Pharmacokinetics and immunogenicity of TNF-inhibitors, towards optimised treatment of rheumatoid arthritis
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Methotrexate reduces immunogenicity in adalimumab treated rheumatoid arthritis patients in a dose-dependent manner

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Immunogenicity of adalimumab could impair important treatment outcome parameters in patients with rheumatoid arthritis (RA). Patients who developed antiadalimumab antibodies (AAA) during a 3 year time period achieved less often minimal disease activity or remission and treatment failure occurred more often compared with patients without AAA. There were remarkable baseline differences: patients developing AAA had more long-standing, severe disease and less often used concomitant medication including lower doses of methotrexate (MTX), compared with patients not developing AAA. In literature, a favourable effect of concomitant MTX use on the immunogenicity of adalimumab for several inflammatory conditions is suggested. To investigate which MTX dose is sufficient to reduce immunogenicity, patients of the adalimumab cohort (n=272) at the Jan van Breemen Research Institute | Reade, were stratified according to the baseline MTX dose: no concomitant MTX (n=70), low dose MTX (5-10 mg/week, n=40), intermediate dose MTX (12.5-20 mg/week, n=54), or high dose MTX (≥22.5 mg/week, n=108). In figure 1, the percentages of patients developing AAA during follow-up per baseline MTX dose group are shown.

Figure 1. Percentage of patients developing antiadalimumab antibodies (AAA) per baseline methotrexate (MTX) dose group. No MTX (0 mg/week, n=70), low dose MTX (5-10 mg/week, n=40), intermediate dose MTX (12.5-20 mg/week, n=54), or high dose MTX (≥22.5 mg/week, n=108).
To compare these percentages over time generalised estimation equations (GEE) were used. GEE models revealed that, overall, patients using MTX developed AAA less often compared with patients without MTX: OR 0.20 (95%CI 0.12 to 0.34, p<0.001). Additional OR for the differences between the baseline MTX groups are displayed in table 1. Median (SD) height of the AAA titre for AAA positive patients per MTX group was 57 (26-249) AU/ml, 52 (18-623) AU/ml, 51 (23-107) AU/ml and 32 (16-45) AU/ml for patients without concomitant MTX and low, intermediate or high dose, respectively and this did not reach statistical significance.

Table 1. OR (95%CI) for the development of antiadalimumab antibodies (AAA) when comparing groups based on baseline methotrexate (MTX) use.

<table>
<thead>
<tr>
<th>Dose</th>
<th>No MTX</th>
<th>Low dose</th>
<th>Intermediate dose</th>
<th>High dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>70</td>
<td>40</td>
<td>54</td>
<td>108</td>
</tr>
<tr>
<td>Baseline DAS28, mean (SD)</td>
<td>5.4 (1.3)</td>
<td>5.2 (1.1)</td>
<td>5.5 (1.2)</td>
<td>5.0 (1.2)</td>
</tr>
<tr>
<td>No MTX</td>
<td>-</td>
<td>0.36 (0.18 to 0.74)</td>
<td>0.22 (0.10 to 0.46)</td>
<td>0.14 (0.07 to 0.28)</td>
</tr>
<tr>
<td>Low dose</td>
<td>-</td>
<td>-</td>
<td>0.60 (0.25 to 1.44)</td>
<td>0.39 (0.17 to 0.88)</td>
</tr>
<tr>
<td>Intermediate dose</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.65 (0.28 to 1.50)</td>
</tr>
<tr>
<td>High dose</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

MTX appears to be efficient in reducing immunogenicity in a dose-dependent manner. This should be investigated further as this has implications for other biological therapeutics and inflammatory diseases in which concomitant MTX administration is less common. For example, in psoriasis patients, before the initiation of adalimumab therapy, MTX was discontinued.

Additionally, in ankylosing spondylitis patients with axial symptoms there is no proof for efficacy of MTX. In a murine Pompe disease model, low dose administration of MTX (0.5 mg/kg) within 24 h after enzyme replacement treatment induced a significant reduction in antidrug antibody formation. In this model, 0.5 mg/kg, administered three times, represented a human dose of 0.6 mg/week for a 5 kg infant, which is lower than the MTX dose prescribed for the treatment of adult RA. Furthermore, this model showed that MTX should be initiated at the start of the immunogenic therapy because with MTX therapy it was not possible to abolish ongoing anti-drug antibody formation. In a human study with infliximab treated RA patients, 7.5 mg MTX weekly was sufficient in reducing immunogenicity of infliximab; however, in that study there was no comparison with other MTX doses.
The mechanism whereby MTX acts on the immune response remained unsolved; however, we hypothesise that suppression of early T and B cell expansion might be responsible for the modulation of the immune response. Others hypothesise that there is an additional or synergistic effect because MTX reduces inflammation whereby drug levels and response rates are increased.⁸

Altogether, the immune-tolerating ability of MTX and assessment of the optimal dose should be investigated further and the results of our present study are promising for the optimization of treatment responses and easy applicable in clinical practice.
Reference list


