PostScript

MATTERS ARISING

Will pharmacogenetics allow better prediction of methotrexate toxicity and efficacy in patients with RA?

We read with interest the paper by Ranganathan et al proposing that pharmacogenetics may be a useful tool to help predict methotrexate (MTX) toxicity and efficacy in rheumatoid arthritis (RA). One aspect they highlight is the potential role of drug efflux mechanisms in contributing to the lack of response to MTX in some patients. It is important to note that although they discuss the drug efflux transporter P-glycoprotein (P-gp) as being of interest, the paper they cite in support of this view actually reports an experiment in which MTX resistance was mediated by a different drug transporter, multidrug resistance protein 1 (MRP1). A range of efflux transporters have been described, including P-gp, MRP, and breast cancer resistance protein (BCRP). Data appear to be substantial for different efflux transporters. The drug transporter that mediates MTX resistance remains somewhat controversial.

Llorente et al studied 16 patients with RA and found higher P-glycoprotein (P-gp) levels in patients who were defined as being refractory to disease modifying drug treatment than in treatment responders. In contrast, Norrie et al demonstrated increased P-gp expression in leukaemic cell lines resistant to methotrexate. In a study using mdr transgenic mice (which overexpress P-gp) showed they remain susceptible to MTX non-responders (DAS28 >3.7) 40.0 (11.6) MTX responders (DAS28 <3.7) 45.2 (7.3) Control 46.5 (10.4) No significant difference was seen between the groups (Kruskal-Wallis, p=0.27).

Table 1 Percentage positive P-gp cells according to disease activity

<table>
<thead>
<tr>
<th>Disease Activity</th>
<th>% Positive cells</th>
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<tbody>
<tr>
<td>Control</td>
<td>46.5 (10.4)</td>
</tr>
<tr>
<td>MTX responders</td>
<td>45.2 (7.3)</td>
</tr>
<tr>
<td>MTX non-responders</td>
<td>40.0 (11.6)</td>
</tr>
</tbody>
</table>

We therefore agree with Ranganathan et al that drug efflux transporters may contribute to the response to MTX in RA. We also agree that genetic variability in the expression of such transporters may explain part of the heterogeneity of treatment response. The evidence to date, including our own observations, does not, however, support a significant role of P-gp in mediating this further. Studies are therefore required to determine which other drug transporters are most important in RA in determining MTX resistance. Given the central role played by MTX as a disease modifying antirheumatic drug in RA, modulation of any of such transporters using specific chemosensitising agents may provide a new and rational additional intervention in patients with RA.

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References

Authors’ reply
Hider and colleagues correctly highlight the complexity surrounding the regulation of methotrexate (MTX) cellular transport. Members of both the ATP binding cassette (ABC) and solute carrier (SLC) families of transporters have been shown to include MTX among their many substrates. Transfection of the multidrug resistance proteins MRP1 (ABCC1) and MRP2 (ABCC2) in human cells was associated with a two- to threefold lower accumulation of MTX and reduced retention of long chain polyglutamate forms of MTX. Increased expression and function of multidrug resistance 1 (MDR1, ABCB1) messenger RNA and increased P-glycoprotein expression was also seen in some of the leukemic sublines resistant to MTX. A similar study showed that P-glycoprotein may mediate MTX resistance in cells with deficient carrier mediated MTX uptake. An MDR1 carrier deficient variant of murine 3T3 fibroblasts when inserted with a recombinant retrovirus expressing the human MDR1 gene showed increased survival of resistant cells. The peripheral blood mononuclear cells of patients with rheumatoid arthritis who were refractory to treatment with MTX might influence disease outcome. Joint Bone Spine 2000;67:30–9.

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MTX also had higher expression of P-glycoprotein than those who responded to treatment. As highlighted in our review, there are multiple mechanisms underlying MTX transport and resistance. Some of these may be clinically significant, leading to trials of co-administration of inhibitors of transporters as a therapeutic strategy to improve the efficacy of the drug. Indeed, genetic variants in a number of components of the MTX pathway appear to contribute to the efficacy and toxicity of this agent. In the future, pharmacogenetics, together with demographic, clinical, and immunologic variables, should allow better selection of patients with a high likelihood of therapeutic success and minimal toxicity.

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References

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