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Original article

Methotrexate therapy for rheumatoid arthritis: clinical practice guidelines based on published evidence and expert opinion ☆

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Abstract

Objectives: To develop clinical practice guidelines for the use of methotrexate in rheumatoid arthritis (RA), using the evidence-based approach and expert opinion.

Methods: A scientific committee used a Delphi procedure to select five questions, which formed the basis for developing recommendations. Evidence providing answers to the five questions was sought in the Cochrane databases, PubMed, and proceedings of meetings of the French Society for Rheumatology, European League Against Rheumatism, and American College of Rheumatology. Using this evidence, a group of rheumatologists developed and validated the recommendations. For each recommendation, the level of evidence and the extent of agreement among experts were specified.

Results: The recommendations were as follows: 1: The starting dosage for methotrexate in patients with RA should not be less than 10 mg/week and should be determined based on disease severity and patient-related factors; 2: When a patient with RA shows an inadequate response to methotrexate, the dosage should be increased at intervals of 6 weeks, up to 20 mg/week, according to tolerance and patient-related factors; 3: When starting methotrexate treatment in a patient with RA, preference should be given to the oral route. A switch to the intramuscular or subcutaneous route should be considered in patients with poor compliance, inadequate effectiveness, or gastrointestinal side effects; 4: At present, there is no evidence indicating that a change in methotrexate dosage is in order when a TNF antagonist is given concomitantly; 5: The investigations that are mandatory before starting methotrexate therapy in a patient with RA consist of a full blood cell count, serum transaminase levels, serum creatinine with computation of creatinine clearance, and a chest radiograph. In addition, serological tests for the hepatitis viruses B and C

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and a serum albumin assay are recommended. In patients with a history of respiratory disease or current respiratory symptoms, lung function tests with determination of the diffusing capacity for carbon monoxide are recommended; 6: Investigations that are mandatory for monitoring methotrexate therapy in patients with RA consist of full blood cell counts and serum transaminase and creatinine assays. These tests should be obtained at least once a month for the first 3 months then every 4–12 weeks; 7: Folate supplementation can be given routinely to patients treated with methotrexate for RA. In practice, a minimal dosage of 5 mg of folic acid once a week, at a distance from the methotrexate dose, is appropriate; 8: In the event of respiratory symptoms possibly related to methotrexate toxicity, the drug must be stopped and symptom severity evaluated. Should evidence of serious disease be found, the patient should be admitted immediately or advice from a pulmonologist should be obtained immediately.

Conclusion: Recommendations about methotrexate therapy for RA were developed. These recommendations should help to improve practice uniformity and, ultimately, to improve the management of RA.

Keywords: Rheumatoid arthritis; Methotrexate; Recommendations

1. Introduction

Methotrexate is used by most rheumatologists as the first-line disease-modifying antirheumatic drug for patients with rheumatoid arthritis (RA). This choice rests on the good effectiveness and safety profile of the drug, its low cost, and the availability of long-term follow-up data on RA patients given methotrexate [1,2]. In addition, recent data indicate that methotrexate can produce substantial survival benefits by reducing cardiovascular mortality in patients with RA [3].

However, 20 years after the first randomized controlled trials (RCTs) demonstrated that methotrexate as monotherapy was effective in decreasing disease activity in RA [4,5], 15 years after the first RCTs established its ability to slow the progression of structural joint damage [6,7], and nearly 10 years after the first RCTs of the efficacy and safety of methotrexate combined with other conventional disease-modifying antirheumatic drugs [8,9] or biotherapies [10–12], considerable variability continues to exist in the modalities of methotrexate use in RA, most notably regarding starting and maximal dosages, dosage adjustment, criteria used to monitor patients in daily practice, and the use of folate supplementation.

The objective of this work was to develop clinical practice guidelines for the use of methotrexate in patients with RA, using evidence from the international literature and expert opinion, with the goal of optimizing everyday clinical practice [13].

2. Methods

The procedure for developing the recommendations involved several steps, as detailed in the article by Pham et al. [14,15].

2.1. Selection of topics by the scientific committee members

The scientific committee selected three topics: cardiovascular risk and RA [15], use of methotrexate in RA, and nonpharmacological management of patients with recent-onset RA

2.2. Selection of questions

Five questions were selected using a Delphi prioritization procedure:

1. What dosages and routes of administration should be used: more specifically, what is the optimal starting dose, how and when should the dosage be adjusted, what is the maximal dosage, and which routes of administration should be used and when?
2. Does the methotrexate dosage deserve special consideration in patients who are also receiving TNFα antagonist therapy?
3. What investigations (including pulmonary investigations) should be performed before starting, and during, low-dose methotrexate treatment in patients with RA?
4. Should folate supplementation be given routinely (product, dosage, frequency, expected benefit).
5. What is the optimal management strategy when respiratory symptoms develop in an RA patient taking methotrexate?

2.3. Literature review

We searched the Cochrane databases, PubMed, and the databases of the meetings of the French Society for Rheumatology (2003 and 2004), European League Against Rheumatism (2003, 2004, and 2005), and American College of Rheumatology (2003 and 2004). Articles published in French or in English before June 2005 were considered. The keywords *rheumatoid arthritis* and *methotrexate* were used in combination with other keywords: *dosage, intramuscular, subcutaneous,* and *parenteral* for question 1; *adalimumab*, *etanercept*, and *infliximab* for question 2; *monitoring*, *hepatitis B virus*, *hepatitis C virus*, *hematologic diseases*, *renal function*, *respiratory tract diseases*, and *pneumonitis* for questions 3 and 5; and *folic acid* and *folinic acid* for question 4.

Of the 1859 publications retrieved by the literature search, 764 were selected based on the titles, and of those 285 based on the abstracts. The full texts of relevant publications were reviewed. The level of evidence in each publication was deter-

The procedure used to select the experts, to present the literature review results to them and to develop and evaluate the recommendations are detailed in the article by Pham et al. [15].

3. Results and discussion

Eight recommendations about using methotrexate in patients with RA were developed during the 2005 Meeting of Rheumatology Experts. The wording and strength of the recommendations are shown in Table 1, as well as the extent of agreement of the experts with each recommendation.

3.1. The starting dosage for methotrexate in patients with RA should not be less than 10 mg/week and should be determined based on disease severity and patient-related factors

The therapeutic effectiveness of methotrexate is dose-dependent, and effects have been reported with a dosage as low as 5 mg/week [18]. Nevertheless, the first RCTs of methotrexate versus placebo showed that a starting dosage of 7.5 mg/week was often inadequately effective, requiring a dosage increase after 6 weeks in 66–97% of cases [4,5]. In addition, a starting dosage of 10 mg/m^2 per week (12.5–20 mg/week) was more effective than 5 mg/m^2 per week (5–7.5 mg/week), with no statistically significant safety differences between the two groups [19]. Based on these data and on their experience with methotrexate used to treat RA, the experts recommended a starting dosage of at least 10 mg/week.

The experts agreed that the starting dosage should be adjusted according to the patient's body weight and co-morbidities. Moderate to severe renal failure usually requires a starting dosage below 10 mg/week. Two pharmacokinetic studies showed that methotrexate clearance was correlated with creatinine clearance [20,21]. In patients whose creatinine clearance was lower than 45 ml/min, serum methotrexate levels were 30–60% higher than in patients with normal renal function. A meta-analysis of 11 controlled trials showed that moderate renal failure (creatinine clearance < 60 ml/min) significantly increased the risk of serious methotrexate toxicity, most notably for the lung and liver [22]. Other co-morbidities may require a starting dosage of less than 10 mg/week; a history of drug-induced hepatitis is an example.

Several experts underlined the need to consider body weight when selecting the starting dosage. We are not aware of any clinical studies in which methotrexate dosages are reported in mg/kg body weight. The article by Furst et al. [19] is the only study that used a relative methotrexate dosage, in mg/m^2 per week, which can be difficult to compute in everyday rheumatological practice. Given this lack of scientific data, the recom-

Table 1
The eight recommendations about methotrexate used to treat rheumatoid arthritis, with the strength of each recommendation and the degree of agreement among experts at the 2005 Rheumatology Expert Panel meetings [17]

		Level of evidence	Strength of the recommendation	Agreement among experts (%)*
1	The starting dosage for methotrexate in patients with RA should not be less than 10 mg/week and should be determined based on disease severity and patient-related factors.	1b/2	C	82.5
2	When a patient with RA shows an inadequate response to methotrexate, the dosage should be increased at intervals of 6 weeks, up to 20 mg/week, according to tolerance and patient-related factors.	1b/2	C	88.8
3	When starting methotrexate treatment in a patient with RA, preference should be given to the oral route. A switch to the intramuscular or subcutaneous route should be considered in patients with poor compliance, inadequate effectiveness, or gastrointestinal side effects.	2/3	D	91.7
4	At present, there is no evidence indicating that a change in methotrexate dosage is in order when a TNF antagonist is given concomitantly.	–	–	–
5	The investigations that are mandatory before starting methotrexate therapy in a patient with RA consist of a full blood cell count, serum transaminase levels, serum creatinine with computation of creatinine clearance, and a chest radiograph. In addition, serological tests for the hepatitis viruses B and C and a serum albumin assay are recommended. In patients with a history of respiratory disease or current respiratory symptoms, lung function tests with determination of the diffusing capacity for carbon monoxide are recommended.	1b/3	D	73.4
6	Investigations that are mandatory for monitoring methotrexate therapy in patients with RA consist of full blood cell counts and serum transaminase and creatinine assays. These tests should be obtained at least once a month for the first 3 months then every 4–12 weeks.	3	D	88.1
7	Folate supplementation can be given routinely to patients treated with methotrexate for RA. In practice, a minimal dosage of 5 mg of folic acid once a week, at a distance from the methotrexate dose, is appropriate.	1a/1b	A	88.5
8	In the event of respiratory symptoms possibly related to methotrexate toxicity, the drug must be stopped and symptom severity evaluated. Should evidence of serious disease be found, the patient should be admitted immediately or advice from a pulmonologist should be obtained immediately.	2/3	D	80.4

mendation states the methotrexate starting dosage as a minimal total dosage. However, in overweight patients, a starting dosage close to the maximum recommended dosage can be used.

The presence of characteristics suggesting particularly severe disease [14] may warrant the use of a starting dosage greater than 10 mg/week in order to rapidly induce the maximum treatment response, despite the risk of minor side effects [1].

3.2. When a patient with RA shows an inadequate response to methotrexate, the dosage should be increased at intervals of 6 weeks, up to 20 mg/week, according to tolerance and patient-related factors

A single RCT investigated the additional efficacy obtained by increasing the methotrexate dosage above 15 mg/week in patients with RA [23]. Fifty-four patients with an inadequate response to oral methotrexate in a dosage of 15–20 mg/week were divided into two groups: the controls received 15 mg/week of methotrexate intramuscularly and the intensive treatment group had their intramuscular methotrexate dosage increased every 4 weeks as long as the DAS28 was greater than 3.2, up to 45 mg/week. At the end of the trial, no significant differences were found between the two groups regarding disease activity or the number of patients whose DAS28 was less than 3.2. One of the RCTs vs. placebo was started with three methotrexate dosages, 5, 10, and 20 mg/m^2 per week [19]. With the highest dosage, which resulted in administration of 25–35 mg of methotrexate per week, one third of patients discontinued methotrexate therapy prematurely because of serious adverse events, and recruitment to this group was stopped.

The mean relative bioavailability of oral methotrexate compared to intramuscular methotrexate varies from 0.64 to 0.85 according to the dosage [24,25]. Based on this fact and on their own experience, the experts decided to recommend 20 mg/week as the maximal dosage. Good tolerance of methotrexate in its current dosage is a prerequisite to a dosage increase.

For the reasons listed in the previous recommendation, increasing the methotrexate dosage above 20 mg/week may be appropriate in severely overweight or obese patients. The experts recommended a 6-week interval between dosage increments for inadequate effectiveness. This interval is warranted by the active nature of the disease. It is consistent with the recommendation about clinical and laboratory test monitoring developed at the 2004 Meeting of Rheumatology Experts [14].

3.3. When starting methotrexate treatment in a patient with RA, preference should be given to the oral route

A switch to the intramuscular or subcutaneous route should be considered in patients with poor compliance, inadequate effectiveness, or gastrointestinal side effects

Bioavailability data for methotrexate in dosages of less than 20 mg/week, together with the ease of use and low cost of oral methotrexate, warrant first-line use of the oral route. Pharmacokinetic data show that the bioavailability of methotrexate by the oral route compared to the intramuscular route is good with low dosages but decreases as the methotrexate dosage increases. With 7.5 mg/week, the absolute oral bioavailability of methotrexate is close to 1 [26]. In a group of patients given 10–17.5 mg/week of methotrexate, the mean relative bioavailability of the oral route compared to the intramuscular route was 0.85 (95% CI, 0.77–0.93) [24]. The lower value of 0.64 (95% CI, 0.21–0.94) was found with dosages greater than 20 mg/week [25]. In these studies, no statistically significant differences in bioavailability were detected between the intramuscular and the subcutaneous routes. The clinical efficacy and/or safety of methotrexate, according to the route of administration has been evaluated only in open-label trials and retrospective studies. In the above-mentioned study investigating the potential benefits of methotrexate dosages greater than 15 mg/week [23], 64 patients with inadequate responses to oral methotrexate in dosages of 15–20 mg/week were given 15 mg/week intramuscularly during the 6 weeks preceding the randomization phase. The switch from oral to intramuscular administration resulted in a 0.42 (95% CI, 0.15–0.69) point decrease in the DAS28; this reduced the DAS28 to less than 3.2 in 4 (6.25%) patients. A similar open-label prospective study showed a significant reduction in the DAS28, by a mean of 0.6, in 33 patients switched from oral to intramuscular methotrexate [27]. Three retrospective studies showed that gastrointestinal symptoms related to methotrexate administration decreased after switching from the oral to the parenteral route [28–30].

3.4. At present, there is no evidence indicating that a change in methotrexate dosage is in order when a TNF antagonist is given concomitantly

In RCTs of the efficacy and/or safety of methotrexate combined with TNF antagonist therapy, the mean methotrexate dosage ranged from 7.5 to 16 mg with infliximab [10,31], 14.5–18.5 mg with etanercept [11,32], and 17–20 mg with adalimumab [12,33]. The influence of the methotrexate dosage on efficacy and safety was not investigated in these studies. In a single uncontrolled study of 22 RA patients with an inadequate response to infliximab (3 mg/kg) and methotrexate in combination, increasing the methotrexate dosage from a mean of 9.9 ± 3.9 mg/week to a mean of 15 ± 4.3 mg/week improved the therapeutic response to infliximab in 36.4% of cases (8/22 patients), within 16 weeks. However, this study was not controlled, and in seven of the eight patients the improvement was moderate according to EULAR criteria [34].

3.5. The investigations that are mandatory before starting methotrexate therapy in a patient with RA consist of a full blood cell count, serum transaminase levels, serum creatinine with computation of creatinine clearance, and a chest radiograph

In addition, serological tests for the hepatitis viruses B and

with a history of respiratory disease or current respiratory symptoms, lung function tests with determination of the diffusing capacity for carbon monoxide are recommended.

Determination of serum transaminase levels before starting methotrexate therapy is mandated by the risk of methotrexate-induced liver toxicity. A meta-analysis of 17 prospective or retrospective studies reporting the results of liver biopsies in 719 patients taking methotrexate for RA showed 103 (14%) cases of mild fibrosis (Roenigk class IIIA), 6 (0.8%) cases of moderate fibrosis (Roenigk class IIIB), and 2 (2.8‰) cases of cirrhosis (including one patient who had known cirrhosis before the initiation of methotrexate therapy) [35]. The frequency of clinically serious liver disease in patients taking methotrexate for RA can be estimated at 1% to 1‰ and the cumulative risk of developing clinically serious liver disease at about 1‰ after 5 years [35]. A meta-analysis of six RCTs reporting the results of serial liver tests done over a 3-month period in 657 RA patients taking methotrexate or a placebo showed that patients taking methotrexate had higher rates of ALAT elevation (x 1-2 N, 6.7% vs. 0.4%), ASAT elevation (x 1-2 N, 4.9% vs. 0.4%), and serum alkaline phosphatase (x 1-2 N, 16% vs. 3%) [35]. The far higher rate of alkaline phosphatase elevation (16% with methotrexate and 3% with a placebo) compared to ALAT and ASAT elevation suggested to the authors of this meta-analysis that alkaline phosphatase may be too sensitive to serve as a marker for liver injury [35]. Finally, in a prospective study of three cohorts including a total of 94 patients treated with methotrexate for RA, serial testing showed a correlation between serum transaminase levels and liver biopsy results: elevation of the mean pre-biopsy serum transaminase level was correlated with an increased risk of finding an abnormal histological grade, whereas normal values for over 50% of pre-biopsy serum transaminase levels had 97% specificity for a normal histological grade [36].

The recommendation that serological tests for the hepatitis viruses B and C be performed before the initiation of methotrexate therapy rests on the theoretical risk of potentiated methotrexate-induced liver toxicity in patients who have hepatitis B or C. Reactivation of the hepatitis B virus has been reported in five patients given methotrexate to treat RA, including four patients who experienced fulminating hepatitis at methotrexate discontinuation [37–41]. A single case of hepatitis C reactivation, with a good response to ribavirin, was reported among six patients given methotrexate (12.5 ± 3 mg/week for 15.2 ± 9.9 months) to treat joint manifestations related to chronic hepatitis C [42]. Two patients with RA and hepatitis C infection were treated with methotrexate for 6 months without experiencing transaminase elevation [43]. Based on these data, and considering that no conclusions can be drawn from the few anecdotal cases available to date, the experts recommend obtaining serological tests for the hepatitis viruses B and C before initiating methotrexate therapy in patients with RA.

The hematological toxicity of methotrexate requires that a full blood cell count be obtained before treatment initiation. Cytopenia (pancytopenia, neutropenia, or thrombocytopenia) dies of RA patients given low-dose methotrexate therapy. Cytopenia can occur at any time during treatment, even after the first dose, and may be fatal in as many as 15%–25% of cases. Risk factors for cytopenia may include renal dysfunction, hypoalbuminemia, infection, interactions with specific medications (e.g. trimethoprim-sulfamethoxazole), and accidental overdosage [44–46].

Renal dysfunction may potentiate the toxicity of methotrexate in patients with RA. Consequently, a serum creatinine assay with creatinine clearance estimation should be performed before methotrexate initiation. As specified in the recommendation on the starting dosage of methotrexate, moderate to severe renal failure is associated with elevated serum methotrexate levels that result in a significant increase in the risk of serious adverse effects, most notably hepatic and pulmonary toxicity [20–22].

Because hypoalbuminemia is associated with increased methotrexate toxicity, serum albumin should be assayed before treatment initiation. Hypoalbuminemia has been reported as a potential risk factor for methotrexate-induced hematological and pulmonary toxicity [45,47].

The well-established pulmonary toxicity of methotrexate requires that a chest radiograph be obtained before treatment initiation. In patients with a history of respiratory disease or current respiratory symptoms, lung function tests with determination of the diffusing capacity for carbon monoxide (DLCO) should be performed also. Methotrexate-induced pulmonary toxicity manifests chiefly as infectious or immunoallergic pneumonia. Immunoallergic pneumonia, which causes interstitial pneumonitis, occurs in nearly 2% of patients given methotrexate to treat RA and carries a mortality rate of about 10–20%. Methotrexate pneumonitis can develop at any time during methotrexate therapy but may be more common during the first year. Potential risk factors may include pre-existing lung disease, most notably with interstitial involvement; older age; renal dysfunction; and diabetes mellitus. The symptoms of methotrexate pneumonitis set in gradually, over several days to weeks. They are nonspecific, consisting chiefly of a fever, a nonproductive cough, and dyspnea. Among tests that can assist in the diagnosis of methotrexate pneumonitis, chest radiography has low sensitivity and low specificity but may disclose interstitial and/or alveolar densities predominating in the lung bases. Lung function testing with determination of blood gas values and DLCO is sensitive but lacks specificity; the results may show hypoxia, a DLCO reduction ($\leq 70\%$ of the predicted age-specific value), and/or a restrictive ventilatory pattern. High-resolution computed tomography is sensitive and more specific than lung function testing. Findings may include interstitial infiltrates and/or ground-glass densities predominating in the lung bases. The appropriateness of bronchoscopy with bronchoalveolar lavage and transbronchial lung biopsies should be discussed on a case-by-case basis with a pulmonologist. Based on these facts, the experts concluded that a chest radiograph, and lung function testing with DLCO determination in patients having a history of respiratory disease or cur-

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