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). Distinct drugs appear to be substrates 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. Similarly, Norris et al showed increased P-gp expression in leukaemic cell lines resistant to methotrexate. In contrast, a study using mdrl transgenic mice (which overexpress P-gp) showed they remain susceptible to MTX when it enters cells by passive diffusion.

To examine the effect of P-gp expression on MTX response we recently studied 20 patients with RA who were taking parenteral MTX at a stable dose for at least eight weeks. We compared P-gp expression on peripheral blood lymphocytes (PBLs) of patients with RA with those of 10 healthy controls. The patients had established RA, with a mean (SD) age and disease duration of 57.7 (9.7) and 15.9 (12.9) years respectively. Eighteen (90%) were seropositive, and 14 (70%) had been treated with ≥3 drugs which had failed. The median (range) MTX dose and disease activity score (DAS28) at study entry were 17.5 mg (range 7.5–25) weekly and 4.5 (range 1.8–6.7) respectively. PBLs were separated by gradient centrifugation. P-gp expression was measured using a monoclonal antibody directed to an external epitope of P-gp (UIC2). Samples were fixed and analysed by flow cytometry. The percentage positive P-gp cells were calculated using CellQuest software. No significant difference was seen in P-gp expression between patients with RA and healthy controls. Within the RA group, response to MTX (as measured by the DAS score) was not associated with P-gp expression and there was no significant difference between responders (DAS28 <3.7) and non-responders to MTX (DAS28 >3.7) (Kruskal-Wallis, p=0.27) (Table 1).

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

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

No significant difference was seen between the groups (Kruskal-Wallis, p=0.27).

The patients had mean (SD) disease activity scores at study entry of 7.5–25 mg (range) MTX dose and disease activity score (DAS)28 at study entry were 17.5 mg (range). The percentage positive P-gp cells were calculated using CellQuest software. No significant difference was seen in P-gp expression between patients with RA and healthy controls. Within the RA group, response to MTX (as measured by the DAS score) was not associated with P-gp expression and there was no significant difference between responders (DAS28 <3.7) and non-responders to MTX (DAS28 >3.7) (Kruskal-Wallis, p=0.27).
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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