EDITOR'S CHOICE

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

K Visser,[1] W Katchamart,[2] E Loza,[3] J A Martinez-Lopez,[4] C Salliot,[5] J Trudeau,[6] C Bombardier,[2,7] L Carmona,[4] D van der Heijde,[1] J W J Bijlsma,[8] D T Boumpas,[9] H Canhao,[10] C J Edwards,[11] V Hamuryudan,[12] T K Kvien,[13] B F Leeb,[14] E M Martín-Mola,[15] H. Mielants,[16] U Müller-Ladner,[17] G Murphy,[18] M Østergaard,[19] I A Pereira,[20] C Ramos-Remus,[21] G Valentini,[22] J Zochling,[23] M Dougados[5]

For numbered affiliations see end of article

Correspondence to:
Dr K Visser, Leiden University Medical Center, Department of Rheumatology, PO Box 9600, 2300 RC Leiden, The Netherlands; k.visser@lumc.nl

WK, EL, JAM-L, CS and JT contributed equally to the work

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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 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

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 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.

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	16 979	304

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 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 randomised controlled trials (RCT) in RA from the past 15 years: significant renal disease, hepatic disorders, leucopenia less than 3.0×10^9/l, thrombocytopenia less than 100×10^9/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 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

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 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.	4	C	8.2 (1.9)
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.	2b	B	7.8 (2.6)
3	Prescription of at least 5 mg folic acid per week with methotrexate therapy is strongly recommended.	1a–	A	7.5 (2.7)
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.	4	C	8.1 (2.1)
5	Methotrexate should be stopped if there is a confirmed increase in ALT/AST greater than three times the 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 persistently elevated ALT/AST more than three times the ULN after discontinuation.	2b	C	7.4 (2.3)
6	Based on its acceptable safety profile, methotrexate is appropriate for long-term use.	2b	B	8.7 (1.9)
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.	1a–	A	8.3 (2.1)
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.	1b	B	7.7 (2.1)
9	Methotrexate can be safely continued in the perioperative period in RA patients undergoing elective orthopaedic surgery.	1b	B	8.8 (1.9)
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.	4	C	8.2 (2.7)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; DMARD, disease-modifying antirheumatic drug; RA, rheumatoid arthritis; ULN, upper limit of normal.

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

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

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 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.[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, 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.

Author affiliations: [1] Leiden University Medical Center, Leiden, The Netherlands; [2] Rheumatology Division, Department of Medicine, University of Toronto, Ontario, Canada; [3] Department of Rheumatology, Hospital Clinico San Carlos, Madrid, Spain; [4] Research Unit, Fundación Española de Reumatología, Madrid, Spain; [5] Paris Descartes University, Medicine Faculty; UPRES-EA 4058; APHP, Rheumatology B Department, Cochin Hospital, Paris, France; [6] CHUM-Hôpital Notre-Dame, Université de Montréal, Montréal, Canada; [7] Division of Clinical Decision Making and Health Care Research, Health Network Research Institute, Toronto, Ontario, Canada; [8] Department of Rheumatology and Clinical Immunology, University Medical Center, Utrecht, The Netherlands; [9] Division of Rheumatology, University of Crete, Heraklion, Greece; [10] Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa; Serviço de Reumatologia e Doenças Ósseas Metabólicas, Hospital de Santa Maria, Lisbon, Portugal; [11] Southampton University Hospital, Southampton, UK; [12] Istanbul University, Cerrahpasa Medical Faculty, Department of Internal Medicine, Division of Rheumatology, Istanbul, Turkey; [13] Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway; [14] State

Hospital Stockerau, Center for Rheumatology, Lower Austria, Stockerau, Austria; [15] Hospital Universitario La Paz, Department of Rheumatology, Universidad Autónoma, Madrid, Spain; [16] Department of Rheumatology, University of Gent, Gent, Belgium; [17] Department of Rheumatology and Clinical Immunology, Justus-Liebig-University Giessen, Kerckhoff Clinic, Bad Nauheim, Germany; [18] Cork University Hospital, Wilton, Cork, Ireland; [19] Departments of Rheumatology, Copenhagen University Hospitals at Hvidovre and Herlev, Denmark; [20] University Hospital of Santa Catarina, UFSC, Division of Rheumatology, Florianopolis, Brazil; [21] Unidad de Investigación en Enf Cronico-Degenerativas, Guadalajara, Mexico; [22] University of Naples, Department of Internal Medicine, Rheumatology Unit, Naples, Italy; [23] Menzies Research Institute, University of Tasmania, Hobart, Australia

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