Portuguese recommendations for the use of methotrexate in rheumatic diseases – 2016 update

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ABSTRACT

Background: Methotrexate (MTX) is the first-line drug in the treatment of rheumatoid arthritis (RA) and the most commonly prescribed disease modifying anti-rheumatic drug. Moreover, it is also used as an adjuvant drug in patients under biologic therapies, enhancing the efficacy of biologic agents.

Objectives: To review the literature and update the Portuguese recommendations for the use of MTX in rheumatic diseases first published in 2009.

Methods: The first Portuguese guidelines for the use of MTX in rheumatic diseases were published in 2009 and were integrated in the multinational 3E Initiative (Evidence Expertise Exchange) project. The Portuguese rheumatologists based on literature evidence and consensus opinion formulated 13 recommendations. At a national meeting, the recommendations included in this document were further discussed and updated. The document resulting from this meeting circulated to all Portuguese rheumatologists, who anonymously voted online on the level of agreement with the updated recommendations.

Results: Results presented in this article are mainly in accordance with previous guidelines, with some new information regarding hepatitis B infection during MTX treatment, pulmonary toxicity monitoring, hepatotoxicity management, association with hematologic neoplasms, combination therapy and tuberculosis screening during treatment.

Conclusion: The present recommendations combine scientific evidence with expert opinion and attained desirable agreement among Portuguese rheumatologists. The regular update of these recommendations is essential in order to keep them a valid and useful tool in daily practice.

Keywords: Recommendations; Rheumatoid arthritis; Portugal; Rheumatic diseases; Methotrexate

INTRODUCTION

Methotrexate (MTX) is the first line drug in the treatment of rheumatoid arthritis (RA) and the most commonly prescribed conventional synthetic disease modifying anti-rheumatic drug (csDMARD). Moreover, it is also used as an adjuvant drug in patients under biologic therapies, enhancing the efficacy of biologic agents[1].

According to Rheumatic Disease Portuguese Register (Reuma.pt) annual report, in 2015 only 7.35% of the rheumatoid arthritis patients were treated with biologics in monotherapy. MTX was administered to 76.2% of the rheumatic patients registered in Reuma.pt[2].

The multinational 2007-2008 3E Initiative (Evi-

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dence Expertise Exchange) included rheumatologists from 17 countries who worked on recommendations for the management of MTX use in several clinical scenarios[3]. Therefore, its main objective was to develop practical recommendations for the use of MTX in rheumatic diseases, integrating systematically generated evidence and expert opinion of a broad panel of international rheumatologists. The guidelines were published in 2009, providing a total of 10 recommendations[3].

Within this effort, the Portuguese delegates elected three relevant questions for their practice, which were not covered by the multinational recommendations. It was performed a systematic literature review regarding these questions, in agreement with the 3E Initiative project and procedures[4,5].

The Portuguese recommendations for the use of MTX were published in 2009 with 13 recommendations, including the 10 international recommendations (with specific aspects considering the Portuguese context) and three additional national recommendations[4].

This article presents the 2016 update of the Portuguese recommendations for the use of MTX in rheumatic diseases.

METHODS

We performed a comprehensive search for systematic literature reviews (SLR) and meta-analysis published after 2007 (after the original international SLR and the additional Portuguese SLR). The search strategies were designed to be broad enough to cover studies addressing all the recommendations questions.

We searched Medline (until 10 August 2015), Embase (until 10 August 2015) and Cochrane (until 18 August 2015) databases.

The inclusion criteria for SLR were: SLR/ meta-analysis addressing efficacy and/ or safety of MTX (alone or in combination with other csDMARDs) in adult patients with RA, psoriatic arthritis (PsA) or other rheumatic diseases, namely polymyositis (PM)/dermatomyositis (DM), polymyalgia rheumatic (PMR), systemic lupus erythematous (SLE) and vasculitis. The exclusion criteria for SLR were inadequate type of article (reviews that were not systematic, editorials, conference abstracts or opinion papers were not included to avoid duplicate information); wrong population (not a rheumatic disease) or intervention (not MTX alone or in combination with other csDMARD); and languages (other than English or Portuguese).

The references of the included studies were submitted to detailed review and screened for studies related to each of the 13 questions. We performed a complementary hand search for each question.

Furthermore, the new evidence was graded according to the *levels of evidence of the Oxford Centre for Evidence-Based Medicine*[6] and compared to the previous level of evidence.

The Portuguese rheumatologists based on literature evidence and consensus opinion formulated these recommendations. A draft and respective supporting evidence was first circulated to all Portuguese rheumatologists. Secondly, at a national meeting, the recommendations were presented, discussed and revised. Finally, the document resulting from this meeting was again circulated to all Portuguese rheumatologists, who anonymously voted online on the level of agreement with the recommendations (total of 79 participants). Agreement was measured on a 10-point numerical rating scale (1=no agreement, 10=full agreement).

RESULTS

The flowchart for the systemic literature search and results of the selection process are presented in Figure 1.

On the first search we retrieved 1499 articles, followed by the elimination of duplicates, with 1161 articles identified. After title and abstract selection, followed by the detailed review, 45 SLR/meta-analysis were obtained. The references of the included studies identified 128 new articles, submitted subsequently to detailed review.

The articles were selected and screened according to the specific inclusion and exclusion criteria for each of the questions, with 47 articles included, after an additional hand search (Figure 1).

Table I summarizes the distribution of the included papers according to the question and respective levels of evidence, in 2009 and 2015.

RECOMMENDATIONS

Thirteen recommendations were formulated, reaching high level of agreement among Portuguese rheumatologists (Table II).

In all recommendations new information is highlighted in bold.

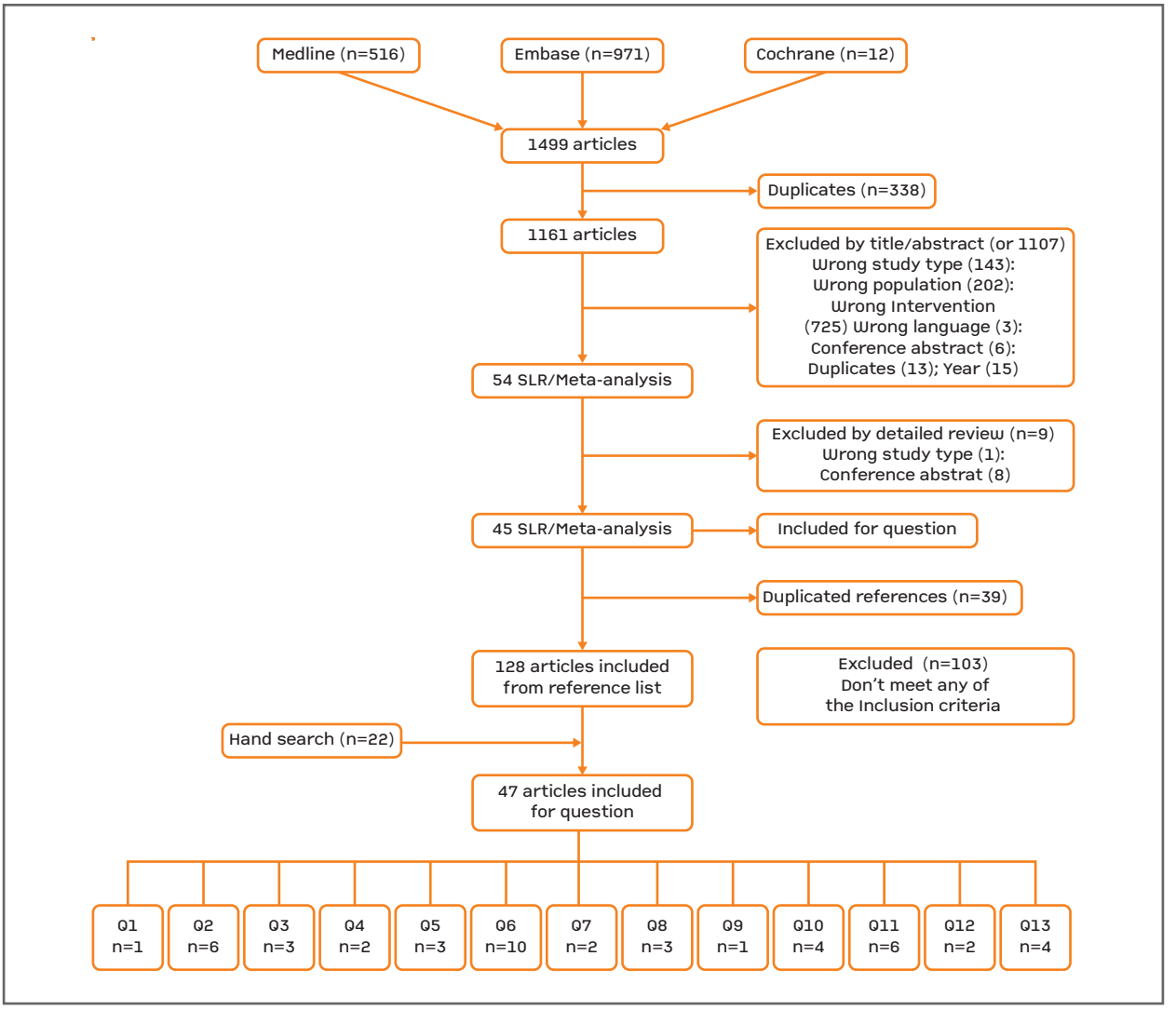

FIGURE 1. Flowchart for the systematic literature search and results of the selection process
SLR: systematic literature review

RECOMMENDATION 1

What pre-administration work-up is needed (comorbidities/ social behaviour, physical, laboratory and radiographic data) to identify MTX contra-indications and/or get a baseline evaluation?

The work-up for patients starting MTX should include patient education, clinical assessment of risk factors for MTX toxicity (including alcohol intake), levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, complete blood count (CBC), creatinine, ***serology for hepatitis B virus (HBV)****, consider serology for human immunodeficiency virus (HIV) and hepatitis C, blood fasting glucose, lipid profile, pregnancy test, chest x-ray (obtained within the previous year); and* ***body mass index (BMI).***

Screening for HBV infection and careful monitoring during the use of MTX are important because MTX can induce HBV reactivation in patients with chronic HBV infection and, possibly, also in patients with past/'resolved' HBV infection.

In early RA patients, increased ALT, AST and creatinine levels at the start of the treatment were associated with liver toxicity at follow-up[7]. Furthermore, high BMI was associated with withdrawal due to MTX-related adverse events (AEs)[7]. A case–control study[8] has shown an association between HBV reactivation and antirheumatic

TABLE I. NUMBER OF INCLUDED PAPERS AND LEVEL OF EVIDENCE IN 2009 AND 2016 FOR EACH RECOMMENDATION

Recommendation	2009 number of papers	2009 level of evidence*	2016 number of new publications	2016 level of evidence 2016¥
1. Pre-MTX workup	52	5	1	4
2. Dose and route	50	5	6	2
3. Folic acid	9	1b	3	2
4. Monitoring	23	5	2	4
5. Hepatotoxicity	46	2a	3	4
6. Long-term safety	88	2b	10	2
7. Mono vs combination	20	1b	2	1
8. Corticosteroid sparing effect	6	1b	3	1
9. Surgery	4	2b	1	2
10. Pregnancy	6	5	4	3
11. Remission	1	5	6	2
12. Infections	11	4	2	3
13. Tuberculosis	1	5	4	5
Total	317		47	

*Oxford Centre for Evidence-Based Medicine. Levels of evidence. 1995. ¥ OCEBM Levels of Evidence Working Group(6)

drugs, specifically for MTX (OR: 4.9; 95% confidence interval (CI): 3.9-6.0). Six of 92 (6.5%) HBV reactivations on patients receiving antirheumatic drugs were reported as fulminant hepatitis and among these, four (66.7%) occurred in patients treated with MTX. Nevertheless, fatal HBV cases were mostly observed in patients who received a combination of two or more csDMARDs. However, due to the lack of detailed information pertaining to antibody/antigen status prior to treatment, it is not possible to understand if HBV-reactivation occurred in patients who were HBsAg-positive or also in HBsAg-negative patients[8].

RECOMMENDATION 2

What is the best dosing strategy and route of administration of MTX in patients with RA to optimize an early response and minimize toxicity?

Oral MTX should be started at 10–15 mg/week, with escalation of 5 mg every two to four weeks up to ***25*** *mg/week, depending on clinical response and tolerability; parenteral administration should be considered in the case of inadequate clinical response or intolerance.*

Starting MTX therapy by parenteral route may be an option.

Data concerning the starting dose described in a Randomized controlled trial (RCT)[9] do not support the use of a high starting dose (25 mg) strategy for oral MTX treatment, compared to a standard starting dose (15 mg). Pharmacokinetic parameters were significantly higher with 25mg/week than with 15mg/week, but without any measurable clinical advantage. There were no differences between groups in minor and self-limited AEs, however given the small sample size (n=19), this study was not powered to detect differences in the incidence of AEs.

A two-year RCT[7,10] in early RA, comparing intensive dose escalation of 5mg/week monthly with dose escalation of 5mg/week three-monthly, has found that, in spite of the more frequently occurrence of AEs in the intensive strategy group, their severity was relatively mild and the observed clinical efficacy seemed to outweigh the toxicity profile[7]. Furthermore, the switch from oral MTX to subcutaneous (SC) was effective, when facing insufficient response, probably due to the higher bioavailability compared to oral MTX[10].

The use of SC MTX and higher maximum MTX dose (>15 mg/week) were independently associated with higher likelihood to remain on MTX monotherapy, while older age and renal failure limited the use of higher MTX maximum dosages[11]. An observational study[12] has shown that patients on parenteral therapy were younger and were more likely to have extreme

TABLE II. RECOMMENDATIONS FOR THE USE OF METHOTREXATE IN RHEUMATIC DISEASES – 2016 UPDATE

Recommendations	Level of evidence	Grade of recommendation	Agreement (0-10) mean (SD)
1. The work-up for patients starting MTX should include patient education, clinical assessment of risk factors for MTX toxicity (including alcohol intake), levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, complete blood count (CBC), creatinine, serology for hepatitis B virus (HBV), consider serology for human immunodeficiency virus (HIV) and hepatitis C, blood fasting glucose, lipid profile, pregnancy test, chest x-ray (obtained within the previous year); and body mass index (BMI). Screening for HBV infection and careful monitoring during the use of MTX are important because MTX can induce HBV reactivation in patients with chronic HBV infection and, possibly, also in patients with past/'resolved' HBV infection.	4	C	8.7 (1.7)
2. Oral methotrexate should be started at 10–15 mg/week, with escalation of 5 mg every two to four weeks up to 25 mg/week, depending on clinical response and tolerability; parenteral administration should be considered in the case of inadequate clinical response or intolerance. Starting MTX therapy by parenteral route may be an option.	2	B	8.9 (1.7)
3. Folic acid supplementation is strongly indicated for reducing GI side effects of MTX, particularly transaminases elevation, in a recommended dose of 5-10 mg in one to two doses per week. Folinic acid seems to have the same efficacy as folic acid, but with a higher cost, making it a less cost-effective treatment. There is no data regarding the ideal time interval between MTX and folic acid administration.	2	B	8.9 (1.8)
4. After four to six weeks of treatment beginning or escalation, ALT, AST, CBC and creatinine should be performed. Thereafter, if a stable dose of MTX is reached, the same analytical evaluation should be performed every three to four months. Clinical assessment should be performed at each visit. Pulmonary function tests (PFTs) are not recommended on a routine basis, neither previous to MTX-treatment start, nor during therapy.	4	C	8.8 (1.6)
5. MTX should be transiently stopped or its dose lowered if AST and/or ALT is greater than two times the upper limit of normal (ULN) in three consecutive monthly laboratorial evaluations (other causes of transaminase elevation must be ruled out). MTX can be reinstituted after transaminase levels return to normal. MTX should never be readministered to patients with clinical hepatitis without any other apparent cause, in whom transaminase levels remain persistently elevated even after MTX temporary discontinuation. Liver fibrosis is more likely in patients taking MTX if concomitant predisposing factors for hepatotoxicity are present, including diabetes mellitus, obesity and alcohol consumption. Therefore, these patients should be carefully monitored, and modifiable risk factors corrected. Treatment decision should be taken in collaboration with a hepatologist.	4	C	8.7 (1.6)

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TABLE II. *CONTINUATION*

Recommendations	Level of evidence	Grade of recommendation	Agreement (0-10) mean (SD)
6. MTX can be used for long-term treatment and its use is safe as far as risk of infectious and cardiovascular diseases is concerned. Surveillance of pulmonary toxicity and of lymphoproliferative disorders is advised.	2	B	9.1 (1.6)
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. In early RA consider implementation of a tight control and rapid step-up strategy with MTX plus low-dose PDN (≤10mg/day) for up to six months.	1	B	8.9 (1.5)
8. MTX can be considered as a steroid-sparing agent in giant-cell arteritis, PMR, SLE and juvenile DM.	1	A	9.0 (1.7)
9. Methotrexate can be safely continued in the perioperative period in RA patients undergoing elective orthopaedic surgery. Still no data regarding MTX dose management in patients undergoing (non-) elective non-orthopaedic surgery.	2	C	8.7 (2.1)
10. We recommend MTX suspension at least three months before conception, during pregnancy and breastfeeding. In men, when MTX therapy is unavoidable, there is recent evidence that MTX doesn´t need to be stopped before conception. Previous use of MTX was not associated with fertility problems in female and male RA patients, as assessed by time to pregnancy.	3	B	8.7 (1.7)
11. A gradual dose reduction to the lowest effective MTX dose may be attempted after achieving sustained clinical remission for at least 6 months, with clinical and radiological monitoring. In some early RA patients in remission, drug-free remission may be achieved, but it could be associated with an increased risk of flaring.	2	B	8.0 (2.1)
12. MTX must be withold in serious and opportunistic infections. In mild community-acquired infections, there is no evidence that MTX should be discontinued.	3	C	8.9 (1.6)
13. Screening for tuberculosis should ideally be performed in all patients with immune-mediated inflammatory diseases at diagnosis or before starting immunosuppressive therapy. Screening is based on clinical history, chest x-ray and tests for immunological memory against Mycobacterium tuberculosis (both tuberculin skin test and interferon-γ release assay). These patients must be referred to a pulmonologist and, when indicated, begin tuberculosis treatment adjusted to patients' immunosuppressive state.	5	D	8.4 (1.8

values of BMI than those on oral therapy. The response to parenteral therapy were predicted by low BMI (<22 Kg/m^2), possibly due to malabsorption, or by high BMI (>30 Kg/m^2) maybe as a result of gastrointestinal intolerance (mainly symptoms of gastro-oesophageal reflux disease) with oral therapy[12]. In RA patients who have failed to achieve an adequate response to oral MTX, as result of intolerance or resistance, the majority (74%) achieved response [decreased disease activity scores (DAS) scores by at least 1.2] after switching

to parenteral treatment, thus further supporting that parenteral MTX should be tried in all RA patients unresponsive to oral therapy prior to treatment with anti-tumor necrosis factor (anti-TNF) therapy[12].

The efficacy and safety of oral (n=187) versus SC (n=188) administration of the same dose of MTX (15 mg/week) were assessed in a six-month RCT[13] and it was found that starting SC MTX was more effective than oral administration, with ACR20 and ACR70 responses at six months significantly higher in the SC MTX group (78% versus 70% and 41% versus 33%, respectively; $p<0.05$), with no increase in side effects. Remarkably, gastrointestinal AEs were similar between the two groups.

RECOMMENDATION 3

Is folic/folinic acid supplementation to MTX useful in reducing toxicity for adult patients with RA? What is the most effective regimen?

Folic acid supplementation is strongly indicated for reducing GI side effects of MTX, particularly transaminases elevation, in a recommended dose of 5-10 mg in one to two doses per week. Folinic acid seems to have the same efficacy as folic acid, but with a higher cost, making it a less cost-effective treatment.

There is no data regarding the ideal time interval between MTX and folic acid administration.

Protective effect of folic and folinic acid is fully recognized in patients with RA treated with MTX. According to a SLR, including six RCT, folic and folinic acid are associated with a statistically significant reduction in the incidence of transaminases elevation (RR 0.19, 95% CI 0.1-0.36 and RR 0.27, 95% CI 0.16-0.44, respectively), without reducing MTX efficacy[14]. Besides, both drugs have shown a trend towards a reduction in GI side effects and stomatitis, although not statistically significant[14]. Analysis of hematologic side effects was not possible, as this outcome was poorly reported in the studies included[14]. In this SLR, no evidence of a significant difference between folic and folinic acid was found and the authors state that due to similar efficacy outcomes, folic acid lower cost makes it a more cost-effective drug[14].

Regarding folic acid dose, an inception-cohort on early RA patients starting MTX (n=347) demonstrated that supplementation with 10 mg folic acid weekly (in one to two doses) is associated with a higher hazard of GI complaints when compared to 1 mg daily (HR = 4.2 [1.25-14.13])[15]. For liver enzyme abnormalities, no significant difference was found, although a trend towards higher risk of liver enzyme abnormalities in the bi-weekly dosage group was observed[15]. In a RCT, comparing supplementation with folic acid at a 10 mg dose per week (n=51) vs. 30 mg per week (n=49) there was no additional benefit of a higher dose of folic acid, regarding the presence of undesirable symptoms (including GI), development of cytopenia and transaminases elevation[16].

RECOMMENDATION 4

What is the optimal safety monitoring of patients with MTX? How frequent should it be repeated?

After four to six weeks of treatment beginning or escalation, ALT, AST, CBC and creatinine should be performed. Thereafter, if a stable dose of MTX is reached, the same analytical evaluation should be performed every three to four months. Clinical assessment should be performed at each visit.

Pulmonary function tests (PFTs) are not recommended on a routine basis, neither previous to MTX-treatment start, nor during therapy.

Acute pneumonitis can occur at any time during MTX therapy and rheumatologists need to be constantly aware of it. Although its exact incidence is difficult to determine, it is estimated to occur in 0.3 to 8% of the MTX-treated patients[17].

Lung function screening remains a controversial issue. In a 6-month prospective study, in which spirometry was performed at the beginning of the study, patients who developed MTX pneumonitis were found to have no abnormalities at treatment baseline[17]. The main benefit from this exam was to detect patients that have comorbidities, such as chronic obstructive pulmonary disease, that further decrease pulmonary function[17]. High-resolution computerized tomography (HRCT) request was determined by clinical findings (respiratory symptoms, chest x-ray and spirometry)[17]. A SLR also concluded that changes in PFT did not predict the occurrence of MTX-induced pneumonitis and should rather be performed in patients with new onset dyspnoea to differentiate it from other clinical conditions[18].

Therefore, the diagnosis of MTX-induced lung toxicity should be based on a combination of clinical and imaging data, including the response to drug cessation. Chest x-ray and HRCT usually show diffuse interstitial infiltrates and patchy ground-glass opacities and PFTs depicts evidence of a restrictive pattern, with decreased carbon monoxide diffusing capacity[18]. Bronchoalveolar

lavage shows frequently an increase in the number of CD4 lymphocytes and CD4/CD8 ratio and is useful to rule out infection; lung biopsy is not required in most cases[18].

Lung toxicity can also be raised when MTX dosage is not adjusted to renal function. Creatinine clearance should be determined or estimated previously and during therapy, in order to perform dosage adjustment, if needed (Figure 2).

RECOMMENDATION 5

What are the indications for pausing/stopping/restarting MTX in case of elevated liver tests and when is liver biopsy indicated?

MTX should be transiently stopped or its dose lowered if AST and/or ALT is greater than two times the upper limit of normal (ULN) in three consecutive monthly laboratorial evaluations (other causes of transaminase elevation must be ruled out). MTX can be reinstituted after transaminase levels return to normal. MTX should never be readministered to patients with clinical hepatitis without any other apparent cause, in whom transaminase levels remain persistently elevated even after MTX temporary discontinuation.

Liver fibrosis is more likely in patients taking MTX if concomitant predisposing factors for hepatotoxicity are present, including diabetes mellitus, obesity and alcohol consumption. Therefore, these patients should be carefully monitored, and modifiable risk factors corrected. Treatment decision should be taken in collaboration with a hepatologist.

Liver toxicity after prolonged treatment with MTX has been extensively described and is one of the most concerning adverse effects of this therapy, although severe liver fibrosis rarely occurs[19]. In a case control-study including patients with inflammatory diseases treated with MTX (cases) and before beginning treatment (controls), liver fibrosis was evaluated by transaminases, elastography and liver biopsy (when elastography score was >7.9 kPa). The authors found that the cumulative dose of MTX did not have a significant impact on ALT elevation or elastography results[19]. Features of non-alcoholic steatohepatitis were found in 61.5% of the patients submitted to liver biopsy, irrespective of the MTX cumulative dose, and only two had chronic liver disease lesions associated with mild fibrosis (one case and one control)[19].

Creatinine clearance (ml/min)	% of dose to administrate
≥60	Full-dose
46-60	65
31-45	50
≥30	Avoid use

FIGURE 2. MTX dose adjustment according to creatinine clearance. (Adapted from Kintzel PE and Dorr RT, "Anticancer Drug Renal Toxicity and Elimination: Dosing Guidelines for Altered Renal Function", *Cancer Treat Rev,* 1995, 21(1):33-64)

A prospective study on patients with psoriatic arthritis and psoriasis did not show any significant association between MTX dosing, treatment duration, cumulative dose or disease duration and hepatic fibrosis[20]. Patients with MTX cumulative dose superior to 1g were submitted to liver biopsy, but only 36.2% had pathological changes. Liver fibrosis appeared to be more likely among patients with higher number of hepatotoxicity predisposing factors (diabetes mellitus, obesity and alcohol consumption; p=0.01)[20].

One retrospective study demonstrated a significant association between liver stiffness (assessed by elastography) and MTX cumulative dose/treatment duration (p<0.001)[21].

These studies highlight that although transaminases still play an important role in hepatotoxicity monitoring, elastography is coming up as an eligible non-invasive method for evaluating liver stiffness (as a marker of fibrosis) and can help the decision for liver biopsy. Liver biopsy should only be considered in the case of persistently elevated transaminase levels or increased elastography values, after risk-benefit evaluation with a hepatologist.

RECOMMENDATION 6

What is the long-term safety of methotrexate, including cardiovascular diseases, malignancies, infections and liver toxicity?

MTX can be used for long-term treatment and its use is safe as far as risk of infectious and cardiovascular diseases is concerned. Surveillance of pulmonary toxicity and of lymphoproliferative disorders (LPD) is advised.

Patients with RA have higher mortality rate as compared to the general population. However, MTX use for more than one year was associated with a reduction in the mortality rate (adjusted total HR 0.3 [0.09--1.03])[22]. Similar results were presented on a prospective study, in which current treatment strategies for early RA, such as MTX monotherapy or in combination

with other csDMARDs, decreased the excess mortality risk in RA patients[23].

In a prospective study, the three-year incidence of cardiovascular disease (CVD) (fatal and non-fatal) was two-fold higher in RA patients when compared to the general population (HR: 1.9 [1.24-3.05])[24]and the magnitude of the risk was comparable with type 2 diabetes[24]. Importantly, MTX use was associated with a significant reduction of CVD risk (OR: 0.73 [0.7-0.77]; $p<0.001$)[25].

RA patients have a higher risk of being hospitalized when compared to the general population[26]. In one study with a total of 27 710 RA patients, 92% had at least one mild infection (requiring a physician visit or use of antibiotics) and 18% had one serious infection (requiring hospitalization)[27]. However, MTX use (without concomitant use of oral steroids) was not associated with higher infection-rates when compared to other csDMARDs[27], being even described in some studies a reduction of the risk of infections requiring hospitalization (HR = 0.76 [0.67-0.86])[26].

Pulmonary toxicity of MTX can occur even after long-term use and is a serious and potentially life--threatening AE. When comparing MTX with leflunomide after two years of use, the risk of adverse respiratory events tends to be higher with leflunomide (RR 1.24 [0.83-1,85])[28].

MTX has also been recognized as a LPD-inducing drug. RA patients with LPDs have a worse 5-years survival rate ($p<0.05$) when compared with patients without RA[29]. Besides, the association between *Epstein–Barr* virus (EBV) infection and LPDs is significantly more common among RA patients[29,30]. According to a retrospective cohort study, MTX is associated with a standardized incidence of LPDs of 8.21[30], and there are even some cases of spontaneous regression after MTX withdrawal[29,30]. Patients treated with MTX tend to have shorter interval between RA at LPDs diagnosis[29,30], but clinicopathological characteristics and 5-year survival rates in RA patients are similar irrespective of MTX[29]. Therefore, although studies outline MTX as a possible LPD-inducing drug, the risk seems to be higher with other immunosuppressive drugs, particularly cyclophosphamide[31].

RECOMMENDATION 7

What is the difference between MTX combination therapy vs. monotherapy in terms of efficacy and toxicity in RA?

In DMARD-naive patients, treatment should start with MTX monotherapy over combination with other csDMARDs, taking into account the efficacy/toxicity balance;

MTX should be considered as the anchor for combination therapy when MTX monotherapy does not achieve disease control.

In early RA consider implementation of a tight control and rapid step-up strategy with MTX plus low-dose prednisolone (PDN) (≤ 10mg/day) for up to six months.

The addition of PDN 10 mg/day at the start of MTX therapy in early RA decreases erosive joint damage and further enhances clinical efficacy, without increasing the risk of AEs, after two years of treatment. Early sustained remission and decreased need for further treatment (SC MTX, cyclosporine or biologic agents) was observed in the combination group (MTX plus PDN) as compared to the monotherapy group. Thus this study supports the implementation of a tight control, rapid step-up strategy with MTX plus low-dose PDN (6.25-10 mg)[32].

Additionally, clinical disease activity measures and ultrasonographic (US)-defined remission rates were compared in early RA patients[33] on MTX monotherapy or combination therapy (MTX plus low-dose [6.25 mg/day] oral PDN). The proportion of patients achieving clinical remission (DAS28 <2.6) and the probability of power Doppler (PD) negativity were significantly higher in the MTX + PDN group at one year of follow-up, with negligible side effects attributable to PDN. Most of the PDN benefits on DAS28 response were explained by significantly greater, faster and persistent control over time of the acute-phase reactant serum levels. As the persistency of a positive PD signal is the main predictor of early relapse and radiographic progression in patients in clinical remission, the higher effect of PDN on PD may justify the long-term beneficial effect on structural damage[33].

RECOMMENDATION 8

Is MTX effective as a glucocorticoid-sparing (adjuvant) treatment in chronic inflammatory rheumatic disorders, such as PMR, SLE, vasculitis, PM, DM?

MTX can be considered as a steroid-sparing agent in giant--cell arteritis, PMR, SLE and juvenile DM.

According to a five-year RCT, patients with PMR treated with PDN and MTX 10 mg/week (n=29) achieved lower erythrocyte sedimentation rate and C-reactive

protein values than those treated with corticosteroids and placebo (n=28; p=0.04)[34]. However, there was no significant difference in the prednisone cumulative dose (p=0.6)[34].

In another 12-month RCT, MTX (starting dose 7.5 mg/week up to a maximum 20 mg/week) was associated with a significant reduction in corticosteroids dose (p=0.01) in 86 patients with moderately active SLE (41 treated with MTX and 45 with placebo)[35]. Similar results were also found in a small open-labelled prospective controlled study, in which SLE patients treated with MTX (7.5 mg/week) and PDN (n=30) had a higher reduction in PDN dose (p<0.05) and in systemic lupus erythematosus disease activity index (p<0.001) than those treated with corticosteroids and placebo (n=18)[36].

There were no studies comparing MTX with other csDMARD as steroid-sparing agents.

RECOMMENDATION 9

What is the optimum MTX dose in RA patients in the perioperative period in order to minimize perioperative morbidity, while maintaining disease control?

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

There is still no data available regarding MTX dose management in patients undergoing (non-) elective non-orthopaedic surgery.

A previous RCT (2001) with 388 patients has shown that maintaining MTX therapy during orthopaedic surgery did not increase the risk of infection or surgical complications in patients with RA within one year after surgery[37]. The long-term extension of this study (up to 10 years) has also shown no increase in the incidence of late postoperative complications or infections in any patient group. Thus, as previously advised, in the absence of renal failure or sepsis, MTX therapy should not be stopped before elective orthopaedic surgery in patients with RA whose disease is adequately controlled[37].

RECOMMENDATION 10

How should MTX be managed when planning pregnancy (male and female patients), during pregnancy and after pregnancy?

We recommend MTX suspension at least three months before conception, during pregnancy and breastfeeding. ***In men, when MTX therapy is unavoidable, there is recent evidence that MTX does not need to be stopped before conception.***

Previous use of MTX was not associated with fertility problems in female and male RA patients, as assessed by time to pregnancy.

A nationwide prospective cohort study (the *PARA* study) evaluated fertility of female RA patients, including women preconceptionally or during the first trimester[38]. Previous use of MTX did not have a measurable effect on time to pregnancy, while therapy with nonsteroidal anti-inflammatory drugs and oral PDN (>7.5 mg/day) was associated with longer time to pregnancy[38].

According to an observational study, Food and Drug Administration (FDA) categories D and X medications' prescription were higher in women with spontaneous abortions, particularly MTX (p<0.05)[39].

Similar data was demonstrated by a multicenter study, including pregnancies with pre and post-conception exposure to MTX that were compared to disease-matched women and women without autoimmune diseases[40]. In this study, MTX was associated with higher rates of spontaneous abortions, but only in the post-conception group and there was a significantly increased risk of major birth defects in the MTX post--conception group compared to the general population (OR: 3.1). However, the number of pregnancies with pre-conception MTX exposure included in this study was limited[40]. Therapy with other csDMARDs and/or oral steroids did not significantly increase this risk[40].

Regarding males, an observational cohort study including 525 patients (113 with paternal low-dose MTX exposure and 412 non-exposed) found no evidence for an increased risk of adverse pregnancy outcomes after paternal MTX exposure (<30 mg) in patients with RA and other inflammatory arthropathies, including major birth defects and spontaneous abortions[41]. Though this result needs further confirmation, this study suggests that in cases of unavoidable MTX therapy in males, postponing conception might not be necessary.

RECOMMENDATION 11

How should we manage MTX dosing after achieving clinical remission?

A gradual dose reduction to the lowest effective MTX dose may be attempted after achieving sustained clinical remission for at least 6 months, with clinical and radiological monitoring.

In some early RA patients in remission, drug-free remission (DFR) may be achieved, but it could be associated with an increased risk of flaring.

The evidence underlying the effect of MTX tapering and withdrawal on disease outcomes in RA patients is somewhat limited, generally restricted to small observational studies and clinical trials conducted in the 1980s and 1990s, in patients with established RA[42]. A 2015 SLR[42] do not support the practice of complete MTX monotherapy withdrawal, which is associated with a significantly increased risk of flaring.

In the BeSt study[43] 508 patients with recent-onset (p=0.14). The treatment strategy was not independently associated with DFR. The mean duration of DFR at four years was 11 months. Patients achieving DFR appeared to have milder RA at baseline. However, among these patients, 69% had erosive disease at baseline, 52% and 43% were rheumatoid factor (RF) and anti citrullinated protein antibodies (ACPA) positive, at baseline. ACPA negativity, male gender and short symptom duration were independently associated with DFR at four years[43]. After five years, 23% of the 508 patients achieved DFR with no significant differences between all treatment groups[44]. However, almost half of these (46%) had to restart treatment after a median period of five (2-16) months, but the majority (47%) of the 'restarters' re-achieved clinical remission within three to six months and with no further structural damage progression. ACPA positivity was the strongest independent predictor for restarting treatment. 30% of the patients with sustained DFR were ACPA positive[44].

The IMROVED[45] study evaluated how often remission or even DFR could be achieved in 610 patients with early RA or undifferentiated arthritis (UA) that started treatment with MTX and PDN. After 1 year, of the 61% of patients who started tapering medication after being in remission (DAS <1.6) at 4 months, 68% were in remission and 32% in DFR. After 2 years[46] 49% and 23% were in DAS-remission and ACR/EULAR remission, respectively, but significantly more UA patients, of whom 94% were ACPA-negative, achieved DFR compared to RA patients (34% and 19%, respectively).

The follow-up study of Rotterdam Early Arthritis Cohort[47] investigated the frequency and time to remission and subsequent tapering of csDMARDs and biologic (b)DMARDs and the frequency and time to flare and regained remission in patients tapering therapies. 281 patients with early arthritis (<1 year) were randomized for induction treatment strategies with triple DMARD therapy (MTX 25mg/week, SSZ 2000mg/day and HCQ 400mg/day) or MTX monotherapy (25mg/week) and if sustained remission was achieved with DAS <1.6 at 2 consecutive visits (every 3 months), medication was tapered while remission remained. During 2 years of follow-up, sustained remission was achieved in 57% of patients. Of 118 patients tapering csDMARDs, 44% experienced a flare during the 2-year follow-up and, after flare, 53% (95% CI 40% to 68%) of patients tapering csDMARDs regained DAS-remission within 3 months and 65% (95% CI 50% to 79%) within 6 months, after treatment intensification.

To the best of our knowledge, there are no other studies that have evaluated the effect of tapering MTX monotherapy dosage on RA outcomes, although this is undertaken in clinical practice.

RECOMMENDATION 12

How should we manage MTX during infections?

MTX must be withhold in serious and opportunistic infections. In mild community-acquired viral infections, there is no evidence that MTX should be discontinued.

New studies reinforced the idea that MTX continuation is safe in mild infections (such as viral infections, not requiring antibiotics)[48]. On the other hand, in severe bacterial infections, with hospital admission and intravenous antibiotics, MTX must be suspended until antibiotic treatment is concluded, symptoms resolved and inflammatory parameters returned to baseline[48].

Regarding possible interactions with antibiotics, trimethoprim-sulfamethoxazole (TMP-SMX) was found to be an important risk factor for developing bone marrow suppression[49]. As MTX, TMP-SMX inhibits dihydrofolate reductase, thus potentiating bone marrow toxicity. The duration of antibiotic treatment before the finding of cytopenias ranged from two days to two months, with the majority of cytopenias occurring within the first two weeks[49]. Therefore, TMP-SMX should not be used for treatment of cystitis in patients receiving MTX. There are no reported cases of this serious AE with the regimen used for *Pneumocystis jiroveci* prophylaxis 3 times/week. There is no information regarding the possible "protective" effect of folic acid in this situation[49].

RECOMMENDATION 13

How should we screen for and treat tuberculosis in patients on MTX?

Screening for tuberculosis should ideally be performed in all patients with immune-mediated inflammatory diseases at diagnosis or before starting immunosu-

ppressive therapy. Screening is based on clinical history, chest x-ray and tests for immunological memory against Mycobacterium tuberculosis (both tuberculin skin test and interferon-g release assay).

These patients must be referred to a tuberculosis expert and, when indicated, begin tuberculosis treatment adjusted to patients' immunosuppressive state.

In Quebec, a case-control study reported an incidence rate of tuberculosis (TB) 10 times higher in RA patients, when compared to the general population[50]. When trying to evaluate possible effects of RA therapy, a nested case-control analysis demonstrated an adjusted risk--ratio for developing TB in the year prior to the index date of 3.4 in MTX-users as compared to control subjects[50].

Given the increased risk of TB, all patients with immune-mediated inflammatory diseases should be screened for TB when the disease is diagnosed and, most importantly, before starting any immunosuppressive therapy. Indeed, chronic immunosuppressive therapy (including > 15 mg/day of PDN for more than two weeks) compromises the sensitivity of tuberculin skin test (TST) and interferon-g release assay (IGRA), screening[51]. Screening includes a detailed medical history, chest x-ray, TST and IGRA. Compared to the TST, IGRA is more specific and sensitive, especially after starting immunosuppressive therapy. On the other hand IGRA is more expensive[52].

Patients are eligible for latent TB treatment according to their immunosuppressive state and TST and IGRA results, as advised in the position paper on tuberculosis screening in patients with immune mediated inflammatory diseases candidates for biological therapy[51].

Regarding the safety of TB treatment, co-treatment with MTX and isoniazid (INH 300 mg/day with pyridoxine at 50 mg/day) was associated with a transient LFT elevation similar to patients treated with MTX without hepatotoxic co-treatment (less than twice the ULN values), with no need to stop medication[53]. There were no reported cases of severe hepatotoxicity or hepatic failure[53].

CONCLUSION

The thirteen recommendations were updated after a careful systematic review of the literature published since 2009 and agreement among Portuguese rheumatologists. Therefore, they constitute a useful tool in daily practice, helping professionals to improve the care for patients with rheumatic diseases. However, it should be mentioned that some of the data presented was based on retrospective studies or expert opinion and must be analysed carefully. In addition, new data presented, such as MTX management during pregnancy and breastfeeding or association between MTX and LPD, are particularly interesting and relevant, but evidence is still scarce to achieve definite conclusions.

There are some limitations in these recommendations that the authors would like to outline. In some articles regarding long-term safety or hepatotoxicity management, folic acid use is not mentioned or the dose is not specified. Moreover, in the recommendation about the most effective regimen of folic acid, one of the studies included refers to the use of 1 mg daily, although this dose is not available in Portugal.

The authors would like to reinforce the importance of updating recommendations for the use of MTX in rheumatic diseases on a regular basis, as MTX is one of the most effective, and probably the most commonly prescribed csDMARD, even in patients under biologic therapy.

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