PostScript

MATTERS ARISING

Methotrexate related adverse effects in patients with RA

In their report on the genetics of methotrexate (MTX) related adverse effects, Berkun *et al* describe a high rate of 1298CC homozygosity among their patients with rheumatoid arthritis (RA) (24.7%) compared with the study group (12.8%).[1] They conclude that RA may be more common in the 1298CC homozygotes in their population, although conceding that this result may be biased by the cross sectional design of their study. Frequencies of the 1298C allele for Caucasian, Japanese, and African populations have been reported at 34, 21, and 9%, respectively,[2] placing the frequency of 24.7% in their patients with RA well within this range, questioning the influence of the 1298C allele on susceptibility to RA in this population.

The authors speculate that the protective effects of the 1298CC genotype on adverse events from MTX may be related to the absence of the 677T allele in 1298CC carriers. They further state that this is unlikely because of the lack of association between the 677T polymorphism and raised homocysteine levels and adverse effects in their study. An alternative explanation may be that the 677T-1298C haplotype is quite uncommon. Although these polymorphisms in the methylenetetrahydrofolate reductase (MTHFR) gene are in linkage disequilibrium, and occur on three out of four possible haplotypes, the 677T-1298C haplotype almost never occurs.[3]

The study does not report whether the 677T polymorphism or specific MTHFR 677–1298 haplotypes influenced MTX efficacy or disease activity, or both. Decreased MTHFR activity associated with variant genotypes, although reducing 5-methyl tetrahydrofolate (THF) levels, can lead to higher levels of 5, 10-methylene-THF, required for the conversion of deoxyuridine monophosphate to deoxythymidine monophosphate. By facilitating the action of thymidylate synthase (TS), this can reduce MTX efficacy. Indeed, breast and colon cell lines transfected with 677T cDNA show decreased MTHFR activity, accelerated cell growth, increased TS activity, and decreased sensitivity to MTX.[4]

The authors state that hepatotoxicity was not a major adverse effect in their patients. This may be secondary to the relatively low doses (range 11.4–12.4 mg weekly) of MTX these patients were receiving. The authors also report that nodulosis was one of the major adverse effects in their patients. The lack of association between the 677T polymorphism and MTX adverse effects in this study is then not surprising, given the strong association between this polymorphism and hepatotoxicity,[5] and the implication of the adenosine, not folate pathway, in MTX associated nodulosis.[6]

Berkun and colleagues are to be commended for their fine contribution to the growing body of reports on MTX pharmacogenetics. This is an exciting, rapidly advancing, but controversial field, as evident from the comments outlined above. Clearly, several future studies are needed to clarify these controversies in this emerging area of research.

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Authors' reply

We thank Dr Ranganathan for useful comments about our study.

One of the findings in this study was that the frequency of the 1298CC genotype (24.7%) among patients with rheumatoid arthritis (RA) was greater than that expected in the general population (12.8%).[1] Dr Ranganathan has compared the genotype frequency reported in our study with the allele frequency reported by others. The 34% allele frequency of the 1298C allele noted among Caucasians, which includes both homozygotes and heterozygotes, would be close to our results for the genotype 1298CC genotype frequency among our healthy controls (12.8%), and is significantly lower than in our patients with RA.

Unfortunately, the number of patients with RA in our study (93) was too small to analyse the association between haplotype frequencies and clinical outcome. It may, be that the 677T-1298C haplotype is infrequent in our RA population and may theoretically contribute to the protective effect of the 1298CC genotype. We did not find any association between the 677T allele and disease activity or methotrexate efficacy. It will be difficult to explain how the 677T allele is associated with both reduced MTX efficacy and the increased rate of methotrexate related side effects, many of which are dependent on the dose and activity of a drug.

As regards the drug dosage and hepatotoxicity, it should be noted that the doses of methotrexate used were similar to those reported in other studies evaluating this association.[2 3]

The suggestion by Dr Ranganathan of a possible association between the adenosine pathway, nodulosis, and MTHFR-1298 polymorphisms is interesting and certainly deserves further study.

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