Towards improved treatment of undifferentiated and rheumatoid arthritis

Visser, K.

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

Ann Rheum Dis 2009 68:1086-1093

6

K. Visser, W. Katchamart, E. Loza, J.A. Martinez-Lopez, C. Salliot, J. Trudeau, C. Bombardier, L. Carmona, D. van der Heijde, J.W.J. Bijlsma, D.T. Boumpas, H. Canhao, C.J. Edwards, V. Hamuryudan, T.K. Kvien, B.F. Leeb, E.M. Martín- Mola, H. Mielants, U. Müller-Ladner, G. Murphy, M. Østergaard, I.A. Pereira, C. Ramos-Remus, G. Valentini, J. Zochling, M. Dougados

Abstract

Objectives

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 16979 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.

INTRODUCTION

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)), longterm safety (>2 years), mono versus combination 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.[7] 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.[8] Comprehensive search strategies were developed in collaboration with experienced librarians, including terms for methotrexate, RA and specific key words, 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.[9] 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).[10] 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 16979 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.[11–15] In addition, lung abnormalities on radiographs, but not pulmonary function tests, are predictive of the development of methotrexate- induced pneumonitis.[16–18] Additional subgroups at risk of

Table 1. Results of the systematic literature search for each recommendation topic.

	Retrieved references by systematic literature search (n)	Articles included in the systematic reviews (n)
Pre-methotrexate work-up	1214	52
Dosage and route	1748	50
Folic acid	334	9
Monitoring	857	23
Hepatotoxicity	426	46
Long-term safety	2449	88
Mono vs combination	6958	20
Steroid-sparing agent	527	6
Perioperative period	303	4
Pregnancy	2163	6
Total	16979	304

exacerbation of hepatic disease with methotrexate are obese patients, patients with diabetes and patients with viral or alcoholic hepatitis.[19–23] This observational evidence was combined with expert opinion, following from contraindications to methotrexate use frequently listed in randomized 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 preadministration work-up.[24]

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; parenteral 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.[25–27] A starting dose of 25 mg/week compared with 15 mg/week was more effective, but with a trend towards more gastrointestinal toxicity.[26] Starting doses of 12.5–20 mg/week versus 5–10 mg/week resulted in higher clinical efficacy, without more toxicity.[25] 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/3 months.[27] Regarding the

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

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

AST=aspartate aminotransferase, ALT=alanine aminotransferase, CBC=complete blood count, HIV=human immunodeficiency virus, ULN=upper limit of normal, DMARDs=disease-modifying antirheumatic drugs, SD=standard deviation.

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

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

optimal route of administration, retrospective studies suggest higher efficacy and less gastrointestinal toxicity with parenteral versus oral methotrexate, [28 29] which might be explained by the greater bioavailability of the parenteral form.[30 31] Indeed, the single RCT that compared 15 mg/week subcutaneous with oral methotrexate showed greater clinical efficacy, but also more withdrawal as a result of toxicity with subcutaneous methotrexate in early methotrexate-naive RA patients.[32] In contrast, in RA patients who failed methotrexate 15–20 mg/week plus other DMARD, neither a switch to 15 mg/week administered intramuscularly, nor subsequent dose escalation resulted in increased efficacy.[33] In conclusion, the experts preferred the oral route, dosed according to the recommendation, with a possible switch to parenteral in case of an insufficient response at the highest tolerable dose.

Recommendation 3

Prescription of at least 5 mg folic acid per week with methotrexate therapy is strongly recommended.

A meta-analysis of nine studies including 788 RA patients suggested that folic acid supplementation reduces gastrointestinal and liver toxicity of methotrexate, without reducing efficacy.[34] Four 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),[35–38] in contrast with only one study using 5 mg/week folic acid, which did not reach significance.[37] 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)[36 37] and not in the two largest studies using methotrexate 14–18 mg/week (OR 0.61; 95% CI 0.25 to 1.48).[35 38] 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.[35 36] Only folinic 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).[35 39–41] Furthermore, folinic acid at greater than 5 mg/week was associated with a significant increase in 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 43] 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.[48 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. [48] 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.[11 51] 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 52] 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 reinstituted 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 16.8%

above two to three times the ULN.[53] 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 0.3% cirrhosis.[53] 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 54–57] 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 antiinflammatory drugs, obesity and alcohol and other diagnostic procedures than liver biopsy in the case of persistently elevated liver enzymes after the discontinuation of methotrexate.[22 44 58]

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).[59] 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 0.3; 95% CI 0.2 to 0.7) in a large 6-year prospective study.[60] 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 62] 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.[63 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.[69–73]

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.[74] 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.[75–78] In contrast, in patients who failed other DMARD, only significantly more ACR20 responses (RR 1.85; 95% CI 1.21 to 2.83) 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).[81–85] 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.[76 79 81 82 86 87] In contrast, methotrexate combined with sulfasalazine and hydroxychloroquine did not increase the risk of withdrawal due to toxicity.[88] Weighing efficacy and toxicity, the experts favoured methotrexate monotherapy over the combination with conventional DMARD in DMARD-naive RA patients. As such, the recommendation does not contradict the well-established superiority of combination therapies including either prednisone or anti-tumour necrosis factor.[89–92]

Recommendation 8

Methotrexate, as a steroid-sparing agent, is recommended in giant-cell arteritis and polymyalgia rheumatica and can be considered in patients with systemic lupus erythematosus or (juvenile) dermatomyositis.

An individual patient data meta-analysis evaluated the steroid-sparing effect of methotrexate 7.5–17.5 mg/week versus placebo in giant-cell arteritis patients on high-dose prednisone.[93] The results showed a higher prednisone discontinuation rate (HR 2.84; 95% CI 1.52 to 5.28), significantly lower cumulative steroid dose and fewer relapses with methotrexate therapy after 1 year. Two RCT in polymyalgia rheumatica also showed significantly more prednisone discontinuation with methotrexate 10 mg/week compared with placebo, significantly fewer relapses and a trend towards lower prednisone duration and cumulative dose.[94 95] Systemic lupus erythematosus patients in two RCT evaluating methotrexate 7.5–20 mg/week versus placebo had significantly more prednisone reduction, fewer skin and joint flares, but more adverse events with methotrexate therapy.[96 97] Finally, in a cohort study, juvenile dermatomyositis patients discontinued prednisone significantly earlier and had significantly lower cumulative prednisone doses with concomitant methotrexate therapy, but without an additional beneficial effect on disease activity.[98] No studies were found comparing the steroid-sparing effect of methotrexate with other DMARD.

Recommendation 9

Methotrexate can be safely continued in the perioperative period in RA patients undergoing elective orthopaedic surgery.

Four studies evaluated stopping or continuing methotrexate one or more weeks before elective orthopaedic surgery in RA. In one RCT, no differences in postoperative complications were observed between patients who continued or stopped methotrexate (mean dose 10 mg/week).[99] In a second RCT, patients who continued methotrexate (mean dose 10 mg/week) reported significantly fewer RA flares than patients who stopped methotrexate.[100] In contrast, in a prospective cohort study postoperative infections occurred in 30% of patients who continued methotrexate compared with none of the patients who stopped methotrexate, without postoperative flares of RA in either group.[101] However, a multivariate analysis in another cohort study showed that the perioperative use of methotrexate was not associated with wound morbidity (p=0.84) and significantly reduced RA flares.[102] Although these studies suggest that methotrexate can be safely continued in the perioperative period of elective orthopaedic surgery, no studies were found regarding (non-)elective non-orthopaedic surgery.

Recommendation 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.

Six studies assessed the outcome of continued methotrexate therapy before/during pregnancy in (mostly) RA patients by surveys and database searches.[103–108] A total of 101 pregnancies was exposed to methotrexate during pregnancy (n = 92) or before conception (n = 9). Eighteen induced abortions were reported, but the reasons were not stated. A total of 20 (24%) miscarriages, five (6%) congenital malformations and 62 (75%) live births was reported, with one (1%) patient lost to follow-up. In healthy women, corresponding percentages are 12–16% miscarriages and 3–5% congenital malformations.[109 110] In contrast, no studies were found that evaluated the effect of methotrexate for men on miscarriages/birth defects, male and female fertility or on newborns during lactation. Nevertheless, expert opinion is to stop methotrexate at least 3 months before planned pregnancy in both men and women and not to use methotrexate during pregnancy or breast feeding.

DISCUSSION

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, re-

flecting 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.

References

1. Pincus T, Yazici Y, Sokka T, Aletaha D, Smolen JS. Methotrexate as the "anchor drug" for the treatment of early rheumatoid arthritis. Clin Exp Rheumatol 2003;21:S179–85.
2. Wong JM, Esdaile JM. Methotrexate in systemic lupus erythematosus. Lupus 2005; 14:101–5.
3. Pope JE, Hong P, Koehler BE. Prescribing trends in disease modifying antirheumatic drugs for rheumatoid arthritis: a survey of practicing Canadian rheumatologists.J Rheumatol 2002;29:255–60.
4. Criswell LA, Henke CJ. What explains the variation among rheumatologists in their use of prednisone and second line agents for the treatment of rheumatoid arthritis? J Rheumatol 1995;22:829–35.
5. Combe B, Landewe R, Lukas C, Bolosiu HD, Breedveld F, Dougados M, et al. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2007;66:34–45.
6. Sidiropoulos PI, Hatemi G, Song IH, Avouac J, Collantes E, Hamuryudan V, et al. Evidence-based recommendations for the management of ankylosing spondylitis: systematic literature search of the 3E Initiative in Rheumatology involving a broad panel of experts and practising rheumatologists. Rheumatology (Oxford) 2008;47:355–61.
7. van Tulder M, Furlan A, Bombardier C, Bouter L. Updated method guidelines for systematic reviews in the Cochrane Collaboration Back Review Group. Spine 2003;28:1290–9.
8. Sackett DL, Richardson WS, Rosenberg WM, Haynes RB. Evidence-based medicine: how to practice and teach EBM. London, UK: Churchill Livingstone, 1997.
9. Oxford Centre for Evidence-Based Medicine. Levels of evidence. 1995. http://www.cebm.net/index.aspx?o=1025 (accessed March 2008).
10. Roddy E, Zhang W, Doherty M, Arden NK, Barlow J, Birrell F, et al. Evidence-based clinical guidelines: a new system to better determine true strength of recommendation. J Eval Clin Pract 2006;12:347–52.
11. Rheumatoid Arthritis Clinical Trial Archive Group. The effect of age and renal function on the efficacy and toxicity of methotrexate in rheumatoid arthritis. J Rheumatol 1995;22:218–23.
12. Alarcon GS, Kremer JM, Macaluso M, Weinblatt ME, Cannon GW, Palmer WR, et al. Risk factors for methotrexate-induced lung injury in patients with rheumatoid arthritis. A multicenter, case–control study. Methotrexate-Lung Study Group. Ann Intern Med 1997;127:356–64.
13. Kent PD, Luthra HS, Michet C Jr. Risk factors for methotrexate-induced abnormal laboratory monitoring results in patients with rheumatoid arthritis. J Rheumatol 2004;31:1727–31.
14. Kremer JM, Kaye GI, Kaye NW, Ishak KG, Axiotis CA. Light and electron microscopic analysis of sequential liver biopsy samples from rheumatoid arthritis patients receiving long-term methotrexate therapy. Followup over long treatment intervals and correlation with clinical and laboratory variables. Arthritis Rheum 1995;38:1194–203.
15. Walker AM, Funch D, Dreyer NA, Tolman KG, Kremer JM, Alarcon GS, et al. Determinants of serious liver disease among patients receiving low-dose methotrexate for rheumatoid arthritis. Arthritis Rheum 1993;36:329–35.
16. Golden MR, Katz RS, Balk RA, Golden HE. The relationship of preexisting lung disease to the development of methotrexate pneumonitis in patients with rheumatoid arthritis. J Rheumatol 1995;22:1043–7.
17. Cottin V, Tebib J, Massonnet B, Souquet PJ, Bernard JP. Pulmonary function in patients receiving long-term low-dose methotrexate. Chest 1996;109:933–8.
18. Beyeler C, Jordi B, Gerber NJ, Im Hof V. Pulmonary function in rheumatoid arthritis treated with low-dose methotrexate: a longitudinal study. Br J Rheumatol 1996;35:446–52.
19. Ito S, Nakazono K, Murasawa A, Mita Y, Hata K, Saito N, et al. Development of fulminant hepatitis B (precore variant mutant type) after the discontinuation of lowdose methotrexate therapy in a rheumatoid arthritis patient. Arthritis Rheum 2001;44:339–42.
20. Hagiyama H, Kubota T, Komano Y, Kurosaki

M, Watanabe M, Miyasaka N. Fulminant hepatitis in an asymptomatic chronic carrier of hepatitis B virus mutant after withdrawal of low-dose methotrexate therapy for rheumatoid arthritis. Clin Exp Rheumatol 2004;22:375–6.
21. Shergy WJ, Polisson RP, Caldwell DS, Rice JR, Pisetsky DS, Allen NB. Methotrexate-associated hepatotoxicity: retrospective analysis of 210 patients with rheumatoid arthritis. Am J Med 1988;85:771–4.
22. Phillips CA, Cera PJ, Mangan TF, Newman ED. Clinical liver disease in patients with rheumatoid arthritis taking methotrexate. J Rheumatol 1992;19:229–33.
23. Minocha A, Dean HA, Pittsley RA. Liver cirrhosis in rheumatoid arthritis patients treated with long-term methotrexate. Vet Hum Toxicol 1993;35:45–8.
24. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Guidelines for monitoring drug therapy in rheumatoid arthritis. Arthritis Rheum 1996;39:723–31.
25. Furst DE, Koehnke R, Burmeister LF, Kohler J, Cargill I. Increasing methotrexate effect with increasing dose in the treatment of resistant rheumatoid arthritis. J Rheumatol 1989; 16:313–20.
26. Schnabel A, Reinhold-Keller E, Willmann V, Gross WL. Tolerability of methotrexate starting with 15 or 25 mg/week for rheumatoid arthritis. Rheumatol Int 1994;14:33–8.
27. Verstappen SM, Jacobs JW, van der Veen MJ, Heurkens AH, Schenk Y, Ter Borg EJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). Ann Rheum Dis 2007;66:1443–9.
28. Wegrzyn J, Adeleine P, Miossec P. Better efficacy of methotrexate given by intramuscular injection than orally in patients with rheumatoid arthritis. Ann Rheum Dis 2004;63:1232–4.
29. Rozin A, Schapira D, Balbir-Gurman A, Braun-Moscovici Y, Markovits D, Militianu D, et al. Relapse of rheumatoid arthritis after substitution of oral for parenteral administration of methotrexate. Ann Rheum Dis 2002;61:756–7.
30. Jundt JW, Browne BA, Fiocco GP, Steele AD, Mock D. A comparison of low dose methotrexate bioavailability: oral solution, oral tablet, subcutaneous and intramuscular dosing. J Rheumatol 1993;20:1845–9.
31. Hoekstra M, Haagsma C, Neef C, Proost J, Knuif A, van de Laar M. Bioavailability of higher dose methotrexate comparing oral and subcutaneous administration in patients with rheumatoid arthritis. J Rheumatol 2004;31:645–8.
32. Braun J, Kaestner P, Flaxenberg P, Waehrisch J, Hanke P, Demary W, et al. Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis. Arthritis Rheum 2008;58:73–81.
33. Lambert CM, Sandhu S, Lochhead A, Hurst NP, McRorie E, Dhillon V. Dose escalation of parenteral methotrexate in active rheumatoid arthritis that has been unresponsive to conventional doses of methotrexate: a randomized, controlled trial. Arthritis Rheum 2004;50:364–71.
34. Katchamart W, Ortiz Z, Shea B, Tugwell P, Bombardier C. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis (an update systematic review and metaanalysis). Arthritis Rheum 2008;58(suppl):S473.
35. van Ede AE, Laan RF, Rood MJ, Huizinga TW, van de Laar MA, van Denderen CJ, et al. Effect of folic or folinic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis: a forty-eight week, multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum 2001;44:1515–24.
36. Morgan SL, Baggott JE, Vaughn WH, Young PK, Austin JV, Krumdieck CL, et al. The effect of folic acid supplementation on the toxicity of low-dose methotrexate in patients with rheumatoid arthritis. Arthritis Rheum 1990;33:9–18.
37. Morgan SL, Baggott JE, Vaughn WH, Austin JS, Veitch TA, Lee JY, et al. Supplementation with folic acid during methotrexate therapy for rheumatoid arthritis. A double-blind, placebo-controlled trial. Ann Intern Med 1994;121:833–41.
38. Griffith SM, Fisher J, Clarke S, Montgomery B, Jones PW, Saklatvala J, et al. Do patients with rheumatoid arthritis established on methotrexate and folic acid 5 mg daily need to continue folic acid supplements long term? Rheumatology (Oxford) 2000;39:1102–9.

39. Buckley LM, Vacek PM, Cooper SM. Administration of folinic acid after low dose methotrexate in patients with rheumatoid arthritis. J Rheumatol 1990;17:1158–61.
40. Shiroky JB, Neville C, Esdaile JM, Choquette D, Zummer M, Hazeltine M, et al. Low-dose methotrexate with leucovorin (folinic acid) in the management of rheumatoid arthritis. Results of a multicenter randomized, double-blind, placebocontrolled trial. Arthritis Rheum 1993;36:795–803.
41. Weinblatt ME, Maier AL, Coblyn JS. Low dose leucovorin does not interfere with the efficacy of methotrexate in rheumatoid arthritis: an 8 week randomized placebo controlled trial. J Rheumatol 1993;20:950–2.
42. Hanrahan PS, Russell AS. Concurrent use of folinic acid and methotrexate in rheumatoid arthritis. J Rheumatol 1988;15:1078–80.
43. Joyce DA, Will RK, Hoffman DM, Laing B, Blackbourn SJ. Exacerbation of rheumatoid arthritis in patients treated with methotrexate after administration of folinic acid. Ann Rheum Dis 1991;50:913–14.
44. Kremer JM, Lee RG, Tolman KG. Liver histology in rheumatoid arthritis patients receiving long-term methotrexate therapy. A prospective study with baseline and sequential biopsy samples. Arthritis Rheum 1989;32:121–7.
45. Kremer JM, Furst DE, Weinblatt ME, Blotner SD. Significant changes in serum AST across hepatic histological biopsy grades: prospective analysis of 3 cohorts receiving methotrexate therapy for rheumatoid arthritis. J Rheumatol 1996;23:459–61.
46. Tolman KG, Clegg DO, Lee RG, Ward JR. Methotrexate and the liver. J Rheumatol 1985;12(suppl 12):29–34.
47. Willkens RF, Leonard PA, Clegg DO, Tolman KG, Ward JR, Marks CR, et al. Liver histology in patients receiving low dose pulse methotrexate for the treatment of rheumatoid arthritis. Ann Rheum Dis 1990;49:591–3.
48. Kremer JM, Alarcon GS, Lightfoot RW Jr, Willkens RF, Furst DE, Williams HJ, et al. Methotrexate for rheumatoid arthritis. Suggested guidelines for monitoring liver toxicity. American College of Rheumatology. Arthritis Rheum 1994;37:316–28.
49. Erickson AR, Reddy V, Vogelgesang SA, West SG. Usefulness of the American College of Rheumatology recommendations for liver biopsy in methotrexate-treated rheumatoid arthritis patients. Arthritis Rheum 1995;38: 1115–19.
50. Mckendry RJ, Freeman C, Dale P. Ast and/or Alt for methotrexate monitoring. Arthritis Rheum 1995;38:9(suppl):680.
51. Gutierrez-Urena S, Molina JF, Garcia CO, Cuellar ML, Espinoza LR. Pancytopenia secondary to methotrexate therapy in rheumatoid arthritis. Arthritis Rheum 1996;39:272–6.
52. Rau R, Karger T, Herborn G, Frenzel H. Liver biopsy findings in patients with rheumatoid arthritis undergoing longterm treatment with methotrexate. J Rheumatol 1989;16:489–93.
53. Visser K, van der Heijde D. Incidence of liver enzyme elevations and liver biopsy abnormalities during methotrexate treatment in rheumatoid arthritis: a systematic review of the literature. Arthritis Rheum 2008;58 (suppl):S557.
54. Espinoza LR, Zakraoui L, Espinoza CG, Gutierrez F, Jara LJ, Silveira LH, et al. Psoriatic arthritis: clinical response and side effects to methotrexate therapy. J Rheumatol 1992;19: 872–7.
55. Grismer LE, Gill SA, Harris MD. Liver biopsy in psoriatic arthritis to detect methotrexate hepatotoxicity. J Clin Rheumatol 2001;7:224–7.
56. Tilling L, Townsend S, David J. Methotrexate and hepatic toxicity in rheumatoid arthritis and psoriatic arthritis. Clin Drug Invest 2006;26:55–62.
57. Ujfalussy I, Koo E, Sesztak M, Gergely P. Termination of disease-modifying antirheumatic drugs in rheumatoid arthritis and in psoriatic arthritis. A comparative study of 270 cases. Z Rheumatol 2003;62:155–60.
58. Ros S, Juanola X, Condom E, Canas C, Riera J, Guardiola J, et al. Light and electron microscopic analysis of liver biopsy samples from rheumatoid arthritis patients receiving long-term methotrexate therapy. Scand J Rheumatol 2002;31:330–6.
59. Alarcon GS, Tracy IC, Strand GM, Singh K, Macaluso M. Survival and drug discontinuation analyses in a large cohort of methotrexate treated rheumatoid arthritis patients. Ann Rheum Dis 1995;54:708–12.
60. Choi HK, Hernan MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a

prospective study. Lancet 2002;359:1173–7.
61. Assous N, Touze E, Meune C, Kahan A, Allanore Y. Cardiovascular disease in rheumatoid arthritis: single-center hospital-based cohort study in France. Joint Bone Spine 2007;74:66–72.
62. van Halm VP, Nurmohamed MT, Twisk JW, Dijkmans BA, Voskuyl AE. Diseasemodifying antirheumatic drugs are associated with a reduced risk for cardiovascular disease in patients with rheumatoid arthritis: a case control study. Arthritis Res Ther 2006;8:R151.
63. Maetzel A, Wong A, Strand V, Tugwell P, Wells G, Bombardier C. Meta-analysis of treatment termination rates among rheumatoid arthritis patients receiving diseasemodifying anti-rheumatic drugs. Rheumatology (Oxford) 2000;39:975–81.
64. Salliot C, van der Heijde D. Long term safety of methotrexate monotherapy in rheumatoid arthritis patients: a systematic literature research. Ann Rheum Dis 2009;68:1100–4.
65. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Predictors of infection in rheumatoid arthritis. Arthritis Rheum 2002;46:2294–300.
66. Wolfe F, Michaud K, Chakravarty EF. Rates and predictors of herpes zoster in patients with rheumatoid arthritis and non-inflammatory musculoskeletal disorders. Rheumatology (Oxford) 2006;45:1370–5.
67. Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. Arthritis Rheum 2004;50:1740–51.
68. Mariette X, Cazals-Hatem D, Warszawki J, Liote F, Balandraud N, Sibilia J. Lymphomas in rheumatoid arthritis patients treated with methotrexate: a 3-year prospective study in France. Blood 2002;99:3909–15.
69. Hoshida Y, Xu JX, Fujita S, Nakamichi I, Ikeda JI, Tomita Y, et al. Lymphoproliferative disorders in rheumatoid arthritis: clinicopathological analysis of 76 cases in relation to methotrexate medication. J Rheumatol 2007;34: 322–31.
70. Kojima M, Itoh H, Hirabayashi K, Igarashi S, Tamaki Y, Murayama K, et al. Methtrexate-associated lymphoproliferative disorders. A clinicopathological study of 13 Japanese cases. Pathol Res Pract 2006;202:679–85.
71. Kamel OW, Weiss LM, van de Rijn M, Colby TV, Kingma DW, Jaffe ES. Hodgkin's disease and lymphoproliferations resembling Hodgkin's disease in patients receiving long-term low-dose methotrexate therapy. Am J Surg Pathol 1996;20:1279–87.
72. Kamel OW, van de Rijn M, Lebrun DP, Weiss LM, Warnke RA, Dorfman RF. Lymphoid neoplasms in patients with rheumatoid arthritis and dermatomyositis: frequency of Epstein–Barr virus and other features associated with immunosuppression. Hum Pathol 1994;25 :638–43.
73. Tutor-Ureta P, Yebra-Bango M, Salas-Anton C, Andreu JL. Rheumatoid arthritis, methotrexate and non-Hodgkin's lymphoma. A report of 3 patients. Medicina Clinica 2005;125:637.
74. Katchamart W, Trudeau J, Phumethum V, Bombardier C. The efficacy and toxicity of methotrexate (MTX) monotherapy vs MTX combination therapy with non-biologic disease-modifying anti-rheumatic drugs in rheumatoid arthritis: a systematic review and metaanalysis. Ann Rheum Dis 2009;68: 1105–12.
75. Tugwell P, Pincus T, Yocum D, Stein M, Gluck O, Kraag G, et al. Combination therapy with cyclosporine and methotrexate in severe rheumatoid arthritis. The Methotrexate–Cyclosporine Combination Study Group. N Engl J Med 1995;333:137–41.
76. Kremer JM, Genovese MC, Cannon GW, Caldwell JR, Cush JJ, Furst DE, et al. Concomitant leflunomide therapy in patients with active rheumatoid arthritis despite stable doses of methotrexate. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 2002;137:726–33.
77. Lehman AJ, Esdaile JM, Klinkhoff AV, Grant E, Fitzgerald A, Canvin J. A 48-week, randomized, double-blind, double-observer, placebo-controlled multicenter trial of combination methotrexate and intramuscular gold therapy in rheumatoid arthritis: results of the METGO study. Arthritis Rheum 2005;52:1360–70.
78. Ogrendik M. Levofloxacin treatment in patients with rheumatoid arthritis receiving methotrexate. South Med J 2007;100:135–9.
79. Capell HA, Madhok R, Porter DR, Munro RA, McInnes IB, Hunter JA, et al. Combination therapy with sulfasalazine and methotrexate is more effective than either drug alone in patients with rheumatoid arthritis with a suboptimal response to sulfasalazine:

results from the double-blind placebo-controlled MASCOT study. Ann Rheum Dis 2007;66:235–41.
80. Ichikawa Y, Saito T, Yamanaka H, Akizuki M, Kondo H, Kobayashi S, et al. Therapeutic effects of the combination of methotrexate and bucillamine in early rheumatoid arthritis: a multicenter, double-blind, randomized controlled study. Mod Rheumatol 2005;15:323–8.
81. Haagsma CJ, van Riel PL, de Jong AJ, van de Putte LB. Combination of sulphasalazine and methotrexate versus the single components in early rheumatoid arthritis: a randomized, controlled, double-blind, 52 week clinical trial. Br J Rheumatol 1997;36:1082–8.
82. Dougados M, Combe B, Cantagrel A, Goupille P, Olive P, Schattenkirchner M, et al. Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components. Ann Rheum Dis 1999;58:220–5.
83. Marchesoni A, Battafarano N, Arreghini M, Panni B, Gallazzi M, Tosi S. Radiographic progression in early rheumatoid arthritis: a 12-month randomized controlled study comparing the combination of cyclosporin and methotrexate with methotrexate alone. Rheumatology (Oxford) 2003;42:1545–9.
84. Hetland ML, Stengaard-Pedersen K, Junker P, Lottenburger T, Ellingsen T,Andersen LS, et al. Combination treatment with methotrexate, cyclosporine, and intraarticular betamethasone compared with methotrexate and intraarticular betamethasone in early active rheumatoid arthritis: an investigator-initiated, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Arthritis Rheum 2006;54:1401–9.
85. O'Dell JR, Elliott JR, Mallek JA, Mikuls TR, Weaver CA, Glickstein S, et al. Treatment of early seropositive rheumatoid arthritis: doxycycline plus methotrexate versus methotrexate alone. Arthritis Rheum 2006;54:621–7.
86. Islam MN, Alam MN, Haq SA, Moyenuzzaman M, Patwary MI, Rahman MH.Efficacy of sulphasalazine plus methotrexate in rheumatoid arthritis. Bangladesh Medl Res CouncBull 2000;26:1–7.
87. Tascioglu FO, Oner C, Armagan O. Comparison of low dose methotrexate and combination therapy with methotrexate and sulphasalazine in the treatment of early rheumatoid arthritis. J Rheumatol Med Rehabil 2003; 14:142–9.
88. O'Dell JR, Haire CE, Erikson N, Drymalski W, Palmer W, Eckhoff PJ, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. N Engl J Med 1996;334:1287–91.
89. Boers M, Verhoeven AC, Markusse HM, van de Laar MA, Westhovens R, van Denderen JC, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350: 309–18.
90. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006;54:26–37.
91. Genovese MC, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis Rheum 2002;46:1443–50.
92. Goekoop-Ruiterman YP, Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study)—a randomized, controlled trial. Arthritis Rheum 2005;52:3381–90.
93. Mahr AD, Jover JA, Spiera RF, Hernandez-Garcia C, Fernandez-Gutierrez B, Lavalley MP, et al. Adjunctive methotrexate for treatment of giant cell arteritis: an individual patient data meta-analysis. Arthritis Rheum 2007;56: 2789–97.
94. Ferraccioli G, Salaffi F, De Vita S, Casatta L, Bartoli E. Methotrexate in polymyalgia rheumatica: preliminary results of an open, randomized study. J Rheumatol 1996;23:624–8.
95. Caporali R, Cimmino MA, Ferraccioli G, Gerli R, Klersy C, Salvarani C, et al. Prednisone plus methotrexate for polymyalgia rheumatica: a randomized, doubleblind, placebo-controlled

trial. Ann Intern Med 2004;141:493–500.
96. Fortin PR, Abrahamowicz M, Ferland D, Lacaille D, Smith CD, Zummer M. Study of methotrexate in lupus erythematosus (SMILE): significant decreased disease activity and steroid sparing effect in patients without damage. Arthritis Rheum 2001;44(suppl):S387.
97. Carneiro JR, Sato EI. Double blind, randomized, placebo controlled clinical trial of methotrexate in systemic lupus erythematosus. J Rheumatol 1999;26:1275–9.
98. Ramanan AV, Campbell-Webster N, Ota S, Parker S, Tran D, Tyrrell PN, et al. The effectiveness of treating juvenile dermatomyositis with methotrexate and aggressively tapered corticosteroids. Arthritis Rheum 2005;52:3570–8.
99. Sany J, Anaya JM, Canovas F, Combe B, Jorgensen C, Saker S, et al. Influence of methotrexate on the frequency of postoperative infectious complications in patients with rheumatoid arthritis. J Rheumatol 1993;20: 1129–32.
100. Grennan DM, Gray J, Loudon J, Fear S. Methotrexate and early postoperative complications in patients with rheumatoid arthritis undergoing elective orthopaedic surgery. Ann Rheum Dis 2001;60:214–17.
101. Carpenter MT, West SG, Vogelgesang SA, Casey Jones DE. Postoperative joint infections in rheumatoid arthritis patients on methotrexate therapy. Orthopedics 1996;19:207–10.
102. Murata K, Yasuda T, Ito H, Yoshida M, Shimizu M, Nakamura T. Lack of increase in postoperative complications with low-dose methotrexate therapy in patients with rheumatoid arthritis undergoing elective orthopedic surgery. Mod Rheumatol 2006;16:14–19.
103. Ostensen M, von Esebeck M, Villiger PM. Therapy with immunosuppressive drugs and biological agents and use of contraception in patients with rheumatic disease. J Rheumatol 2007;34:1266–9.
104. Ostensen M, Hartmann H, Salvesen K. Low dose weekly methotrexate in early pregnancy. A case series and review of the literature. J Rheumatol 2000;27:1872–5.
105. Lewden B, Vial T, Elefant E, Nelva A, Carlier P, Descotes J. Low dose methotrexate in the first trimester of pregnancy: results of a French collaborative study. J Rheumatol 2004;31: 2360–5.
106. Kozlowski RD, Steinbrunner JV, MacKenzie AH, Clough JD, Wilke WS, Segal AM. Outcome of first-trimester exposure to low-dose methotrexate in eight patients with rheumatic disease. Am J Med 1990;88:589–92.
107. Donnenfeld AE, Pastuszak A, Noah JS, Schick B, Rose NC, Koren G. Methotrexate exposure prior to and during pregnancy. Teratology 1994;49:79–81.
108. Chakravarty EF, Sanchez-Yamamoto D, Bush TM. The use of disease modifying antirheumatic drugs in women with rheumatoid arthritis of childbearing age: a survey of practice patterns and pregnancy outcomes. J Rheumatol 2003;30:241–6.
109 Regan L, Rai R. Epidemiology and the medical causes of miscarriage. Baillieres Best Pract Res Clin Obstet Gynaecol 2000;14:839–54.
110. Otis. Información para mujeres embarazadas y amamantando sobre el estrés. March 2006. http://www.otispregnancy.org/pdf/es_estres.pdf (accessed March 2008).