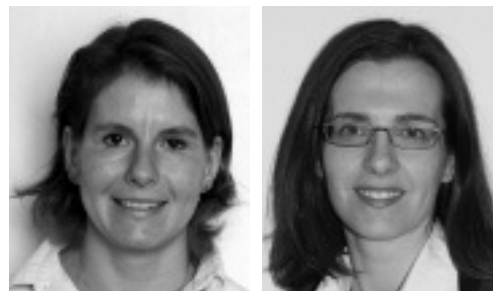


Methotrexate for Rheumatoid Arthritis: A Guide from Canada



Methotrexate (MTX) has been on the market for the treatment of rheumatoid arthritis (RA) for some decades. The first, larger studies showing efficacy of MTX treatment in patients with RA were published in 1985^{1,2}. In 1986 the US Food and Drug Administration approved the drug for the treatment of RA, starting MTX therapy at an initial test dose of 2.5 mg to establish hematologic tolerance to a maximum of 20 mg/week³. Since then, MTX has increasingly been prescribed for patients with RA and is now considered by many to be the disease-modifying drug (DMARD) of first choice for most patients with RA⁴.

To develop practical recommendations for the use of MTX in rheumatic diseases, the 3E initiative (Evidence, Expertise, Exchange) set up an international consensus meeting 2007–2008. The aim of this meeting was to define recommendations for MTX use in daily practice according to evidence-based medicine, by integrating systematically generated evidence from the literature with expert opinion. During this meeting 10 questions were addressed by rheumatologists from 17 countries in Europe and North and South America. Published recommendations cover starting dose and escalation dose of MTX, prescription of at least 5 mg folic acid with MTX therapy, adjustment or discontinuation of MTX therapy in case of persistent elevated liver enzyme levels, and discontinuation of MTX prior to planned pregnancy in men and women⁵.

Next to these internationally chosen recommendations, the Canadian rheumatologists addressed 5 additional questions on drug interaction, monitoring, predictors of response, patients' preference, and management of nuisance side effects; their recommendations are reported in this issue of *The Journal*⁶.

Recommendations

Recommendation 1. The majority of the drugs including nonsteroidal antiinflammatory drugs (NSAID) may be used safely in combination with MTX in rheumatic diseases. Trimethoprim and sulfamethoxazole (TMP-SMX) should be avoided in patients treated with MTX. Defining drug interactions can be challenging, particularly among patients who

may be receiving multiple medications. Indeed, the evidence base for Recommendation 1 was relatively scarce and was based on many case reports and case series. This may explain why a similar exercise in the United Kingdom has resulted in slightly different recommendations on potential drug interactions, based on how much weight is given to each report. British Society for Rheumatology/British Health Professionals in Rheumatology (BSR/BHRP) guidelines⁷, in addition to those noted by the Canadian group, included a warning about the use of phenytoin, which may increase the antifolate effect of MTX; probenecid and penicillin, which may reduce MTX excretion; and tolbutamide, which may increase MTX serum concentration. Although there are differences in the recommendations established by the Canadian rheumatologists versus the BSR/BHRP, the overall consensus is that NSAID can be used safely in combination with MTX as long as monitoring is performed regularly, especially for increased liver enzymes and cytopenia. Since many NSAID are bought over the counter, it is important to advise patients to inform their rheumatologist beforehand when considering buying over the counter medication.

Recommendation 2. In determining treatment strategy of patients treated with MTX, the characteristics of poor prognosis should be considered, such as female gender and persistent disease activity. The overall predictive ability of these factors was relatively weak. Studies to date in this area have often been very small and are limited by including only specific groups of independent variables, such as demographic characteristics, disease activity, or genetic factors^{8–10}. It is interesting that a drug with such a long history and which is now considered the standard of care in RA should lack this evidence, when many of these same issues are actively being researched with the new anti-tumor necrosis factor (TNF) agents. One issue is cost, where the annual cost of MTX therapy is just a fraction of that of anti-TNF therapies and thus identification of responders and nonresponders to anti-TNF therapy seems to be more important to “justify” the higher costs of anti-TNF

See Canadian recommendations for MTX in RA, page 1422

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therapy. There also remains a concern about the potential toxicity of these newer agents due to lack of experience and concerning case reports. That said, MTX remains our gold standard, but it is well recognized that a proportion of patients will not respond and a further proportion will experience adverse effects. Indeed, we do not even fully understand the drug's mechanism of action in patients with RA. If adverse effects could be predicted or avoided or better managed through increased knowledge regarding drug interactions, patients least likely to respond could be expedited to receive anti-TNF therapies.

Recommendation 3. To minimize non-serious gastrointestinal side effects of MTX one could switch from oral to parenteral (subcutaneous or intramuscular) MTX. Other strategies to minimize non-serious side effects include splitting the dose of MTX. Oral MTX is often prescribed first when starting MTX therapy because of convenience and ease of administration. A subsequent switch to parenteral administration is made in case of nonresponse or adverse events. However, when switching to parenteral administration, one should consider the difference in bioavailability between oral and parenteral administration. Although bioavailability varies widely between patients, the bioavailability of oral administration is reduced at higher doses, whereas bioavailability of parenteral MTX continues to increase when escalating the dose of MTX^{11,12}. The second recommendation focuses on splitting the dose of MTX to reduce side effects. However, no advantage of a twice-weekly schedule of MTX over a once-weekly schedule has been found and, in addition to the fact that it is also less practical, this recommendation is less strong¹³.

Recommendation 4. Use of validated outcome measures to reach a target of low disease activity or remission is recommended. Joint counts should be included in the assessment of disease activity in RA. In addition to joint counts, other measures in the assessment of disease activity in RA could include validated measures of global assessment and acute-phase reactants. Treatment strategies have changed in the last 2 decades, from the pyramid approach towards an early aggressive treatment strategy with (combinations of) DMARD including MTX. The current aim of achieving low disease activity or even remission and a "tight control" approach, based on predefined protocols for therapy changes and frequent followup visits, has proven to be effective¹⁴⁻¹⁶. Although there was lack of evidence regarding which measures should be used to assess response to treatment thus leading to a treatment strategy change, joint assessment was found to be the most important indicator reflecting the state of disease activity. It was, however, recognized that other variables such as global assessments and acute-phase reactants were also important to assess. This recommendation is probably a first step towards a more standardized "tight disease control approach" aiming for

remission in all patients receiving MTX (and indeed other disease-modifying antirheumatic treatments) for RA.

Recommendation 5. Patients need to be educated on their disease and treatment options and involved in the decision-making process. This recommendation was entirely based on expert opinion. As discussed, little research has been undertaken to date into which factors are associated with treatment response. One factor that has been largely ignored is patient adherence and factors associated with adherence. One study estimated that only 64% of more than 80% of 1668 patients with RA were adherent to MTX therapy¹⁷. Although it seems intuitive, there has been little research on whether patient education could alter a patient's belief in the usefulness of taking treatment and help find a balance between understanding potential risks and benefits¹⁸. There are likely to be other factors associated with a patient's beliefs about medications and past illness experiences that may be more important in determining longterm treatment outcomes. In general, patients need to be convinced of the usefulness of their treatment, and treatment strategies should be discussed and reviewed on a regular basis.

Evidence, Expertise, and Exchange in the Canadian Recommendations

The biggest challenge the Canadian group faced when researching these recommendations was the general lack of an evidence base. In some areas this was adequate (i.e., level 1a studies for Recommendation 4); in others evidence was limited to level 4 studies only (i.e., Recommendations 1 and 3). To help make sense of the often limited and sometimes contradictory evidence, the next step after literature review was to rely on the opinion of a group of experts, primarily clinical rheumatologists, with years of personal experience in prescribing of MTX. But even here there can be substantial differences in opinion, witnessed by reviewing the same evidence differently or by lack of ability to agree. The wording of recommendations based on evidence from the literature may be changed accordingly until agreement has been reached. Unfortunately, this process could also lead to weakening of the final recommendations if evidence is scarce and therefore less suitable for daily practice.

While the Canadians should be commended for their efforts, the process also makes us aware that more research is necessary to obtain additional evidence on the pharmacokinetics and mechanisms of response to MTX, currently the DMARD of first choice. These recommendations can be used as a starting point.

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