Methotrexate in rheumatoid arthritis: experience and recommendations from the 3E initiative

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Karen Visser[†]
[†]Author for correspondence: Leiden University Medical Center, PO BOX 9600, 2300 RC Leiden, The Netherlands Tel.: +31 715 263 598 ; Fax: +31 715 266 752 ; k.visser@lumc.nl

Désirée van der Heijde
Leiden University Medical Center, Department of Rheumatology, Leiden, The Netherlands

Maxime Dougados
Paris Descartes University, Medicine Faculty, Rheumatology B Department Cochin Hospital, Paris, France

Major advances have been made in the treatment of rheumatoid arthritis (RA), an autoimmune inflammatory disease of still unknown etiology, which has the potential to follow a chronic destructive course [1]. RA is characterized by inflammation of synovial joints, leading to symptoms of pain, swelling and, ultimately, progressive joint destruction [2]. The disease results in functional impairment, decreased quality of life, work loss and even increased mortality [3–5]. However, in recent years it has become clear that early initiation of DMARDs and tight control of the disease by aiming at the goal of low disease activity, can substantially alter the course and improve the outcome of RA [6,7]. In addition, new highly effective biologic drugs including TNF-α inhibitors have become available for RA. Despite these rapidly changing insights and upcoming new therapeutics, there is one DMARD that fiercely stood the test of time: methotrexate (MTX).

Since its first use in patients with RA in the 1960s, the efficacy and toxicity profile of MTX has been well established in randomized, controlled trials (RCTs) in the early 1980s and in longitudinal cohort studies in the 1990s [8–11]. Since then, its position as a cornerstone of RA treatment has only strengthened, although the exact anti-inflammatory mechanisms are still incompletely known. Currently, MTX is recommended by the European league against rheumatism (EULAR) as the first DMARD of choice in patients with recent-onset RA [12]. Surprisingly, despite this widespread use and long-term experience, considerable variation exists among rheumatologists in prescribing and managing MTX [13,14]. Furthermore, only few countries have elaborated national guidelines for the use of MTX, and the existing ones often lack the level of detail required for specific clinical situations. Therefore, evidence and consensus based recommendations for the use of MTX in daily practice would be of great value.

Developing practical recommendations for clinical problems is exactly the aim of the 3E initiative (evidence, expertise and exchange) in rheumatology, which is a multinational effort to promote evidence-based medicine. After a first edition on the management of ankylosing spondylitis, the use of MTX in rheumatic disorders was the central theme in the edition of 2007–2008 [15,16]. A large group of rheumatologists from 17 countries participated in the multistep process, which consisted of several national and international meetings. A strict methodology was followed and Delphi votes were used during the whole process to ensure a democratic outcome [17]. In a first international meeting of delegates from each country, the top ten clinical questions on the use of MTX were selected. Subsequently, fellows performed extensive systematic literature research in Medline, Embase, Cochrane and meeting abstracts, and reviewed the available evidence. Next, the results were discussed both in a joint meeting and separately in national meetings in each country, to which many rheumatologists were invited. By combining the evidence with expert opinion, each country proposed a set of recommendations, which were finally merged into ten multinational recommendations for the use of MTX (Table 1).

Nine recommendations were specific for RA, and concerned the work-up before starting MTX, the optimal dose and route, the use of folic acid, monitoring, management of hepatotoxicity, long-term safety, monotherapy versus combination therapy and management in the perioperative period and during pregnancy. One recommendation concerned MTX as a steroid-sparing agent in other rheumatic diseases. A detailed summary of the results can be found elsewhere, therefore, only some highlights will be given here [15]. We would like to emphasize that the recommendations are intended to provide guidance for clinical decision making and that

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Table 1. Multinational recommendations for the use of methotrexate in rheumatoid arthritis and other rheumatic disorders.

Recommendation	Level of evidence	Grade of recommendation	Agreement mean (SD)
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)
Oral MTX 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 case of inadequate clinical response or intolerance	2b	B	7.8 (2.6)
Prescription of at least 5 mg folic acid per week with MTX therapy is strongly recommended	1a-	A	7.5 (2.7)
When starting MTX 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)
MTX should be stopped if there is a confirmed increase in ALT/AST more than three-times the ULN, but may be reinstituted at a lower dose following normalization. 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)
Based on its acceptable safety profile, MTX is appropriate for long-term use	2b	B	8.7 (1.9)
In DMARD naive patients the balance of the efficacy/toxicity favors 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)
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)
MTX can be safely continued in the perioperative period in rheumatoid arthritis patients undergoing elective orthopaedic surgery	1b	B	8.8 (1.9)
MTX should not be used for at least 3 months prior to planned pregnancy for males and females, 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; MTX: Methotrexate; SD: Standard deviation; ULN: Upper limit of normal.

they are not prescribing. Furthermore, application should always be made in light of individual patient characteristics and circumstances.

A profound evidence base was found for the optimal dosing strategy of MTX, the use of folic acid, monotherapy versus combination therapy and the long-term safety of MTX. The results showed that to obtain higher clinical efficacy, higher starting doses of MTX (>10–15 mg/week) should be used and the dose should be rapidly escalated (with 5 mg every 2–4 weeks) to a maximum of 25–30 mg/week [18]. In addition, folic acid in a dose of at least 5 mg/week is strongly recommended, as in a meta-analysis it was shown to significantly reduce gastrointestinal and liver toxicity, without interfering with efficacy [19]. A number of studies have found that DMARD combination therapies including prednisone or anti-TNF are superior to monotherapy in patients with recent-onset RA [20,21]. However, for the combination of conventional DMARDs (without prednisone) versus MTX monotherapy, findings from a large meta-analysis only suggest a significant advantage for patients who already failed on previous MTX therapy and not for DMARD-naive patients [22]. Only the triple combination of MTX, sulphasalazine and hydroxychloroquine showed a better efficacy:toxicity ratio. In addition to the well-established efficacy of MTX, there is also substantial evidence for its acceptable safety profile [23,24]. For the remaining topics, the evidence was more limited or even absent. Regarding the use of MTX during elective orthopaedic surgery, three trials suggest that continuation of low-dose MTX is safe, as it resulted in equal or less post-operative complications and RA flares in comparison with stopping MTX [25]. A review of six databases/surveys suggests an increased risk for miscarriages and congenital malformations if MTX is used during pregnancy [15]. No evidence was found for what the general recommendation should be, how to screen and monitor exactly and at which time interval to prevent severe toxicity in patients treated with MTX.

The availability of data determines both the strength and the weakness of evidence-based approaches such as 3E. As outlined above, for several areas, evidence from high-quality RCTs was found and even meta-analyses could be performed. By contrast, for other topics no data were available. Further limitations of identified studies included the lack of uniform outcome measures, under-reporting of data that are needed for statistical pooling (such as standard deviations), the absence of correction for confounders or wrong study designs. In addition, the retrospective nature of reviewing the literature can bring along difficulties. Several studies were old, addressing long-standing RA patients, who received low dosages of MTX, without folic acid supplementation. This obviously does not reflect current practice and might hamper translation of the results to the present time.

However, identifying gaps in the literature can also present new research opportunities. For example, future follow-up studies in which MTX is used in higher dosages might reveal new safety data, while adjusting for confounding. Trials evaluating (also nonorthopedic) surgery with higher dosed MTX, are needed to complement the data on perioperative management of MTX. A randomized trial evaluating low- versus high-dosed folic acid with higher dosed MTX might clarify the observation that folic acid did not significantly reduce gastrointestinal toxicity with MTX higher than 10 mg/week. Additional still unanswered questions include the need for regular monitoring of liver enzymes and the possibility of tapering the dose of MTX. In summary, irrespective of the outcome, systematic literature review is a crucial part of evidence-based approaches such as 3E.

> *"...in the 3E initiative a total of 751 practicing rheumatologists from 17 countries were involved."*

The second essential feature is the interpretation of the available evidence by professionals in the field against their own experience and expertise. In that respect, the 3E initiative has several unique characteristics, distinct from other collaborative projects in rheumatology. First, by contrast to limited panels of experts, in the 3E initiative a total of 751 practicing rheumatologists from 17 countries were involved. Second, rheumatology fellows in training were invited to participate, giving them the opportunity to experience a large research project, meet international colleagues and learn how to perform systematic literature research. Furthermore, experienced epidemiologists were involved in all stages and all participants were updated on how to read, verify and value published evidence. Finally, the unique multistep approach led to the challenge of merging the evidence and expert opinion into multinational recommendations, which are as a result broadly supported on both a national and international level.

The success of 3E is illustrated by the ongoing collaboration and activities. In meetings of national and international rheumatologic societies, the recommendations are being promoted.

To measure the potential impact on clinical practice, questionnaires have been sent out to a large number of rheumatologists in each country to evaluate their practice before and after the introduction of the recommendations. Depending on the country, the next step will be the development or revision of national guidelines on the use of MTX. Furthermore, the number of participating countries is still growing and a third edition of the initiative is currently being undertaken, evaluating a new interesting topic; early inflammatory undifferentiated arthritis.

In conclusion, we would like to encourage multinational collaborations like 3E, also in other fields than rheumatology, as they are a perfect means to promote evidence-based medicine, with the potential of changing clinical practice on a large scale. Like MTX has stood the test of time, we hope initiatives such as 3E will do so too.

Acknowledgements

We would like to thank Prof. Claire Bombardier, Prof. Loreto Carmona, Dr Wanda Katchamart, Dr. Estibaliz Loza, Dr Juan Antonio Martinez-Lopez, Dr Carine Salliot and Dr Judith Trudeau for their extensive work in reviewing all the data; all rheumatologists who participated in the international and national meetings; and Margaux Orange for the technical support.

Financial & competing interests disclosure

The 3E Initiative was supported by Abbott with an unrestricted educational grant. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Bibliography

1 Klareskog L, Catrina AI, Paget S: Rheumatoid arthritis. *Lancet* 373(9664), 659–672 (2009).

2 Grassi W, De Angelis R, Lamanna G, Cervini C: The clinical features of rheumatoid arthritis. *Eur. J. Radiol.* 27(Suppl. 1), S18–S24 (1998).

3 Allaire S, Wolfe F, Niu J, Lavalley MP: Contemporary prevalence and incidence of work disability associated with rheumatoid arthritis in the US. *Arthritis Rheum.* 59(4), 474–480 (2008).

4 Naz SM, Symmons DP: Mortality in established rheumatoid arthritis. *Best. Pract. Res. Clin. Rheumatol.* 21(5), 871–883 (2007).

5 Welsing PM, van Gestel AM, Swinkels HL, Kiemeney LA, van Riel PL: The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. *Arthritis Rheum.* 44(9), 2009–2017 (2001).

6 Grigor C, Capell H, Stirling A *et al.*: Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 364(9430), 263–269 (2004).

7 van der Kooij SM, Goekoop-Ruiterman YP, de Vries-Bouwstra JK *et al.*: Drug-free remission, functioning and radiographic damage after 4 years of response-driven treatment in patients with recent onset rheumatoid arthritis. *Ann. Rheum. Dis.* 68(6), 914–921 (2009).

8 Williams HJ, Willkens RF, Samuelson CO Jr *et al.*: Comparison of low-dose oral pulse methotrexate and placebo in the treatment of rheumatoid arthritis. A controlled clinical trial. *Arthritis Rheum.* 28(7), 721–730 (1985).

9 Weinblatt ME, Kaplan H, Germain BF *et al.*: Methotrexate in rheumatoid arthritis. A five-year prospective multicenter study. *Arthritis Rheum.* 37, 1492–1498 (1994).

10 Hoffmeister RT: Methotrexate therapy in rheumatoid arthritis: 15 years experience. *Am. J. Med.* 75(6A), 69–73 (1983).

11 Aletaha D, Stamm T, Kapral T *et al.*: Survival and effectiveness of leflunomide compared with methotrexate and sulfasalazine in rheumatoid arthritis: a matched observational study. *Ann. Rheum. Dis.* 62(10), 944–951 (2003).

12 Combe B, Landewe R, Lukas C *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.* 66(1), 34–45 (2007).

13 Pope JE, Hong P, Koehler BE: Prescribing trends in disease modifying antirheumatic drugs for rheumatoid arthritis: a survey of practicing Canadian rheumatologists. *J. Rheumatol.* 29(2), 255–260 (2002).

14 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.* 22(5), 829–835 (1995).

15 Visser K, Katchamart W, Loza E *et al.*: 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.* doi:10.1136/ard.2008.094474 (2008) (Epub ahead of print).

16 Sidiropoulos PI, Hatemi G, Song IH *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)* 47(3), 355–361 (2008).

17 van Tulder M, Furlan A, Bombardier C, Bouter L: Updated method guidelines for systematic reviews in the Cochrane collaboration back review group. *Spine* 28(12), 1290–1299 (2003).

18 Visser K, van der Heijde D: Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature 3. *Ann. Rheum. Dis.* doi:10.1136/ard.2008.092668 (2008) (Epub ahead of print).

19 Katchamart W, Ortiz Z, Shea B, Tugwe P, Bombardier C: Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis: an update systematic review and meta-analysis. *Arthritis Rheum.* 58(9), S473–S473 (2008) (Abstract).

20 Mottonen T, Hannonen P, Leirisalo-Repo M *et al.*: Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. *Lancet* 353(9164), 1568–1573 (1999).

21 Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF *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.* 58(Suppl. 2), S126–S135 (2008).

22 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 meta-analysis. *Ann. Rheum. Dis.* doi:10.1136/ard.2008.099861 (2008) (Epub ahead of print).

23 Salliot C, van der Heijde D: Long term safety of methotrexate monotherapy in rheumatoid arthritis patients: a systematic literature research. *Ann. Rheum. Dis.* doi:10.1136/ard.2008.093690 (2008) (Epub ahead of print).

24 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.* 58(9), S557 (2008) (Abstract).

25 Loza E, Lopez JAM, Carmona L: Is methotrexate safe in the perioperative period in rheumatoid arthritis patients? *Arthritis Rheum.* 58(9), S735 (2008) (Abstract).