Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative


OBJECTIVE

To develop evidence-based recommendations for the use of methotrexate in daily clinical practice in rheumatic disorders.

Methods: 751 rheumatologists from 17 countries participated in the 3E (Evidence, Expertise, Exchange) Initiative of 2007–8 consisting of three separate rounds of discussions and Delphi votes. Ten clinical questions concerning the use of methotrexate in rheumatic disorders were formulated. A systematic literature search in Medline, Embase, Cochrane Library and 2005–7 American College of Rheumatology/European League Against Rheumatism meeting abstracts was conducted. Selected articles were systematically reviewed and the evidence was appraised according to the Oxford levels of evidence. Each country elaborated a set of national recommendations. Finally, multinational recommendations were formulated and agreement among the participants and the potential impact on their clinical practice was assessed.

Results: A total of 16 979 references was identified, of which 304 articles were included in the systematic reviews. Ten multinational key recommendations on the use of methotrexate were formulated. Nine recommendations were specific for rheumatoid arthritis (RA), including the work-up before initiating methotrexate, optimal dosage and route, use of folic acid, monitoring, management of hepatotoxicity, long-term safety, mono versus combination therapy and management in the perioperative period and before/during pregnancy. One recommendation concerned methotrexate as a steroid-sparing agent in other rheumatic diseases.

Conclusions: Ten recommendations for the use of methotrexate in daily clinical practice focussed on RA were developed, which are evidence based and supported by a large panel of rheumatologists, enhancing their validity and practical use.

Methotrexate is the disease-modifying antirheumatic drug (DMARD) of first choice in the treatment of rheumatoid arthritis (RA) and is also used in other systemic rheumatic disorders.1 2 Despite its widespread use and more than two decades of experience, considerable variation exists among rheumatologists in prescribing methotrexate, including the dosage, folic acid supplementation and safety monitoring.3 4 In addition, little is known about the optimal management of methotrexate in specific clinical situations such as the perioperative period and before/during pregnancy. Existing guidelines often lack this level of detail.5

The 3E Initiative (Evidence, Expertise, Exchange) in rheumatology is a multinational effort, aimed at promoting evidence-based medicine, by formulating detailed recommendations addressing clinical problems.6 In contrast to guidelines developed by a limited panel of experts, the 3E Initiative involves a broad international panel of practising rheumatologists. Furthermore, the initiative promotes epidemiology, by teaching and conducting systematic literature research following a strict methodology.7 Therefore, the objective of the 3E Initiative of 2007–8 was to develop practical recommendations for the use of methotrexate in rheumatic disorders, by integrating systematically generated evidence and expert opinion of a broad panel of international rheumatologists.

METHODS

A total of 751 rheumatologists from 17 countries participated in the 3E Initiative of 2007–8. Each country was represented by a scientific committee, consisting of one principal investigator and five to 16 members. The bibliographic team consisted of six international fellows (WK, EL, JAM-L, CS, JT, KV), three mentors (CB, LC, DvdH) and the scientific organiser (MD). During the first international meeting (n = 87 participants), 10 clinically relevant questions on the use of methotrexate in rheumatic disorders were formulated and selected by a Delphi vote. The areas addressed were, for RA: preadministration work-up, optimal dosage and route, use of folic acid, safety monitoring, hepatotoxicity (also for psoriatic arthritis (PsA)), long-term safety (>2 years), mono versus combination

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therapy, management in the perioperative period and before/ during pregnancy, and methotrexate as a steroid-sparing agent in other rheumatic disorders.

The bibliographic team conducted a systematic literature review, following the updated guidelines of the Cochrane Collaboration. Each question was rephrased according to the PICO (population, intervention, comparison, outcome) method with the population defined as adult RA, PsA or other rheumatic diseases, and specific interventions, comparisons and outcomes defined according to each question. Comprehensive search strategies were developed in collaboration with experienced librarians, including terms for methotrexate, RA and specific keywords, without language restriction. Subsequently, Medline, Embase, Cochrane Library and European League Against Rheumatism (EULAR) 2005–7 and American College of Rheumatology (ACR) 2005–6 abstracts were systematically searched for articles published up to September 2007. Additional references were identified by a hand search. Articles were selected applying predefined inclusion and exclusion criteria and their methodological quality was graded according to the levels of evidence of the Oxford Centre for Evidence-Based Medicine. For each question, relevant data were extracted and appropriate statistics were calculated, including effect sizes, hazard ratios (HR), and standardised mortality ratios with 95% CI. If possible, meta-analyses were conducted using RevMan 4.2.10, calculating odds ratios (OR) with fixed effects and relative risks (RR) with a random effects model.

In the second round, a national meeting was held in each country (total n = 751 participants) to discuss the generated evidence and propose a set of recommendations. In a third joint meeting, the scientific committees (n = 94 participants) merged all propositions to 10 final recommendations by discussion and Delphi vote. The grade of recommendation according to the Oxford Levels of Evidence was assessed and the level of agreement was measured on a 10-point visual analogue scale (1, no agreement; 10, full agreement). Finally, the potential impact among the participants was assessed using three statements: “this recommendation will change my practice”; “this recommendation will not change my practice as it is already my practice”; “this recommendation will not change my practice as I don’t want to change my practice for this aspect”.

RESULTS
A total of 16,979 references was identified, of which 304 articles were systematically reviewed (table 1). The 10 multinational key recommendations are listed in table 2, with the corresponding level of evidence and grade of recommendation. The mean level of agreement among the rheumatologists was 8.1 (range 7.4–8.8). The percentage of rheumatologists who indicated that they would change their clinical practice according to each recommendation is shown in table 3.

Recommendation 1
The work-up for patients starting methotrexate should include a clinical assessment of risk factors for methotrexate toxicity (including alcohol intake), patient education, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, complete blood count (CBC), creatinine, chest x-ray (obtained within the previous year); consider serology for HIV, hepatitis B/C, blood fasting glucose, lipid profile and pregnancy test.

The evidence needed to decide whether to start a patient with RA on methotrexate or not might be extrapolated from data on risk factors for severe toxicity. These data suggest that an estimated creatinine clearance of less than 79 ml/minute increases severe methotrexate (pulmonary) toxicity and that hypoalbuminaemia is associated with methotrexate-induced thrombocytopenia, liver and pulmonary toxicity. In addition, lung abnormalities on radiographs, but not pulmonary function tests, are predictive of the development of methotrexate-induced pneumonitis. Additional subgroups at risk of exacerbation of hepatic disease with methotrexate are obese patients, patients with diabetes and patients with viral or alcoholic hepatitis. This observational evidence was combined with expert opinion, following from contraindications to methotrexate use frequently listed in randomised controlled trials (RCT) in RA from the past 15 years: significant renal disease, hepatic disorders, leucopenia less than 3.0 x 10^9/l, thrombocytopenia less than 100 x 10^9/l, age greater than 70 years, malignancy, pregnancy or inadequate contraception, history of alcohol/drug abuse, acute or chronic infection and pulmonary disease. Finally, four national recommendations from Austria, Germany, The Netherlands and Spain and the 1996 ACR guidelines on monitoring RA treatment, all suggest creatinine, CBC, AST/ALT with or without alkaline phosphatase, albumin, hepatitis B/C serology and a chest radiograph for the prediagnosis work-up.

Recommendation 2
Oral methotrexate should be started at 10–15 mg/week, with escalation of 5 mg every 2–4 weeks up to 20–30 mg/week, depending on clinical response and tolerability; parental administration should be considered in the case of inadequate clinical response or intolerance.

The results of three RCT directly comparing different dosages of oral methotrexate in RA showed dose-dependent efficacy and toxicity. A starting dose of 25 mg/week compared with 15 mg/week was more effective, but with a trend towards more gastrointestinal toxicity. Starting doses of 12.5–20 mg/week versus 5–10 mg/week resulted in higher clinical efficacy, without more toxicity. Rapid dose escalation of 5 mg/month to 25–30 mg/week was associated with higher efficacy, but also with more adverse events, in comparison with slow escalation of 5 mg/5 months. Regarding the optimal route of administration, retrospective studies suggest higher efficacy and less gastrointestinal toxicity with parenteral versus oral methotrexate, which might be explained by the greater bioavailability of the parenteral form. Indeed, the single RCT that compared 15 mg/week subcutaneous with oral methotrexate
Methotrexate should not be used for at least 3 months before planned pregnancy for men and women and nor subsequent dose escalation resulted in increased efficacy. Three studies using folic acid 7–35 mg/week showed a significant reduction in the risk of gastrointestinal side effects (OR 0.42; 95% CI 0.21 to 0.85), in contrast with only one study using 5 mg/week folic acid, which did not reach significance. After further stratification, however, the protective effect was only significant in the two studies that used methotrexate at less than 10 mg/week (OR 0.21; 95% CI 0.07 to 0.69) and not in the two largest studies using methotrexate 14–18 mg/week (OR 0.61; 95% CI 0.25 to 1.48). The two studies in which hepatotoxicity was analysed showed a significant protective effect with 1 mg/day folic acid (OR 0.17; 95% CI 0.09 to 0.32), irrespective of the methotrexate dose. Only folic acid at doses of 5 mg/week or less significantly decreased gastrointestinal side effects and hepatotoxicity (OR 0.39; 95% CI 0.2 to 0.76 and OR 0.16; 95% CI 0.09 to 0.29, respectively). Furthermore, folic acid at greater than 5 mg/week was associated with a significant increase in efficacy.

Table 2 Multinational recommendations for the use of methotrexate in RA (1–7, 9–10) and other rheumatic disorders (8)

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of evidence</th>
<th>Grade of recommendation</th>
<th>Agreement mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 The work-up for patients starting methotrexate should include clinical assessment of risk factors for methotrexate toxicity (including alcohol intake), patient education, AST, ALT, albumin, CBC, creatinine, chest x-ray (obtained within the previous year); consider serology for HIV, hepatitis B/C, blood fasting glucose, lipid profile and pregnancy test.</td>
<td>4</td>
<td>C</td>
<td>8.2 (1.9)</td>
</tr>
<tr>
<td>2 Oral methotrexate should be started at 10–15 mg/week, with escalation of 5 mg every 2–4 weeks up to 20–30 mg/week, depending on clinical response and tolerability; parental administration should be considered in the case of inadequate clinical response or intolerance.</td>
<td>2b</td>
<td>B</td>
<td>7.8 (2.6)</td>
</tr>
<tr>
<td>3 Prescription of at least 5 mg folic acid per week with methotrexate therapy is strongly recommended.</td>
<td>1a</td>
<td>A</td>
<td>7.5 (2.7)</td>
</tr>
<tr>
<td>4 When starting methotrexate or increasing the dose, ALT with or without AST, creatinine and CBC should be performed every 1–1.5 months until a stable dose is reached and every 1–3 months thereafter; clinical assessment for side effects and risk factors should be performed at each visit.</td>
<td>4</td>
<td>C</td>
<td>8.1 (2.1)</td>
</tr>
<tr>
<td>5 Methotrexate should be stopped if there is a confirmed increase in ALT/AST greater than three times the ULN, but may be re instituted at a lower dose following normalisation. If the ALT/AST levels are persistently elevated up to three times the ULN, the dose of methotrexate should be adjusted; diagnostic procedures should be considered in the case of persistently elevated ALT/AST more than three times the ULN after discontinuation.</td>
<td>2b</td>
<td>C</td>
<td>7.4 (2.3)</td>
</tr>
<tr>
<td>6 Based on its acceptable safety profile, methotrexate is appropriate for long-term use.</td>
<td>2b</td>
<td>B</td>
<td>8.7 (1.9)</td>
</tr>
<tr>
<td>7 In DMARD-naive patients the balance of the efficacy/toxicity favours methotrexate monotherapy over combination with other conventional DMARD; methotrexate should be considered as the anchor for combination therapy when methotrexate monotherapy does not achieve disease control.</td>
<td>1a</td>
<td>A</td>
<td>8.3 (2.1)</td>
</tr>
<tr>
<td>8 Methotrexate, as a steroid-sparing agent, is recommended in giant-cell arthritis and polymyalgia rheumatica and can be considered in patients with systemic lupus erythematosus or (juvenile) dermatomyositis.</td>
<td>1b</td>
<td>B</td>
<td>7.7 (2.1)</td>
</tr>
<tr>
<td>9 Methotrexate can be safely continued in the perioperative period in RA patients undergoing elective orthopaedic surgery.</td>
<td>1b</td>
<td>B</td>
<td>8.8 (1.9)</td>
</tr>
<tr>
<td>10 Methotrexate should not be used for at least 3 months before planned pregnancy for men and women and should not be used during pregnancy or breast feeding.</td>
<td>4</td>
<td>C</td>
<td>8.2 (2.7)</td>
</tr>
</tbody>
</table>

Table 3 Percentage of rheumatologists in the 3E Initiative who indicated for each recommendation if it would change their clinical practice

<table>
<thead>
<tr>
<th>Recommendation (number and topic)</th>
<th>The recommendation will change my practice (%)</th>
<th>The recommendation is already my practice (%)</th>
<th>I don’t want to change my practice for this aspect (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Pre-methotrexate work-up</td>
<td>29.8</td>
<td>61.2</td>
<td>9.0</td>
</tr>
<tr>
<td>2 Dosage and route</td>
<td>16.2</td>
<td>68.7</td>
<td>15.1</td>
</tr>
<tr>
<td>3 Folic acid</td>
<td>15.3</td>
<td>78.6</td>
<td>6.1</td>
</tr>
<tr>
<td>4 Monitoring</td>
<td>21.1</td>
<td>53.5</td>
<td>25.4</td>
</tr>
<tr>
<td>5 Hepatotoxicity</td>
<td>16.5</td>
<td>68.0</td>
<td>15.5</td>
</tr>
<tr>
<td>6 Long-term safety</td>
<td>2.0</td>
<td>96.0</td>
<td>2.0</td>
</tr>
<tr>
<td>7 Mono vs combination</td>
<td>5.0</td>
<td>86.9</td>
<td>8.1</td>
</tr>
<tr>
<td>8 Steroid-sparing agent</td>
<td>25.6</td>
<td>67.1</td>
<td>7.3</td>
</tr>
<tr>
<td>9 Perioperative period</td>
<td>41.3</td>
<td>46.7</td>
<td>12.0</td>
</tr>
<tr>
<td>10 Pregnancy</td>
<td>19.5</td>
<td>71.3</td>
<td>9.2</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; DMARD, disease-modifying antirheumatic drug; RA, rheumatoid arthritis; ULN, upper limit of normal.
the number of tender and swollen joints (OR 6.27; 95% CI 1.64 to 10.90 and OR 5.3; 95% CI 0.03 to 10.58, respectively), whereas folic acid or low dosages (≤5 mg/week) of folinic acid were not.39 42 45 In conclusion, the experts favoured folic acid and recommended at least 5 mg/week, taking into account the potential need for higher dosages, with the currently higher dosed methotrexate.

**Recommendation 4**

When starting methotrexate or increasing the dose, ALT with or without AST, creatinine and CBC should be performed every 1–1.5 months until a stable dose is reached and every 1–3 months thereafter; clinical assessment for side effects and risk factors should be performed at each visit.

Both the mean AST and the percentage of elevated AST have been reported to correlate with histological grades of liver disease in RA.15 44–47 The 1994 ACR guidelines for monitoring hepatotoxicity showed 80% sensitivity and 82% specificity for detecting fibrosis/cirrhosis of serial abnormal AST tests, with fewer costs and complications compared with routine liver biopsy.46 49 One study suggests that ALT alone might detect 90% of the elevated AST or paired tests.50 In contrast, alkaline phosphatase seems oversensitive for monitoring hepatotoxicity.43 In addition to transaminases, renal function should be monitored, as it is associated with increased (pulmonary) toxicity and CBC is required to monitor haematological toxicity.51 52 Less evidence is available on the frequency of monitoring, although two observational studies showed an optimal interval for identifying abnormal liver enzymes of 30–60 days and a decreasing incidence of abnormal liver enzymes in the first months of methotrexate therapy.48 53 Accordingly, the four national recommendations and the 1996 ACR guidelines suggest monitoring every 1–3 months, with initially more frequent assessments.24

**Recommendation 5**

Methotrexate should be stopped if there is a confirmed increase in ALT/AST greater than three times the upper limit of normal (ULN), but may be re instituted at a lower dose following normalisation. If the ALT/AST levels are persistently elevated up to three times the ULN, the dose of methotrexate should be adjusted; diagnostic procedures should be considered in the case of persistent elevated ALT/AST more than three times the ULN after discontinuation.

Pooled data of 2062 RA patients after a mean of 3.3 years on methotrexate showed that the cumulative incidence of abnormal ALT/AST was 48.9% above the ULN and 16.3% above two to three times the ULN.35 Methotrexate was frequently continued without a dose change, but the frequency of (spontaneous) normalisation was insufficiently reported. In addition, pooled percentages of mild and severe fibrosis and cirrhosis in 1113 RA patients after a mean of 4.1 years on methotrexate were 15.3%, 1.3% and 0.5%, respectively. However, the results of pre-methotrexate biopsies already showed a prevalence of 9.1% mild fibrosis and 0.5% cirrhosis.33 For PsA, a somewhat higher incidence of elevated liver enzymes and fibrosis/cirrhosis compared with RA was found, but the evidence is very limited.21 32–35 For RA, the evidence suggests that liver enzyme elevation is frequent but often transient, that multiple rather than single findings associate with an abnormal biopsy (as noted earlier) and that methotrexate-induced fibrosis/cirrhosis is rare. The experts emphasised considering other causal factors, including non-steroidal anti-inflammatory drugs, obesity and alcohol and other diagnostic procedures than liver biopsy in the case of persistently elevated liver enzymes after the discontinuation of methotrexate.72 44 55

**Recommendation 6**

Based on its acceptable safety profile, methotrexate is appropriate for long-term use.

RA patients have an increased mortality rate compared with the general population (standardised mortality ratio 1.9; 95% CI 1.3 to 2.8).69 However, RA patients on methotrexate compared with patients without methotrexate had a lower mortality incidence rate (23/1000 versus 26.7/1000 patient-years) and reduced cardiovascular mortality (HR 0.5; 95% CI 0.2 to 0.7) in a large 6-year prospective study.69 In addition, in two case–control studies, methotrexate was not a risk factor and even reduced the risk of cardiovascular disease, respectively (OR 0.11; 95% CI 0.02 to 0.56).61 In a meta-analysis and several cohorts with 5–12 years follow-up, methotrexate was less often discontinued because of toxicity than other DMARD, except for hydroxychloroquine.65 64 Gastrointestinal events and elevated liver enzymes are the most frequently encountered toxicities.64 However, as discussed earlier, the risk of severe fibrosis and cirrhosis seems low. Long-term methotrexate use was not associated with an increased risk of serious infections (HR 0.91; 95% CI 0.57 to 1.45), including herpes zoster (HR 1.0; 95% CI 0.8 to 1.3).65 66 Although RA patients have an increased risk of lymphoma compared with the general population, evidence on the risk of methotrexate use independent of RA is inconclusive, because studies did not address RA as the reference population and the risk was not adjusted for disease severity.67 68 Five case reports suggest that methotrexate might be associated with Epstein–Barr virus-related lymphoproliferative disease and regression after methotrexate withdrawal.69–75

**Recommendation 7**

In DMARD-naive patients the balance of efficacy/toxicity favours methotrexate monotherapy over combination with other conventional DMARD; methotrexate should be considered as the anchor for combination therapy when methotrexate monotherapy does not achieve disease control.

A meta-analysis of 20 RCT evaluated methotrexate mono versus combination therapy in RA, excluding combinations with corticosteroids or biological agents.76 Analyses were stratified for DMARD-naive patients and patients with an inadequate response to previous methotrexate or other DMARD. Methotrexate combination therapy was superior to methotrexate monotherapy mainly in patients with a previous inadequate response to methotrexate, resulting in significantly more ACR20 (RR 2.51; 95% CI 1.92 to 3.28), ACR50 (RR 4.54; 95% CI 2.51 to 8.2) and ACR70 (RR 5.59; 95% CI 2.08 to 15.01) responses.77 78 In contrast, in patients who failed other DMARD, only significantly more ACR20 responses (RR 1.85; 95% CI 1.21 to 2.35) were seen with combination therapy and a trend for more EULAR good response and remission.79 80 In DMARD-naive patients, combination therapy showed a trend for more EULAR moderate response and remission, but only ACR70 responses were significantly more often achieved (RR 2.41; 95% CI 1.07 to 5.44).81 82 Regarding toxicity, methotrexate combined with sulfasalazine and methotrexate combined with leflunomide each significantly increased the risk of gastrointestinal side effects and hepatotoxicity, with a trend towards more withdrawal as a result of toxicity.75 79 83 86 87 In contrast, methotrexate combined with sulfasalazine and hydroxychloroquine
were found regarding (non-)elective non-orthopaedic surgery. 

perioperative period of elective orthopaedic surgery, no studies 

was not associated with wound morbidity (p = 0.84) and 

cohort study showed that the perioperative use of methotrexate 

who continued methotrexate (mean dose 10 mg/week) reported 

in either group. 101 However, a multivariate analysis in another 

continued methotrexate compared with none of the patients 

DMARD.

comparing the steroid-sparing effect of methotrexate with other 

juvenile dermatomyositis. 

tumour necrosis factor. 89–92

recommendation does not contradict the well-established superiority 

of combination therapies including either prednisone or anti-

state therapy.96 97 Finally, in a cohort study, juvenile dermatomyositis patients 

no studies were found comparing the steroid-sparing effect of methotrexate with other 

Steroid-sparing effects may be better in RCT and high-quality cohort studies.

The previous recommendations were made by rheumatologists in the 3E Initiative. 

Ten multinational recommendations for the use of methotrexate in daily clinical practice were developed, which are practical, evidence-based and supported by a large panel of international rheumatologists in the 3E Initiative.

The involvement of 751 rheumatologists from 17 countries was unique in the development of the current recommendations. It allowed a selection of relevant topics, reflecting frequently encountered questions on the use of methotrexate in daily practice. Furthermore, a broad participation increases external validity and enhances future dissemination and implementation into rheumatological practice worldwide.

A second principal feature of the initiative was the systematic literature research. Following a strict methodology, we aimed to find all available evidence regarding each topic, which resulted in a large number of reviewed articles. Although for some areas little to no evidence was found, including (the frequency of) toxicity monitoring, the timing of folic acid, non-orthopaedic surgery and the effect of methotrexate on fertility and lactation, the majority of the recommendations is supported by evidence from RCT and high-quality cohort studies.

The same evidence, however, might limit the recommendations, as many studies were old and included longstanding RA patients who received methotrexate in low dosages without folic acid. As this may not reflect current clinical practice, the results should be interpreted and extrapolated with caution. In addition, patients' participation and preferences may influence the recommendations. Nevertheless, the recommendations are based on currently available evidence and can be adjusted if future studies or clinical experience reveal new insights.

In summary, multinational recommendations for the use of methotrexate in daily clinical practice focussed on RA were developed, integrating systematic literature review and expert opinion, with the aim of promoting evidence-based medicine and ultimately improving patient care.

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