REPORT

Pharmacogenetics in the rheumatic diseases

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Ann Rheum Dis 2004;**63**(Suppl II):ii25–ii27. doi: 10.1136/ard.2004.028217

One of the promises of the human genome project is individualised pharmacological therapy. An individual's genetic type would be determined, and the resulting diseases which the person was susceptible to would be determined. In addition, the drugs to which an individual would respond well would be enumerated, and the drugs which were more likely to be toxic could be established. At present we are just beginning to determine those associations which would help us tailor an individual's pharmacological therapy so as to maximise efficacy and minimise toxicity. In this report we review the considerations involved in determining the pharmacogenetic profile of any given drug and to review the current level of understanding of the association between genetic polymorphisms and drug toxicity/efficacy in rheumatology.

Establishing an association between genetic types and toxicity is perhaps an easier task to accomplish than understanding the association between a given genetic type and drug efficacy. Drug toxicities are generally discrete events and a specific toxicity can often be traced to the agent in question. Thus, it is fairly easy to study a given population and define those with a specific drug toxicity. Nonetheless, a sufficiently large population must be studied to establish an association. Although this restates the obvious, most drugs for chronic conditions such as rheumatoid arthritis (RA) are toxic to only a modest proportion of the patients taking them otherwise they would have long ago been pulled off the market. To establish a relative risk association for a toxicity that occurs in only 5–10% of patients taking a given drug might require hundreds or even thousands of patients if the observed increase in risk of toxicity is modest.

There are many reasons why any given drug may fail in any given individual. Clearly, genetically associated resistance may account for failure of a given agent and being able to predict drug failure can both prevent unnecessarily prolonged suffering as the drug is given "a chance to work" as well as diminishing the exposure of the patient to a potentially toxic reaction. Nonetheless other factors can also account for drug failure in the treatment of a chronic disease. First, as we have found recently for RA, patients with longstanding, severe disease may not respond to any therapy because the disease has progressed too far. Some patients suffer a more severe form of the disease even from the outset and the susceptibility to more severe disease may also be genetic in origin. The best example of a genetic determinant of more severe disease in the rheumatic diseases is the presence of the "shared epitope" in human leucocyte antigen (HLA) molecules in patients with RA who suffer a more severe course.¹ Other drugs or even dietary substances may interfere with the action of a drug—for example, caffeine, an adenosine receptor antagonist present in coffee and other soft drinks, blocks the anti-inflammatory effects of methotrexate in animal studies and patients with RA.^{2–4} Thus, genetics may be only one contributing factor in the failure of a drug in the treatment of a chronic disease such as RA. Moreover, sorting out which patients fail drug therapy due to genetically based

Figure 1 Metabolism of azathioprine. MP, mercaptopurine; TPMT, thiopurine methyl transferase; XO, xanthine oxidase.

resistance from those who fail because of other issues may not be possible in large series.

Azathioprine has long been used to treat systemic lupus erythematosus and severe manifestations of RA. Azathioprine is converted to 6-mercaptopurine in the liver, and 6-mercaptopurine can be further metabolised by xanthine oxidase or metabolised by thiopurine methyl transferase (TPMT) and the products excreted (fig 1). The therapeutic effects of the drug result from hypoxanthine phosphoribosyl transferase mediated conversion to 6-thioguanine nucleotides which are incorporated into DNA by proliferating cells with resulting cytotoxicity. It has been recognised for many years that accumulation of thiopurine metabolites is associated with severe marrow suppression and within the past few years both genetically determined alterations in enzyme activity and the genetic polymorphisms associated with diminished TPMT activity have been elucidated (reviewed in reference 5). In general 10–11% of most Caucasian populations are heterozygous for the wild-type gene and a common variant (G460A and A719G). Patients who are heterozygous for these polymorphisms are at increased risk of developing marrow toxicity although individuals who are homozygous for the variant allele are at risk of catastrophic marrow suppression by standard doses of azathioprine. Different genetic variants seem to occur with similar frequency in other ethnic and racial groups. Thus, susceptibility to severe marrow toxicity induced by standard doses of azathioprine can be predicted based on the genotype of the patient. Although use of azathioprine in the treatment of rheumatic diseases has diminished it remains a potent and effective agent in the right circumstances. Genotyping of individuals can be carried out so as to avoid inducing disastrous marrow toxicity in susceptible individuals.

Methotrexate is currently the most commonly used disease modifying antirheumatic drug (DMARD) in RA for which it is commonly administered alone or in combination with

Abbreviations: AICAR, aminoimidazolecarboxamidoribonucleotide; MTHFR, methylene tetrahydrofolate reductase; RA, rheumatoid arthritis; TPMT, thiopurine methyl transferase

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