OPTIMAL DOSAGE AND ROUTE OF ADMINISTRATION OF METHOTREXATE IN RHEUMATOID ARTHRITIS: A SYSTEMATIC REVIEW OF THE LITERATURE

K. Visser¹, D. van der Heijde¹

¹ Department of Rheumatology, Leiden University Medical Center, The Netherlands

Correspondence to:
Drs. K. Visser
Leiden University Medical Center, Department of Rheumatology, C1-R
P.O. Box 9600
2300 RC Leiden
The Netherlands
Email: K.Visser@lumc.nl

Word count abstract: 248
Word count manuscript: 2668
Keywords: systematic literature review, methotrexate dose escalation and route, rheumatoid arthritis, efficacy, tolerability
ABSTRACT

Objectives
To systematically review the available literature on the optimal dosage and route of administration of methotrexate (MTX) in patients with rheumatoid arthritis (RA), as an evidence base for generating clinical practice recommendations.

Methods
A systematic literature search was carried out in MEDLINE, EMBASE, Cochrane Library and ACR/EULAR meeting abstracts, searching for randomized controlled trials evaluating various dosages or routes of administration of MTX in RA. Articles that fulfilled predefined inclusion criteria were systematically reviewed and the quality was appraised. Effect sizes (ES) and odds ratios (OR) for clinical, radiological and toxicity outcomes were calculated and directly or indirectly compared between study groups using MTX in different dosages or via different routes.

Results
A total of 38 publications out of 1748 identified references were included in the review. Start doses of 25mg/wk or fast escalation with 5mg/month to 25-30mg/wk were associated with higher clinical ES and more (gastrointestinal) adverse events in comparison with doses of 5-15mg/wk or slow escalation. Starting with 15mg/wk subcutaneous versus oral MTX was associated with higher clinical efficacy, but more withdrawal due to toxicity in early RA. In longstanding RA, however, after failure on 15-20mg/wk orally, a switch to 15mg/wk intramuscular with subsequent dose escalation did not result in increased efficacy.

Conclusions
Starting on MTX 15mg/wk orally, escalating with 5mg/month to 25-30mg/wk, or the highest tolerable dose, with a subsequent switch to subcutaneous in case of an insufficient response, seems to be the optimal evidence-based dosing and routing recommendation for MTX in RA.
INTRODUCTION
Methotrexate (MTX) is widely used as the disease modifying anti-rheumatic drug (DMARD) of first choice in the treatment of rheumatoid arthritis (RA), because it is effective, has an acceptable toxicity profile and has low costs.[1-3] Despite more than two decades of experience, considerable variability exists in the way rheumatologists prescribe MTX therapy, including the dosage and route of administration. More knowledge on the optimal use is needed, as this would benefit RA patients, improve education and facilitate treatment evaluation.

This manuscript is part of the 3E (Evidence, Expertise, Exchange) Initiative. This 3E Initiative and the resulting recommendations for the use of MTX are described in more detail in the same issue of this journal.[4] The objective of the current work was to systematically review the available literature concerning one of the 10 selected questions as an evidence base for generating the recommendations. The question was: ‘What is the best dosing strategy and route of administration of MTX in patients with RA to optimize rapid, early, clinical and radiographic response and minimize toxicity?’

METHODS
The systematic literature review was carried out in several steps following the updated guidelines for Cochrane systematic reviews.[5]

Rephrasing research question
The clinical question as formulated by the experts was translated into an epidemiological research question according to the PICO method.[6] Patients were defined as adults with RA according to the American College of Rheumatology (ACR) criteria.[7] The Intervention was defined as MTX in a certain dosage (separate for start, escalation and target dose), and a certain route of administration (oral, subcutaneous (sc), intramuscular (im) or intravenous), with a different dosage or route as Comparator. Outcomes were threefold: clinical efficacy measures among swollen joint count (SJC), tender joint count (TJC), disease activity score (DAS), ACR20/50/70 response, visual analog scale (VAS) for patient-reported outcomes, health assessment questionnaire (HAQ) and erythrocyte sedimentation rate (ESR); radiological progression; and system-specific adverse events (AE) including withdrawal due to toxicity. Effect sizes (ES) and odds ratios (OR) were anticipated effect parameters. The final search question was thus rephrased as: What is the difference in ES and OR for short-term clinical, radiographic and toxicity outcomes in RA patients on various dosages and routes of administration of MTX?

Scenarios
In the optimal scenario we anticipated to find randomized controlled trials (RCTs) directly comparing different dosages or routes of MTX. The suboptimal scenario included RCTs evaluating MTX monotherapy versus placebo, another DMARD, a biological, or a combination of DMARDs without MTX. By grouping the trials per comparator drug, potential indirect comparisons between various MTX schedules were anticipated. The condition for these indirect comparisons was a homogeneous response in the comparator arms within the grouped trials. Observational studies represented the least optimal scenario, as these inherently introduce methodological limitations.
Systematic literature search

A systematic literature search for articles published between 1950 and September 2007 was carried out in MEDLINE, EMBASE and the Cochrane Library, using a comprehensive search strategy (appendix 1 of the online version of this paper available at http://www.annrheumdis.com/supplemental) in collaboration with an experienced librarian.[8] The EULAR 2005-2007 and ACR 2005-2006 meeting abstracts were also searched. The search was limited to RCTs, using a modification of the Cochrane highly sensitive search strategy.[9] No language restriction was used. Review articles were also retrieved for identifying additional references via hand search.

Selection of articles

Relevant articles were selected in a systematic two-step procedure. First, titles and abstracts of all identified references were screened, excluding articles which clearly did not address the topic of interest. Secondly, selected articles were reviewed in full paper, applying the following inclusion criteria: RCT, RA >= 18 years old, monotherapy MTX in one of the treatment groups, data on dosage and route, and data on one or more of the pre-specified outcome measures. Articles that did not fulfil all the inclusion criteria or had insufficient data for analysis were excluded from the systematic review.

Data extraction and quality appraisal

Publication details, patient characteristics, dosage and route of MTX and data on relevant outcomes were extracted from all the included articles using standard forms. Data from non-English language publications were extracted by reviewers from the international panel of 3E. If necessary, authors were contacted to provide additional information. The methodological quality of each RCT was graded by a scale according to Van Tulder, with a maximum score of 11 points.[5] The points were subsequently translated into Levels of Evidence according to the Oxford Centre for Evidence-based Medicine. [http://www.cebm.net/index.aspx?o=1025 (accessed March 2008) and appendix 2 at http://www.annrheumdis.com/supplemental]

Data-analysis

For continuous variables, three types of ES were calculated for the difference between baseline and end of trial data.[10,11] Per treatment group, the ES and the standardized response mean (SRM) were calculated as the mean change in score divided by the baseline standard deviation (SD) (=ES) or the mean change divided by the SD of the change (=SRM). To compare the effect between two treatment groups, the pooled Cohen’s ES was calculated as the mean change in the index group minus the mean change in the comparator group divided by a pooled baseline SD. The corresponding 95% confidence interval (CI) was constructed and indicates a statistically significant effect at the 5% level if zero is outside the interval.[12] In accordance with the literature, we considered an ES around 0.2 as small, around 0.5 as moderate and >0.8 as large, with negative ES indicating worsening. For dichotomous data, OR [95% CI] were calculated for the occurrence of system-specific adverse events (AE). Intention to treat data were used if available.
RESULTS
A total of 1748 references were identified with the systematic search strategy. After title and abstract screening, 86 articles were retrieved for full paper review, of which 45 fulfilled the inclusion criteria. Two congress abstracts, which described a trial yet to be published[13] and 3 additional papers from the hand search, of which 1 was not found in the databases[14], were also included. In conclusion, 50 references were included in the systematic review. A detailed flowchart with excluded references can be found in appendix 3 at http://www.annrheumdis.com/supplemental.
The 50 references described 38 original trials, which were grouped according to the anticipated scenarios. For the optimal scenario, 8 RCTs that directly compared oral MTX in different dosages (n=3)[15-17], im MTX in different dosages (n=1)[18], MTX oral versus sc route (n=1)[13], or MTX weekly versus non-weekly (n=3)[19-21] were found. The suboptimal scenario included 30 RCTs evaluating MTX monotherapy versus placebo (n=5), DMARD monotherapy (n=21), combination therapy (n=1) or anti-tumor necrosis factor (anti-TNF) (n=3) (references available online in appendix 4).

Direct comparisons oral MTX

Study characteristics
The characteristics of the 3 RCTs that directly compared different dosages of oral MTX are shown in table 1.[15-17] Furst et al. evaluated start doses of 5-10mg/wk, 12.5-20mg/wk and 25-35mg/wk (mean 8, 18 and 32mg/wk, respectively) in longstanding RA patients who failed other DMARDs.[17] In a similar population, Schnabel et al. evaluated a start dose of 15 or 25mg/wk, with a possible increase or decrease in case of insufficient efficacy or toxicity.[16] In DMARD-naïve, early RA patients, Verstappen et al. compared an intensive treatment strategy according to a computerized model for disease activity with a conventional strategy according to common practice.[15] This resulted in a fast escalation of MTX from 7.5mg/wk with 5mg/month to a mean maximum of 25mg/wk versus a slow escalation of 5mg/3 months to a mean maximum of 18mg/wk.

Results
Figure 1B shows a clinical dose-effect relation with ES ranging from 0-0.45 in the placebo group, 0.60-1.13 in the MTX 5-10mg/wk group, to 0.92-1.41 in the 12.5-20mg/wk group. MTX 12.5-20mg/wk had a significantly larger effect than placebo on TJC (pooled ES=1.08 [0.35-1.81]), pain (pooled ES=0.92 [0.21-1.64]) and global status (pooled ES=1.58 [0.80-2.37]), while MTX 5-10mg/wk only had a significantly higher effect than placebo on pain and global status (pooled ES=0.81 [0.05-1.57] and 1.26 [0.46-2.06] respectively). A dose-toxicity relation was also seen in the OR for patients with AE, gastrointestinal and mucocutaneous toxicity, with the highest OR for 25-35mg/wk MTX (table 2). Pooled ES of MTX 12.5-20mg/wk versus 5-10mg/wk ranged from 0.22-0.35, indicating an additional effect of the higher dosed group, although not reaching statistical significance, while no increased toxicity was seen (table 2).

Despite the lack of clinical outcomes, Schnabel et al. reported that 27% of the patients who started with 15mg/wk needed a dose increase for inefficacy, compared to 3% of those who started with 25mg/wk (OR=10 [2.9-33.3]). Although a trend for more gastrointestinal toxicity was observed in the higher dosed group, the percentage of
patients decreasing the dose due to toxicity was 9% in both groups (table 2). Finally, a mean tolerable effective dose of 17-20mg/wk was reached.

Larger ES for clinical variables were found for fast escalation (range 1.38-1.83) than for slow escalation of MTX (range 0.91-1.50) (figure 1A). SRM showed similar results (not shown). Differences in effect were significant as indicated by the pooled ES for SJC (pooled ES=0.33 [0.10-0.56]), TJC (pooled ES=0.43 [0.20-0.66]), pain (pooled ES=0.47 [0.24-0.70]) and global status (pooled ES=0.49 [0.26-0.72]). Moreover, significantly more ACR50 responses were observed in the fast escalation group. Although in the fast escalation group significantly more patients experienced adverse events, the nature of the events was similar (table 2).

Only Verstappen and Schnabel reported radiological outcomes. In Verstappen et al. no additional effect on radiological progression was seen of the fast in comparison with the slow escalation group (pooled ES=0.05 [-0.23;0.33]), while in Schnabel et al. 25mg/wk versus 15mg/wk gave an OR of 0.4 [0.1-2.0] for the progression of joint damage in a selection of patients with <3 years disease duration.

**Direct comparisons parenteral MTX**

**Study characteristics**

Two RCTs were found which evaluated parenteral MTX (table 1).[13,18] In longstanding RA patients who had failed on 15-20mg/wk oral MTX and were switched to 15mg/wk im MTX for 6 weeks, without achieving a DAS28 response, Lambert et al. evaluated subsequent im placebo versus im MTX escalation up to 45mg/wk.[18] In contrast, Braun et al. compared start doses of MTX 15mg/wk sc versus orally in MTX-naïve, early RA patients.[13]

**Results**

Small to moderate ES for clinical variables were found in the MTX escalation group (range 0.09-0.67) and the placebo escalation group (range -0.22; 0.82), without any significant differences between the groups (figure 1C). SRM showed similar results (not shown). The pooled ES ranged from -0.38 in favour of the placebo group to 0.33 in favour of the escalation group. The ACR20 response in both groups was low (4%) and toxicity was similar (table 2).

In contrast, significantly more patients who started sc MTX in Braun et al. achieved an ACR20 response than those who started oral MTX (85% versus 77% respectively, OR=1.7 [1.01-2.9]) after 16 weeks. A trend for more ACR20 (OR=1.5 [0.96-2.4]) and ACR70 response (OR=1.4 [0.9-2.1]) after 24 weeks was also seen. However, patients on sc MTX more often discontinued therapy due to toxicity, without differences in the type of AE, including gastrointestinal toxicity (table 2).

**Indirect comparisons**

Indirect comparisons of the MTX arms of 30 trials grouped per comparator drug revealed uninformative, as MTX dosages or routes were not different, the clinical response to the comparator drugs showed large heterogeneity and outcome measures were not uniform. A summary is available in appendix 4 online.

**Direct comparisons MTX frequencies**
In addition to the primary research question, 3 RCTs directly comparing oral MTX weekly versus non-weekly were identified and included.[19-21] The results can be found in the online appendix 5.

**DISCUSSION**

This systematic review summarizes and evaluates the available evidence from the literature on the optimal dosage and route of administration of MTX in RA. Combined with the expert opinion of a broad panel of rheumatologists in the 3E Initiative, the results served as an evidence base for generating one of the 10 clinical recommendations for the use of MTX in rheumatic diseases. A detailed description of all final recommendations can be found elsewhere.[4]

The results showed that start doses of 25mg/wk orally or fast dose escalation with 5mg/month to 25-30mg/wk were associated with higher efficacy, but also with more toxicity, in comparison with start doses of 5-15mg/wk or slow escalation with 5mg/3 months.[15-17] These results strongly support reaching high (25-30mg/wk) doses in a short period of time for efficacy, but with toxicity as a limiting factor. The mean tolerable effective dose of 17-20mg/wk, after adjusting from 15 or 25mg/wk starting dose in Schnabel et al., emphasizes this efficacy/toxicity ratio. However, two of the reviewed studies lacked folic acid supplementation, which might increase the tolerability of higher dosages of MTX. As investigated concurrently in the 3E Initiative as a separate question, a meta-analysis of nine RCTs indicated that folic acid reduces gastrointestinal and liver toxicity, without reducing efficacy.[22] Therefore, as the primary aim of current RA treatment is achieving adequate undelayed disease control, the optimal evidence-based dosing strategy seems to be: starting with 15mg/wk and escalating fast with 5mg/month to 25-30mg/wk, although this should always be individually adapted on the level of disease activity and tolerability, including renal function.[23]

Although oral MTX is widely preferred, because of patient’s preference and low costs, the bioavailability of parenteral MTX is higher with increasing dose.[24,25] Whether this leads to increased efficacy is addressed in only one RCT, which suggests that MTX 15mg/wk sc is indeed associated with a better response compared with 15mg/wk orally.[13] However, escalating the oral dose to 25mg/wk might also have increased clinical efficacy in this trial. This is supported by data from observational studies, in which patients switching from parenteral to oral MTX at an equal dose showed disease exacerbations, but not if the oral dose was 2.5-5mg/wk higher.[26,27] In contrast, in longstanding RA patients who failed 15-20mg/wk oral MTX plus other DMARDs, neither a switch to 15mg/wk im, nor subsequent im dose escalation resulted in increased efficacy.[18] However, for this selected population not responding well to conventional DMARDs, therapy with biologicals is currently indicated.[28] The evidence on toxicity associated with parenteral use of MTX is inconsistent. While more withdrawal due to toxicity, but similar AE were seen in the RCT from Braun et al., observational data suggest a decrease in (gastrointestinal) side effects administering MTX parenterally.[13,26,27] Therefore, in summary, the preferred route of MTX seems to be oral, but a switch to sc is suggested in case of an insufficient response at the highest tolerable oral dose.
The frequency of weekly dosing of MTX was inherited from the dermatological experience in the early 1980s. As the half-life of the active polyglutamate is 3 days, a twice weekly schedule was hypothesized to be more effective and less toxic, although it would also be less practical.[29] However, Pandya et al. showed that a twice weekly schedule of MTX had no advantage over a weekly schedule.[21] In contrast, a change to eow dosing was possible in patients stable or in remission on MTX, although some experienced disease flares.[19,20] In conclusion, weekly MTX is the preferred frequency of administration, with a potential switch to a fortnightly schedule in case of sustained remission.

In this systematic review, we aimed at finding all available evidence on the optimal dosage and route of MTX, by using a strict methodological search and selection strategy.[5] Furthermore, we limited the search to RCTs only, as this design would potentially yield the highest level of evidence without bias from lack of randomization or blinding, which is associated with observational studies. Moreover, indirect comparisons between MTX arms of trials versus placebo, DMARDs or anti-TNF, revealed uninformative in this review, suggesting that observational data would even be more difficult to interpret. In conclusion, 8 out of 38 included RCTs directly addressed the research question and provided level 1b-2b evidence for efficacy and toxicity of various dosages and routes of MTX.

In conclusion, taking patients characteristics into account, a start dose of 15mg/wk orally, escalating with 5mg/month to 25-30mg/wk or the highest tolerable dose, with a subsequent switch to sc in case of an insufficient response, seems to be the optimal evidence-based dosing and routing strategy for MTX in RA. This conclusion was incorporated as one of the recommendations of the 3E Initiative for the use of MTX in rheumatic diseases.[4]

ACKNOWLEDGEMENTS
J.W. Schoones, Walaeus Library, Leiden University Medical Center, The Netherlands, participated in the elaboration of the systematic search strategy. All participants of 3E, and especially the bibliographic team participated in rephrasing the research question, developing the search strategy and planning the analyses.

Funding: The 3E Initiative, including this work, was supported by Abbott with an unrestricted educational grant.

"The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd to permit this article (if accepted) to be published in ARD and any other BMJPGL products and sublicences such use and exploit all subsidiary rights, as set out in our licence (http://ARD.bmjjourrnals.com/ifora/licence.pdf)."
REFERENCES

1 Aletaha D, Smolen JS. The rheumatoid arthritis patient in the clinic: comparing more than 1,300 consecutive DMARD courses. *Rheumatology (Oxford)* 2002;41:1367-74.


FIGURE LEGENDS AND TABLES

**Figure 1.** Effect sizes (95% CI) of clinical variables per treatment group of studies directly comparing different dosages/routes.

**Table 1.** Study and patient characteristics of trials included for direct comparisons of MTX dosages/routes

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Patient characteristics</th>
<th>Treatment groups (MTX dosage/route)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Furst '89</strong></td>
<td>n=52</td>
<td>- oral MTX 20 mg/m²/wk ≈ 25-35 mg/wk</td>
</tr>
<tr>
<td>double-blind RCT</td>
<td>RA 4.8 yr</td>
<td>- oral MTX 10 mg/m²/wk ≈ 12.5-20 mg/wk</td>
</tr>
<tr>
<td>16 wk follow-up</td>
<td>failed gold or D-penicillamine</td>
<td>- oral MTX 5 mg/m²/wk ≈ 5-10 mg/wk</td>
</tr>
<tr>
<td>Van Tulder 10</td>
<td>MTX-naïve</td>
<td>- Placebo</td>
</tr>
<tr>
<td>Evidence level 2b</td>
<td></td>
<td>- Placebo</td>
</tr>
<tr>
<td><strong>Schnabel '94</strong></td>
<td>n=185</td>
<td>- oral MTX 25 mg/wk</td>
</tr>
<tr>
<td>open-label RCT</td>
<td>RA 3-10 yr</td>
<td>- oral MTX 15 mg/wk</td>
</tr>
<tr>
<td>52 wk follow-up</td>
<td>prior DMARDs</td>
<td>- Increase or decrease if necessary</td>
</tr>
<tr>
<td>Van Tulder 7</td>
<td>MTX-naïve</td>
<td>- No folic acid</td>
</tr>
<tr>
<td>Evidence level 2b</td>
<td></td>
<td>- No folic acid</td>
</tr>
<tr>
<td><strong>Verstappen '07</strong></td>
<td>n=299</td>
<td>- Fast escalation: oral MTX 7.5 mg/wk +</td>
</tr>
<tr>
<td>open-label RCT</td>
<td>RA &lt; 1 yr</td>
<td>5 mg/month to mean max 25 g/wk (max 30)</td>
</tr>
<tr>
<td>52 wk follow-up</td>
<td>DMARD-naïve</td>
<td>- Slow escalation: oral MTX 7.5mg/wk +</td>
</tr>
<tr>
<td>Van Tulder 7</td>
<td></td>
<td>5 mg/3 months to mean max 18 mg/wk</td>
</tr>
<tr>
<td>Evidence level 2b</td>
<td></td>
<td>- Folic acid</td>
</tr>
<tr>
<td><strong>Lambert '04</strong></td>
<td>n=54</td>
<td>Switch to im MTX:</td>
</tr>
<tr>
<td>double-blind RCT</td>
<td>RA 10 yr</td>
<td>- 15 mg/wk + escalation 5 mg/month to</td>
</tr>
<tr>
<td>22 wk follow-up</td>
<td>failed oral MTX</td>
<td>max 45 mg/wk</td>
</tr>
<tr>
<td>Van Tulder 9</td>
<td>15-20mg/wk</td>
<td>- 15 mg/wk + placebo escalation</td>
</tr>
<tr>
<td>Evidence level 2b</td>
<td></td>
<td>- Folic acid</td>
</tr>
<tr>
<td><strong>Braun '08</strong></td>
<td>n=375</td>
<td>- Sc MTX 15 mg/wk, escalation to 20 mg/wk</td>
</tr>
<tr>
<td>double-blind RCT</td>
<td>RA &lt; 1 yr</td>
<td>- if no ACR20 at 16 wk</td>
</tr>
<tr>
<td>24 wk follow-up</td>
<td>MTX-naïve</td>
<td>- Oral MTX 15 mg/wk, switch to 15 mg/wk sc</td>
</tr>
<tr>
<td>Van Tulder 11</td>
<td></td>
<td>- if no ACR20 at 16 wk</td>
</tr>
<tr>
<td>Evidence level 1b</td>
<td></td>
<td>- Folic acid</td>
</tr>
</tbody>
</table>
Table 2. Odds ratios (95% CI) of clinical and toxicity outcomes of trials directly comparing different MTX dosages/routes

<table>
<thead>
<tr>
<th>Study comparison</th>
<th>Patients with AE</th>
<th>Withdrawal for toxicity</th>
<th>Pulmonary</th>
<th>Hepatic toxicity</th>
<th>Bone marrow</th>
<th>Infectious</th>
<th>Gastrointestinal</th>
<th>Mucocutaneous</th>
<th>ACR20/ACR50</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Furst</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-35mg/wk vs placebo</td>
<td>8.3# (0.8-89.5)</td>
<td>7.5# (0.5-105.3)</td>
<td>0</td>
<td>0</td>
<td>3.0</td>
<td>11.0</td>
<td>7.0# (0.8-62.0)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>12.5-20mg/wk vs placebo</td>
<td>5.4* (1.2-24.5)</td>
<td>0.9 (0.1-16.4)</td>
<td>0.9</td>
<td>∞</td>
<td>0.9</td>
<td>2.0</td>
<td>5.3* (1.2-23.3)</td>
<td>4.9# (0.8-28.7)</td>
<td></td>
</tr>
<tr>
<td>5-10mg/wk vs placebo</td>
<td>5.6* (1.1-28.6)</td>
<td>0 (0.2-34.0)</td>
<td>2.7</td>
<td>∞</td>
<td>1.3</td>
<td>1.8</td>
<td>3.1</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>12.5-20mg/wk vs 5-10mg/wk</td>
<td>1.0 (0.2-5.4)</td>
<td>∞ (0.03-4.3)</td>
<td>0.8</td>
<td>0.8</td>
<td>1.6</td>
<td>1.5</td>
<td>1.8</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td><strong>Schnabel</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25mg/wk vs 15mg/wk</td>
<td>NA (0.1-16.9)</td>
<td>1.1 (0.5-2.5)</td>
<td>1.3 (0.7-2.3)</td>
<td>1.8 (0.3-11.0)</td>
<td>NA (0.9-3.8)</td>
<td>NA</td>
<td>NA (0.1-16.9)</td>
<td>ACR50</td>
<td></td>
</tr>
<tr>
<td><strong>Verstappen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fast vs slow</td>
<td>2.3* (1.02-5.3)</td>
<td>1.8 (0.8-4.0)</td>
<td>0.4</td>
<td>1.3 (0.7-2.3)</td>
<td>1.9 (0.7-5.2)</td>
<td>NA (0.6-1.7)</td>
<td>0.8 (0.6-1.7)</td>
<td>1.8* (1.1-2.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Lambert</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>im 15-45mg/wk vs 15mg/wk</td>
<td>NA (0.1-16.9)</td>
<td>1.5 (0.4-5.6)</td>
<td>1.0 (0.1-16.9)</td>
<td>NA (0.1-16.9)</td>
<td>1.4 (0.5-4.4)</td>
<td>2.4 (0.6-9.3)</td>
<td>1.0 (0.1-16.9)</td>
<td>ACR20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sc vs oral</td>
<td>ACR20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>------------</td>
<td>-------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15mg/wk</td>
<td>(0.8-1.9)</td>
<td>(0.96-2.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.2-1.9)</td>
<td>(0.4-1.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.1-1.4)</td>
<td>(2.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* OR is significant, # OR shows a trend, ∞ comparator group has zero events, NA=not available, AE=adverse event
APPENDIX 1

Systematic search strategy Medline

1. Methotrexate OR mtx OR Amethopterin OR Methotrexat* OR Mexate* OR abitrexate* OR amethopterin* OR a-methopterin* OR ametopterin* OR antifolan* OR emtexate* OR emthexate* OR emtrexate* OR folex OR ledertrexate* OR methoblastin* OR methohexate* OR methotrate* OR methylaminopterin* OR methotrexat* OR novatrex* OR rheumatrex


3. Drug Administration Routes OR Drug Administration Route OR dosage OR dosing OR dose OR doses OR Drug Dose-Response Relationship OR Maximum Tolerated Dose OR Drug Administration Schedule

4. "Methotrexate/administration and dosage"[Majr]

5. oral OR orally OR subcutaneous OR intravenous OR intramuscular OR enteral OR parenteral OR injection OR injected


7. 1 AND 2 AND 3

8. 2 AND 4

9. 2 AND 5 AND 6

10. 7 OR 8 OR 9

11. Severity of Illness Index OR Treatment Outcome OR Pain Measurement OR outcome OR outcomes OR efficacy OR acr20 OR acr50 OR acr70 OR acr-20 OR acr-50 OR acr-70 OR "disease activity score" OR "disease activity scores" OR DAS*[tw] OR das28 OR das44 OR das-28 OR das-44 OR cdai OR cdai OR haq*[tw] OR "health assessment questionnaire" OR "health assessment questionnaires" OR ((tender OR swollen) AND count) OR "therapy response"

12. radiological damage OR radiographic damage OR radiological response OR radiographic response OR "joint damage" OR "radiological progression" OR "radiographic progression" OR disease progression OR larsen*[tw] OR sharp*[tw] OR "sharp/van der heijde" OR erosion*

13. toxicity OR side effects OR adverse effects OR adverse events OR safety OR drug safety OR "abdominal upset" OR (upset AND (abdominal OR stomach OR gastrointestinal)) OR nausea OR anorexia OR stomatitis OR diarrhea OR liver enzymes OR liver enzyme OR alopecia OR mucositis OR leukopenia OR thrombocytopenia OR pancytopenia OR leukopaenia OR thrombocytopenia OR pancytopenia OR pneumonitis OR infection OR infections OR lymphoma OR lymphomas OR cirrhosis OR fibrosis OR rash OR headache OR fatigue OR malaise

14. 11 OR 12 OR 13

15. 10 AND 14

16. randomized controlled trial OR controlled clinical trial OR randomized controlled trials OR random allocation OR double-blind method OR single-blind method OR clinical trial OR clinical trials OR "clinical trial" OR ((singl* OR doubl* OR trebl* OR tripl*) AND (mask* OR blind* )) OR "latin square" OR placebos OR placebo* OR random* OR research design[mh:noexp] OR comparative study OR evaluation studies OR cross-over studies OR randomised controlled trial OR randomised controlled trials OR groups[tiab] OR follow up studies OR follow up study OR followup OR prospective study OR prospective studies

17. 15 AND 16
APPENDIX 2

Oxford Centre for Evidence-based Medicine Levels of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Evidence (Therapeutic studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a. Systematic review of RCTs</td>
</tr>
<tr>
<td></td>
<td>b. Individual RCT (high quality)</td>
</tr>
<tr>
<td>2</td>
<td>a. Systematic review of cohort studies</td>
</tr>
<tr>
<td></td>
<td>b. Individual cohort study or lower quality RCT*</td>
</tr>
<tr>
<td>3</td>
<td>a. Systematic review of case-control studies</td>
</tr>
<tr>
<td></td>
<td>b. Individual case-control study</td>
</tr>
<tr>
<td>4</td>
<td>Case-series and poor quality cohort and case-control studies</td>
</tr>
<tr>
<td>5</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>

*e.g. <80% follow-up, no double-blind design.*
APPENDIX 3

Flowchart results systematic literature search

Figure 1
EXCLUDED REFERENCES
After full text review with reason for exclusion (n=41)

1 Bathon JM, Genovese MC. The Early Rheumatoid Arthritis (ERA) trial comparing the efficacy and safety of etanercept and methotrexate. Clin Exp Rheumatol 2003;21:S195-S197. Original publication is included in the review.


3 Burgardt C. [Drug therapy and malpractice exemplified by combination leflunomide and methotrexate therapy]. Z Rheumatol 2002;61:189-90. No RCT.


24 Seideman P. Better effect of methotrexate on C-reactive protein during daily compared to weekly treatment in rheumatoid arthritis. Clin Rheumatol 1993;12:210-3. Patients not in remission or stable on MTX, therefore not included for the frequency analysis.


33 Tugwell P, Wells G, Strand V, Maetzel A, Bombardier C, Crawford B et al. Clinical improvement as reflected in measures of function and health-related


APPENDIX 4

Indirect comparisons MTX dosage/route

The MTX arms of 22 out of the 30 trials grouped per comparator drug could not be indirectly compared, as the dosage and route of MTX were not different. Mean oral MTX dose was around 10mg/wk in the trials versus azathioprine[1-5] or im auranofin[6,7]; 12-15mg/wk in the trials versus placebo[8-12] or leflunomide[10,13-16]; 17-19mg/wk versus anti-TNF[17-19]; and 20mg/wk versus cyclosporine[20,21]. Nevertheless, in the remaining 8 studies oral MTX 10, 15 or 20mg/wk was evaluated versus sulphasalazine (SSZ)[20,22-24] and oral/im MTX 10 or 15mg/wk was evaluated versus im gold[25-28]. However, due to large heterogeneity of the clinical responses in the comparator arms and the lack of uniformly reported outcome measures, a comparison of the MTX arms was not possible (data not shown). Interestingly, however, the studies using MTX 10 or 15mg/wk versus SSZ all reported equal efficacy of both compounds, while the study using 20mg/wk showed significantly more ACR50 responses in the MTX group (OR=2.67 [1.10-6.47]).[20]

REFERENCES


APPENDIX 5

Direct comparisons MTX frequencies

In addition to the primary research question, 3 RCTs directly comparing oral MTX weekly versus non-weekly were identified and included.[29,30,31] Pandya et al. evaluated MTX 10mg once weekly versus 5mg twice weekly, in a double-blind RCT.[31] Results showed equally large ES after 16 weeks for SJC, TJC, HAQ and ESR (range 1.03-1.99 and 0.88-1.95 for the twice versus the once weekly schedule, respectively), without a difference in hepatotoxicity (OR=0.9 [0.3-3.6]).

Luis et al. evaluated 7mg MTX weekly versus every other week (eow) in a single-blind trial in RA patients in remission on MTX.[30] SRM for SJC, TJC, VAS, HAQ and ESR for MTX eow (range -0.40; 0.26) versus weekly (range -0.40; 0.56) did not differ and remission percentages were equal in both groups (OR=0.5 [0.04-5.4]), although the negative values indicate worsening in a subset of the patients. Kremer et al. showed similar results in a double-blind trial with 15mg MTX weekly versus eow in patients stable on MTX, showing more flares in the eow group (OR=6.3 [1.5-25]).[29]

REFERENCES


Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature
K Visser and D van der Heijde

Ann Rheum Dis published online November 25, 2008

Updated information and services can be found at:
http://ard.bmj.com/content/early/2008/11/25/ard.2008.092668

These include:
Supplementary Material
Supplementary material can be found at:
http://ard.bmj.com/content/suppl/2009/06/18/ard.2008.092668.DC1

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections
Open access (595)
Connective tissue disease (4253)
Musculoskeletal syndromes (4951)
Rheumatoid arthritis (3258)
Degenerative joint disease (4641)
Immunology (including allergy) (5144)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/