National recommendations based on scientific evidence and opinions of experts on the use of methotrexate in rheumatic disorders, especially in rheumatoid arthritis. Results of the 3E Initiative from Brazil

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ABSTRACT

Objectives: The use of methotrexate (MTX) has been the basis for rheumatoid arthritis (RA) therapy, but there is no uniformity on the guidelines for its clinical use. The objective of this study was to develop recommendations based on scientific evidence and opinions of experts on the use of MTX, which will allow the improvement of our clinical practice. **Methods**: 3E (Evidence, Expertise, Exchange) Initiative in Rheumatology is a multinational group of rheumatologists from 17 countries, including Brazil. After a selection of 10 questions about the use of MTX, held by the Delphi method, a systematic literature review (SLR) was done (Medline, Pubmed, Embase, Cochrane, Abstracts EULAR 2005-2007 and ACR 2006-2007) by six international bibliographic reviewers chosen by the mentors of the 3E study. Two other different national questions from Brazil were also included, and the SLR was done by a national bibliographic reviewer.** The results of SLR were presented by 7 members of our Brazilian 3E scientific committee* at a meeting of 48 rheumatologists, which discussed RSL details, voted, and produced the national recommendations presented here. These recommendations were subsequently used in the creation of multinational recommendations. **Results and conclusions**: 21 recommendations concerning the 10 international and the 2 national questions were formulated, with an agreement level of 77% among the participants (63-100%). Oral MTX should be started at a minimum dose of 10 mg/wk and a maximum dose of 25 mg/wk. Elevation of AST/ALT above 3x the upper limit, for at least 3 times consecutively, justifies the temporary suspension of MTX, which can be restored after normalization of serum liver enzyme levels; MTX is safe for long term use. The use of alcohol (100 g/wk) should be avoided. Combinations of MTX with disease modifying antirheumatic drugs are recommended, although there is risk of greater toxicity. Folic acid should be associated with MTX in dose higher than 5 mg/wk. Total blood cell count, creatinine, AST/ALT, serology for hepatitis B and C virus, and chest X-ray should be ordered before initiating MTX. Inquire about contraception methods, comorbidities, use of

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illicit drugs, alcohol, and liver diseases and hepatotoxic drugs should be performed. The MTX can be maintained during elective surgeries; discontinuation of MTX for at least 3 months before planning of pregnancy is suggested, for both men and women Use of contraception method is justified with the use of MTX in reproductive age. MTX can be used to reduce the cumulative dose of corticosteroid in patients with giant cell arthritis, rheumatic polymyalgia (RPM), juvenile dermatomyositis, and in systemic lupus erythematosus (SLE) with cutaneous or joint involvement.

Keywords: rheumatoid arthritis, methotrexate.

INTRODUCTION

Although many algorithms have been created for treatment guidance in different rheumatic conditions, they were generally prepared by a small number of specialists involved in subcommittees, therefore, not reflecting the opinion of the majority.[1] Another problem is that the published algorithms often do not address specific problems related to some common questions in our daily clinical practice.

The MTX has been widely used in rheumatic diseases especially in patients with RA, psoriasis, and psoriatic arthritis extensive. Other clinical conditions of its use include patients with SLE, RPM, giant cell arthritis and other vasculitis. Despite the frequent use of this medication in several already mentioned diseases for about two decades, there are many doubts about its use, particularly about the initial and maintenance doses, safety of long-term use, reasons for the suspension of the applicability and efficacy in other diseases. The absence of specific guidelines on the use of MTX in RA encouraged the 3E multinational group of rheumatologists, from 17 countries including Brazil, to make recommendations on the subject. The 3E group objective is to allow that the suggested recommendations reflect, after extensive discussion and vote, the opinion of many rheumatologists from different countries who formulate the recommendations after awareness of the evidence already presented.[2] Other objectives of the 3E group are to discuss the differences between countries in the creation of these recommendations, and also to promote the dissemination of epidemiology basic concepts in the rheumatologist community. Specifically in this study, the main objective was to create recommendations on the use of methotrexate in patients with RA and other rheumatic diseases.

METHODS

The national recommendations presented here were presented by 48 Brazilian rheumatologists. This work is part of a broader study of the multinational recommendations elaborated by 751 rheumatologists.[3] The selection of participants in the national meeting was based on technical criteria, which included interest, knowledge and clinical practice in the chosen theme: "Use of MTX in RA and other rheumatic diseases". Finally, the selection included rheumatologists with heterogeneous clinical activity, some with more clinical activity with assistance care and others with academic activities. The final drafting of the recommendations presented in this national study was done after the participation of the members of the 3E scientific committee of Brazil* in two previous international scientific meetings, along with members of other committees of 16 countries, with the study coordinator and three mentors of the international scientific study. In the first international meeting, each participating country presented, on average, ten relevant points to be discussed on the subject, totalizing 179 questions, which were voted to choose the most relevant points that must be discussed. The result of the first international meeting was the selection of ten questions (Table 1) which were divided between six international bibliographic auditors. They performed a systematic literature review (SLR) based on the updated guidelines of the Cochrane Collaboration (Table 2).[4] The SLR started by transforming the questions into epidemiological sentences that could be researched, and it was based on the PICO method (population, interventions, comparisons, outcomes). The databases EMBASE, Cochrane Library and MEDLINE were used to collect the articles. The study research presented in the EULAR Congress in 2005-2007 and also 2005-2006 ACR was included in the SLR. Statistical tests were calculated for each question, including range of treatment effect, probability relations, and relative risk with 95% confidence intervals (CI). When possible, meta-analysis was conducted using RevMan 4.2.10. The methodological quality of each study was classified according to the levels of the Oxford Center for Evidence-based medicine (http://www.cebm.net/index.aspx?o=1025).[5]

In a second international meeting, the SLR were presented to members of different country committees by the international bibliographic auditors and, from then on, national meetings were organized in different countries. In a second international meeting, the SLRs were presented to

Table 1
Relevant issues on the use of MTX in RA and other rheumatic diseases

1	What is the best dose strategy and route of administration to MTX in RA to optimize a rapid clinical and radiographic response and minimize the toxicity?
2	What are the indications for temporary or permanent discontinuation, or to restart MTX in case of elevated liver enzymes, and when indicate a liver biopsy?
3	What is the long term safety of MTX, considering cardiovascular complications, cancer, infections and change in the liver function?
4	What is the difference between combined *versus* MTX monotherapy in terms of efficacy and toxicity in RA?
5	Is the supplementation of folic acid/folinic useful in patients with MTX to reduce the toxicity? What is the most effective treatment?
6	What is the optimal monitoring of patients with MTX (clinical, laboratorial and image)? What is the time interval?
7	What initial assessment is necessary (comorbidities/ living habits, physical, radiographic and laboratory examinations) as baseline parameter and to exclude patients who should avoid the use of MTX?
8	What is the best approach in patients with rheumatic diseases in the use of usual doses of MTX in the perioperative period to reduce morbidity and, at the same time, keep RA under control?
9	How to use MTX in pregnancy planning (both male in female patients); during pregnancy period, and after pregnancy (lactation)?
10	Is MTX effective as a corticosteroid sparing treatment (adjuvant) in chronic inflammatory rheumatic diseases, such as RPM, SLE, vasculitis, polymyositis and dermatomyositis?
11	Is it safe to use MTX in RA patients with mild interstitial lung involvement?
12	What is the efficacy and safety of vaccination and other immunizations in RA patients receiving MTX?

members of different country committees, and from then on, national meetings were organized in different countries. In Brazil, two important questions had not been selected among the 10 selected multinational questions chosen in the first international meeting, and similarly to other countries, these questions were surveyed by a national bibliographic auditor and presented with the multinational questions in this national meeting. One of the two national questions was about the "safety of MTX use in RA patients with lung involvement", and the other was about safety and effectiveness of vaccines in RA patients receiving MTX.

At the national meeting held in Brazil, the SLR was presented to three small discussion groups, and so different recommendations were suggested by the participants. At the final stage of the meeting, suggestions were voted by Delphi system and selected in a plenary session. The level of agreement between the voted recommendations was also recorded.

Table 2
Classification of scientific evidence in systematic literature reviews

Quality	Type of evidence
1	A: systematic review of RCTs B: individual RCT with narrow CI C: series of cases "all or nothing"
2	A: systematic review of cohort studies B: individual cohort studies. RCT with drop outs > 20% C: ecological studies
3	A: systematic review of control cases B: individual case control
4	Series of cases
5	Expert's opinion

RCT: randomized clinical trial. Adapted from *Levels os evidence of the Oxford Centre for Evidence-Based Medicine.*

RESULTS

During the study, SLRs analyzed 319 articles in a search of 17,337 references found, and these SLRs formed the basis for the vote on the national recommendations. The level of agreement for the recommendations in the national meeting among the participants ranged from 63% to 100%.

Below are listed the 12 questions with their recommendations, and the SLR data submitted by the bibliographic auditors:

1) What is the best dose strategy and route of administration to MTX in RA to optimize a rapid clinical and radiographic response and minimize the toxicity?

The original recommendation for the initial administration is orally, considering the parenteral route in intolerance and ineffectiveness (83% agreement). It is recommended as a minimum initial dose of MTX 10 mg/wk, and maximum dose of 25 mg/wk (88% agreement).

For this question, 1,748 publications were found and 38 were of interest for analysis.

The level of evidence reached was 2b for the SLR presented. We highlighted some of the most important studies, such as Fürst *et al.*, which in an analysis of RA patients not previously users of MTX compared the dose-effect relationship between different oral doses of MTX: 5-10 mg/wk, 12.5-20 mg/wk and 25-35 mg/wk. MTX 12.5-20 mg/wk had a significantly greater effect than placebo in the count of painful joints (ES = 1:08 [0.35-1.81]), assessment of pain (ES = 0.92 [0.21-1.64]) and the overall state (ES = 1:58 [0.80-2.37]), while MTX 5-10 mg/wk only had a significantly higher effect than placebo in pain and in the overall state (ES = 0.81 [0.05-1.57] and 1:26 [0:46 to 2:06]), respectively. In this study, a dose/toxicity relationship was seen, with the highest toxicity observed in the group with

25-35 mg/wk.[6] Schnabel *et al.* compared oral doses of MTX 25 mg/wk *versus* 15 mg/wk in patients with established RA. In this study, the doses of 25 mg/wk were associated with higher incidence of gastrointestinal events but no more suspension due to toxicity when compared with 15 mg/wk. On the other hand, in the higher dose group compared with the lower dose group, 3% *versus* 27% required to increase the dose by inefficiency.[7] Verstappen *et al.* demonstrated in patients with initial RA without previous use of DMARDs that beginning with MTX 7.5 mg/wk, with an increase of 5 mg/month up to 25 mg/wk, resulted in greater clinical efficacy, but with more adverse effects than increasing the dose by 5 mg every 3 months.[8] Lambert *et al.* showed that the use of MTX intramuscularly (IM) scaled from 15 to 45 mg/wk was not superior to placebo IM in patients who were previously receiving oral MTX 15-20 mg/wk.[9] Braun *et al.* compared subcutaneous *versus* oral administration of MTX 15 mg/wk in patients with recent onset of RA who had not previously used MTX. The clinical efficacy was higher with the parenteral use but there was a higher discontinuation of medication due to toxicity.[10]

2) What are the indications for temporary or permanent discontinuation, or to restart MTX in case of elevated liver enzymes, and when indicate a liver biopsy?

Increase in three consecutive measurements of liver enzymes above three times the upper limit of normal value justifies the temporary suspension of MTX (67% agreement). MTX can be restored in the normalization of liver enzymes (72% agreement). The level of evidence for the SLR presented was 2b.

With regard to altered liver enzymes and liver biopsy in RA patients, there are 426 references identified, of which 46 are items included in SLR. Accumulate data from 2,062 RA patients showed enzymatic changes in at least one occasion in 48.9% of MTX users after an average follow-up of three years. In this study, the incidence of altered liver enzymes was less frequent with longer duration of MTX use, and the continuation rates (despite the elevation of liver enzymes), dose reduction, and permanent discontinuation were 71%, 22% and 7%, respectively.[11]

Studies show that the lack of folic acid and the presence of obesity increases the chance of high liver enzymes levels.[12,13] On liver biopsy, a study of 1,113 RA patients showed the prevalence of mild fibrosis, severe fibrosis, and cirrhosis in 15%, 1%, and 0.5%, respectively, after an average follow-up of 4.1 years.[11]

It is important to report that liver biopsies performed in 372 of these patients before the introduction of MTX had already demonstrated the presence of mild fibrosis in 9% and cirrhosis in 0.3%. Another relevant data found in the SLR is that repeated liver biopsies in 689 patients showed progression of normal findings to mild fibrosis in only 6% of the patients, and there was no case of progression to cirrhosis.[11] Risk factors for abnormal liver biopsy include older age, long duration of the disease, obesity, and higher cumulative dose of MTX.[14] A follow-up study of 3 years, conducted with 69 patients with psoriatic arthritis taking MTX, demonstrated the presence of elevated liver enzymes above 3 times the upper limit of normal value in 14.5%, and 40% had to discontinue medication.[15] Espinoza *et al.* reported the presence of abnormal liver enzymes in 27.5% of forty patients with psoriatic arthritis taking MTX. Note that, in all of them, there was normalization of the levels previously changed.[16]

3) What is the long-term safety of MTX: cardiovascular, cancer, infections and liver?

The security profile is acceptable for long term use in RA patients, with the recommended monitoring (69% agreement). The use of alcohol (> 100 g/wk) is not recommended in RA patients receiving MTX (90% agreement).

There have been 2,449 studies raised, and 88 of them were analyzed. The level of evidence found for this question was 2b.

From the safety standpoint in the long-term use of MTX, a cohort of 1,240 RA patients showed that the use of MTX was associated with lower mortality from all causes, cardiovascular and non-cardiovascular (OR = 0.4 [0.2 - 0.8], 0.3 [0.2-0.7] and 0.6 [0.2-1.2], respectively.[17]

In a case-control study, van Halm *et al.* showed that RA patients receiving MTX had a risk of cardiovascular disease significantly reduced (OR = 0.11 [0.02-0.56, 95% CI]).[18]

Although RA patients have a higher risk of lymphoma compared with the general population, the evidence on the risk with the use of MTX independent of AR is not conclusive.[19,20]

The long term use of MTX is not associated with the increase of the risk of serious infections (HR = 0,91 [0,57-1,45]), including herpes zoster (HR = 1.0 [0,8-1, 3]).[21,22]

4) What is the difference between combined MTX *versus* monotherapy in terms of efficacy and toxicity in RA?

It is recommended the combination of MTX with other antirheumatic drugs due to its greater effectiveness (63% agreement). Certain combinations of MTX with DMARDS present greater possibility of toxicity (69% agreement).

The presented SLR has evidence level of 1a-.

Study addressing the combination of other DMARDs with MTX *versus* MTX monotherapy showed significant advantage in combining those previously not responsive to MTX alone,

but only one ACR 70 response and a tendency to moderate EULAR response, and remission in those who had not used any DMARDs including MTX.[23] Among various combinations, the one which include sulfasalazine and MTX demonstrated better efficacy/toxicity relation compared with the use of MTX or sulfasalazine alone.[24] The addition of leflunomide combined with MTX in RA patients not responsive to MTX monotherapy has improved efficiency, but discretely increased the risk of toxicity.[25] The risk of toxicity is more significant with combinations that include DMARDs, such as cyclosporine or azathioprine, with the anchor drug combinations of DMARDs, which preferably should be MTX.

5) Is the supplementation of folic acid/folinic useful in patients with MTX to reduce toxicity? What is the most effective?

Folic acid should be associated in all patients who start MTX in doses higher than 5 mg/wk (81% agreement).

SLR found 303 studies, and four of them were analyzed. The level of evidence found was 1a-.

On this issue, a meta-analysis of nine studies including 788 RA patients suggests that supplementation of folic acid reduces the liver and gastrointestinal toxicity of MTX without reducing its effectiveness.[13]

Four studies with high dose of folic acid (> 5 mg/wk) showed benefit in reducing gastrointestinal toxicity from the use of MTX in RA.[27-30] Other evidence found by the SLR is that the use of low dosage folic acid and folinic acid does not interfere with the disease activity. Contrarily, the use of high doses of folinic acid was correlated with an increase in the number of sensitive joints and edema (OR = 6.26 [1.64-10.9] and OR = 5.3 [0.03 -10.58]), respectively.[31]

The use of folic acid can be done in daily practice once or twice a week, about 10 mg, preferably in the days following the use of MTX, although we have not set the dose upper limit in this study.

The use of folic acid can be done in a daily practice once or twice a week, at a dose of 10 mg, preferably in the days following the use of MTX, although we have not set the dose upper limit in this study.

6) What is the optimal monitoring of patients with MTX (clinical, laboratory and image)? What is the time interval?

When MTX is started, the minimum monitoring must be done every 4-12 weeks with dosages of AST, ALT, creatinine, complete blood count (73% agreement).

The level of evidence of the SLR was 2b.

The 1994 guidelines of the American College of Rheumatology (ACR) for monitoring the hepatotoxicity showed 80% of sensitivity and 82% of specificity in AST abnormal serial tests for the detection of fibrosis or cirrhosis.[32,33] The national recommendations and the 1996 ACR guidelines suggest examinations every one to three months with more frequent evaluations in the initial phase.[34,35]

7) What initial assessment is necessary (comorbidity/life habits, physical, radiographic and laboratory exams) as a baseline parameter and criteria to exclude those who should avoid MTX? We should perform complete blood count, creatinine, AST/ALT, hepatitis B and C virus serology and chest X-ray before initiating MTX (79% agreement).

An inquire about contraception, comorbidities, use and abuse of illicit drugs and alcohol, liver disease, hepatotoxic drugs before initiating MTX should be done (100% of agreement).

In the SLR, 1,214 studies were collected, 52 of them were analyzed. Level of evidence: - 4.

Evidence suggests that creatinine clearance below normal increases the chance of pulmonary toxicity and that the presence of hypoalbuminemia is associated with higher chance of hepatotoxicity, thrombocytopenia and pulmonary toxicity.[36,37] Moreover, abnormal pulmonary radiography, but not abnormal pulmonary function, is predictive of MTX-induced pneumonitis.[38,39]

National recommendations of various countries and guidelines of 1996 ACR for monitoring RA treatment indicate the need for tests of creatinine, complete blood count, AST/ALT with or without alkaline phosphatase, albumin, hepatitis B/C serology and chest X-ray as routine pretreatment.

8) What is the best approach in patients with rheumatic diseases receiving usual doses of MTX in the perioperative period to reduce morbidity while maintaining control of RA?

MTX can be continued in the perioperative period, taken into consideration the disease activity, comorbidity and higher doses of corticosteroids (89% agreement).

SLR level of evidence was 1b.

Evidence suggests that continuing MTX in the perioperative period does not increase the risk of complications in elective orthopedic surgeries.[40-43]

In a study of 338 RA patients who were undergoing orthopedic surgery, 88 continued with the same dose of MTX, and 72 suspended two weeks before surgery. Patients who have continued MTX showed no disease reactivation, as opposed to 8% of those who discontinued MTX ($P < 0.001$); on the other hand, there was no difference in infection rates or surgical complications.[41] In another study of Sanny *et al*., 64 RA patients who underwent orthopedic surgery were analyzed (32 patients continued MTX and 32 suspended MTX for more

than a week before surgery). There were no differences in the appearance of operative wound complications (P = 0.50),[40] and no infection was recorded in different groups. In the study by Murata *et al.*, 116 RA patients were studied, 48 continued with MTX and 12 discontinued the use for at least a week before surgery. There was no difference in the appearance of operative wound complications (P > 0.05). Furthermore, the disease reactivation was lower in the group that continued MTX (1% *versus* 14%, P = 0,020).[43]

It is suggested not to maintain MTX in the perioperative period in the presence of leucopenia or comorbidities that increase the risk of infection, such as the presence of diabetes mellitus.

9) How to use MTX in pregnancy planning? During pregnancy period, and after the pregnancy (lactation)?

It is suggested the discontinuation of MTX at least three months before pregnancy planning (88% agreement). It is recommended the immediate discontinuation of MTX in the occurrence of pregnancy (97% agreement).

MTX should not be used during lactation (87% agreement).

Contraception is justified in patients of reproductive age and receiving MTX (71% agreement).

SLR level of evidence was 4.

Regarding the use of MTX in pregnant RA patients, the evidence confirms the increased chance of miscarriage (24%) and congenital malformations (6%).[44]

10) Is MTX effective as a treatment for steroid sparing (adjuvant) in chronic rheumatic inflammatory diseases, such as RPM, SLE, vasculitis, polymyositis and dermatomyositis?

MTX can be used as corticosteroid sparing in the treatment of giant cell arthritis, RPM and juvenile dermatomyositis (100% of concordance).

MTX can be used as corticosteroid sparing agent in the treatment of SLE with skin and /or joint involvement (66% agreement).

Concerning the applicability of MTX in other rheumatic diseases, SLRs show that MTX is effective as corticosteroid sparing and as determinant in the lower chance of recurrence in patients with giant cell arthritis or RPM.[45-7]

In SLE, the use of MTX determined lower activity, particularly in regard to joint and skin manifestations of the disease.[48,49] Finally, in juvenile dermatomyositis, the use of MTX allowed the use of a lower cumulative dose of prednisone but without a defined beneficial effect on the disease activity.[50]

11) Is it safe to use MTX in RA patients with interstitial lung involvement?

RA patients with mild interstitial lung involvement may use MTX, with increased vigilance recommended (68% agreement).

Initially, SLR captured 112 studies; seven of them were kept for final analysis. An open prospective study (n = 26, time of follow-up 2 years) suggests that the use of MTX in RA patients with interstitial lung disease (ILD) does not affect the pulmonary function.[51] Six retrospective studies (n = 1,799) suggest that RA patients with ILD have a greater risk of developing acute interstitial pneumonitis when using MTX.[52-57] However, these studies showed design and definition heterogeneity in the outcomes, which did not allow a quantitative analysis.

12) What are the efficacy and safety of vaccination and other immunizations in RA patients receiving MTX?

It is advisable to vaccinate RA patients receiving MTX, except vaccines containing live attenuated microorganisms, which could be considered only in special situations (72% agreement).

A total of 246 studies were selected. After exclusion criteria evaluation previously established, 8 were retained for final analysis. Four prospective open studies (n = 615) that evaluated vaccine against influenza,[58-61] and two prospective open studies (n = 258) that evaluated vaccine against hepatitis B,[62,63] suggest that these vaccines are effective and do not affect disease activity in RA patients receiving MTX. Two prospective open studies (n = 77) suggest that the *pneumococcus* vaccine is safe but has less effect in that population compared to RA patients in other treatments and healthy controls.[64,65] There are no studies on the use of vaccines with live attenuated microorganisms in this population.

DISCUSSION

This is the first Brazilian study on recommendations based on expert's opinions and scientific evidence on the use of MTX in RA patients with other rheumatic diseases. One of the interesting points of this study is the methodology for making such suggestions, which allowed experienced physicians on the long term use of MTX to formulate each sentence of the 21 recommendations, after knowing all the studies surveyed by the SLR. In this study, other relevant data is that we had a high degree of agreement on the recommendations suggested.

The topics on the use of MTX allows to affirm the proper degree of safety in the long term use of MTX, provided they make not only a baseline assessment, but also an adequate periodic monitoring with the laboratory tests suggested in this study.

An important contribution of this study is the safety demonstrated in the use of higher initial doses of MTX. Moreover, there is a better efficiency of the fast spreading of doses in RA patients.

Also important were the recommendations on the national questions that demonstrate the use of the MTX in RA patients without severe pulmonary involvement, provided that appropriate supervision is made for the possibility of acute pneumonitis occurrence. Another recommendation on the national question confirms the safety and efficacy of vaccination for influenza, *pneumococcus* and hepatitis B.

Finally, the national recommendations suggested by us are similar to those developed later in the final meeting of the 3E multinational study (free access to the site of Annals of the Rheumatic Diseases, website http://ard.bmj.com/cgi/rapidpdf/ ard.2008.094474v1), thus demonstrating the important role of Brazilian rheumatologists in the preparation of those recommendations.

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