokinetics and, most likely, their efficacy although this has not been well studied. Similarly polymorphisms in the target gene product, cyclooxygenase, may affect the efficacy of NSAIDs.

Azathioprine is the drug with the best defined pharma-
Azathioprine is converted to 6-mercaptopurine, which can be metabolized by xanthine oxidase to oxidized metabolites, by hypoxanthine-guanine phosphoribosyl transferase (HPRT) to 6-thioguanine nucleotides, or by thiopurine methyl transferase (TPMT) to 6-methylmercaptopurine (Fig. 1). There are a number of common polymorphisms in the TPMT gene, some of which affect the enzymatic activity and thus the ability to detoxify azathioprine. First characterized enzymatically in red blood cells, low TPMT activity leads to accumulation of 6-mercaptopurine and the development of severe bone marrow suppression and leucopenia on taking either azathioprine or 6-mercaptopurine. Testing for the polymorphisms associated with azathioprine toxicity is available and can be useful in preventing azathioprine toxicity in susceptible patients.

Low-dose methotrexate is a mainstay of therapy in the rheumatic diseases. Methotrexate was originally developed as a folate analogue. In high doses, such as those used to treat malignancies, methotrexate inhibits folate-dependent reactions involved in the de novo synthesis of purines and pyrimidines as well as a host of methylation reactions. Methotrexate is taken up from the gut and by cells via the reverse folate carrier 1 (RFC1). Once inside a cell, methotrexate is polyglutamated, which keeps the drug within the cell and shifts the activity of the agent so that it acts as an enzymatic inhibitor (Fig. 2). Genetic polymorphisms in RFC1, an enzyme involved in methylation reactions, purine and pyrimidine synthesis, and multidrug resistance, have been described, and some of these polymorphisms, alone or in combination with polymorphisms in other genes, affect toxicity and efficacy of methotrexate. The best studied association is between polymorphisms in the gene methylene tetrahydrofolate reductase (MTHFR), the enzyme that catalyzes the formation of 5-methyl tetrahydrofolate, a critical methyl donor for a variety of metabolic reactions.

Complete or near complete absence of MTHFR activity is the most common inherited abnormality of folate metabolism and leads to homocysteinemia/homocystinuria and altered folate distribution; clinically severe MTHFR deficiency is characterized by neuropathy, encephalopathy, coagulopathy, and vasculopathy. Common polymorphisms in MTHFR (C677T and A1298C, Table 1) are associated with diminished enzymatic activity and are associated with greater susceptibility to methotrexate toxicity. Although these same polymorphisms have been associated with enhanced efficacy in some studies, no difference in efficacy could be demonstrated in other studies. Moreover, the studies in which MTHFR polymorphisms have been associated with methotrexate efficacy have been flawed due to the choice of a poor definition of methotrexate responsiveness. (A responsive patient was defined in these papers as one who responds to \( \leq 5 \text{ mg/wk of methotrexate} \).) The metabolism of methotrexate and the metabolic mechanism accounting for its anti-inflammatory actions are complex, and recent studies have suggested that multiple genetic factors contribute to methotrexate’s efficacy.

Recent studies have suggested that response to tumor necrosis factor (TNF) inhibitors might also have a genetic basis. Most of these studies have concentrated on polymorphisms in the gene for TNF, and associations have been found between these polymorphisms and response to anti-TNF agents. Whether these polymorphisms directly alter response to the agents or whether these polymorphisms regulate severity of the disease is difficult to determine, since many patients who do not respond to one anti-TNF agent...
may respond to a different agent.

Study of the relationship between genes and drug responses is in its infancy in the rheumatic diseases. As the relationships among genetics, drug efficacy, and toxicity are unraveled, the treating physician may be able to better tailor drug therapy for patients with rheumatoid arthritis and other rheumatic diseases so as to avoid long periods of poor response to therapy and unnecessary toxicity.

References


