Commentary

Towards personalized medicine – the role of methotrexate

More than half a century ago, an observation that folic acid antagonists interfere with the normal growth of cells led to the introduction, by Farber and colleagues of methotrexate (MTX) in the treatment regimen of children with acute lymphoblastic leukaemia. Soon thereafter, MTX was reported to be effective in controlling disease activity both in patients with psoriatic arthritis and rheumatoid arthritis (RA). MTX continues to be the most widely used disease-modifying antirheumatic drug (DMARD). Patients with these chronic conditions require prolonged and often life-long treatment. However, the drug is not without toxic effects, and 10 to 30 per cent of patients discontinue treatment due to side effects. Also, the dose of MTX required for effective control of disease activity varies among patients and the overall response rates vary between 35-65 per cent. Currently, no reliable tests are available to predict MTX efficacy or toxicity.

In this issue, Ghodke et al. have reported single nucleotide polymorphisms (SNPs) across intracellular folate metabolic pathways in healthy Indian subjects. Folates are single carbon donors for the synthesis of purines, pyrimidines, and methionine and hence critical for DNA synthesis and cellular function. The genes they have looked at are involved in the intracellular transport (reduced folate carrier 1 or rFC1), and conversion (γ glutamyl hydrolase or GGH) of methotrexate, metabolism of purine and pyrimidine (methylenetetrahydrofolate reductase or MTHFR, thymidylate synthase or TS, methionine synthase or MS, serine hydroxymethyltransferase I or SHMT 1, aminoimidazol carboxamide ribinucleotide transformylase or ATIC, methionine synthase reductase or MTRR) and efflux of the drug (multidrug resistance protein 1 or MDR1). While MTX inhibits several of the folate-dependent enzymes, such as DHFR, ATIC, and TS resulting in cellular folate depletion, genetic variants in any of these genes can affect enzyme efficacy, and in turn, influence intracellular folate levels. What is the significance of the data reported by Ghatge et al.?

The study of inherited predisposition and metabolic differences that influence inter-individual variability of responses to drugs is a rapidly growing field. Pharmacogenetics, as this is termed, studies the genetic polymorphisms that correspond to sequence variations in a gene, which are single base changes that can occur at any site in the DNA molecule, in the 5'-regulatory sequence (promoter), the coding region or the untranslated 3'-region after the coding sequence. Single base changes that arise at a frequency of >1 per cent, are called single nucleotide polymorphisms (SNPs) and these may have marked impact on a patient’s response to a particular agent. However, therapeutic response is not dependent on a unique gene but on multiple genes interacting with one another.

Due to the individual variability in both response and propensity to have side effects, there has been considerable interest in trying to predict response as well as toxicity of MTX in a given patient. While it has not been possible to find any clear-cut relationship between demographic/clinical factors such as age, sex, duration or severity of diseases or between laboratory parameters such as C reactive protein (CRP) and rheumatoid factor (RF) levels and RA response to MTX, there has been better success with genetic markers. The most widely reported of these have been with MTX toxicity and C677T and A1298C polymorphisms in MTHFR gene. Other reports have also implicated a number of other SNPs in genes of the folate metabolism pathway, including MDR1, ABCB1, RFC, ATIC, TS enhance region (TSER), adenosine monophosphate demaniase (AMPDA) and inosine triphosphat pyrophosphatase (ITPA). Many of these reported associations are not very strong and it would be logical to assume that...
since MTX acts on several metabolic pathways in a polygenic disease like RA, a single genetic locus would probably be unable to adequately predict the response. In addition, the associations are also compounded by the variable penetrance of different variants. Wessels et al\(^7\) established a model for predicting MTX efficacy in RA patients which consisted of sex, rheumatoid factor and smoking status, the DAS, and 4 polymorphisms in the AMPD1, ATIC, ITPA, and MTHFD1 genes. This prediction model was transformed into a scoring system ranging from 0 to 11.5. Scores of <3.5 had a true positive response rate of 95 per cent. Scores of >6 had a true negative response rate of 86 per cent. Sixty per cent of the patients were categorized as either responders or non responders\(^17\).

Since folic acid supplementation can reduce the toxicity of MTX, the frequency of side effects is confounded by the concurrent administration of folic acid as well as the variability in the dosage in various studies\(^18\). Hence, the real predictive power of these markers has not been appropriately examined in many studies and may explain the lack of consistency in the associations in all studies\(^19,20\). Also, inadequate sample size diminishes the power of a study. The frequency of gene polymorphisms shows considerable variation between populations\(^21\). Appropriate sample size calculation is dependent on the frequencies in the normal population and hence it is important to establish normal values for the Indian population.

Role of genes not involved in folate metabolism, but related to the disease pathogenesis such as major histocompatibility genes and Interleukin (IL)-1, IL-1 receptor antagonist has also been evaluated. It is clear that the way forward will be to simultaneously examine multiple genes, taking forward the rationale used by Wessels et al\(^7\). The advances in technology now allow us to assess several thousand genes simultaneously using microarrays. Microarrays have been used to investigate various aspects of RA\(^22,23\). Today robust platforms allow us to study SNPs across the whole genome. Such studies have the advantage that predictive factors can be looked for without any \textit{a priori} bias.

The 21st century post-genomic era is seeing a transition from the traditional practice of medicine which was based on the best option for a patient taken on the basis of evidence gathered from the larger group, to personalized treatment based on the individual’s response to a drug. The rapid expansion of pharmacogenomics data (http://www.nigms.nih.gov/Initiatives/PGRN, http://www.pharmgkb.org/) is being propelled by the demands of the user community. In fact, the benefits of deploying such a strategy is already being evaluated in some countries\(^24\). In India, we have only recently started to think in these directions and there are a few publications on genetic basis of MTX efficacy in Indian patients\(^20,25\). Establishing normal values is the first step in this direction. The study by Ghotge et al\(^b\) should be a stimulus for Indian scientists to plan robust studies for Indian patients so that they too can benefit from these advances.

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