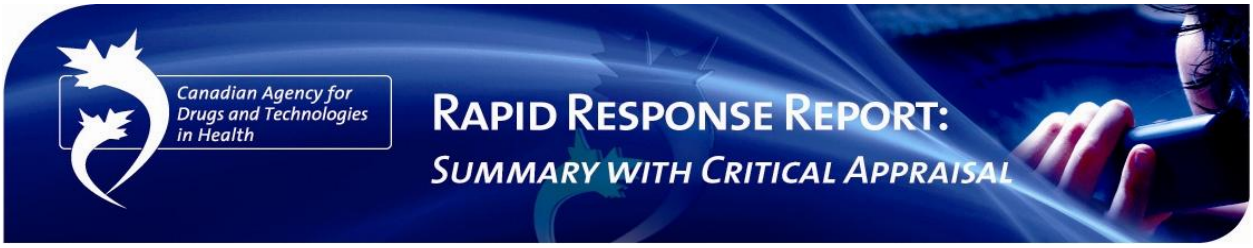

TITLE: Parenteral versus Oral Methotrexate for the Treatment of Rheumatoid Arthritis: A Review of the Clinical Evidence

DATE: 09 May 2011

CONTEXT AND POLICY ISSUES

Methotrexate (MTX) is a disease modifying anti-rheumatic drug (DMARD) that has been widely used to treat rheumatoid arthritis (RA) since the 1980's.[1] RA is a chronic inflammatory disorder that mainly affects the peripheral joints and the surrounding tissue. [2] Although the cellular action of methotrexate is understood (as a structural analogue of folic acid), the mechanism by which it improves the signs and symptoms of rheumatoid arthritis is unknown.[1] The short term efficacy of methotrexate in the treatment of RA has been demonstrated in small randomized placebo controlled trials while the longer term efficacy has been evaluated in observational studies. Methotrexate is generally initiated at a dose of 7.5 mg to 15 mg once weekly, and increased as tolerated and as needed to control symptoms. Several clinical practice guidelines recommend methotrexate as a first line treatment option in patients with RA. [2-6] In addition to being used as monotherapy, methotrexate is also commonly used in combination with biological agents or other DMARDs used in the treatment of RA.

Methotrexate can be given via oral, intramuscular (IM), or subcutaneous (SC) routes. There are differences between the bioavailablity of the different dosage forms. As the methotrexate dose increases, the bioavailability of oral methotrexate decreases, which may be due to an absorption limitation; however when given parenterally, the bioavailability of methotrexate increases as the dose increases.[7-9] Although the parenteral form of methotrexate has greater bioavailability than the oral form, it is not known if it results in improved clinical efficacy.

This report will review the evidence for the comparative efficacy of the parenteral and oral route of administration of methotrexate in rheumatoid arthritis to inform a coverage decision. The term parenteral includes administration by any route other than through the GI tract, including administration by either subcutaneous or intramuscular routes.

RESEARCH QUESTIONS

1. What is the comparative clinical effectiveness of parenteral versus oral methotrexate in adults with rheumatoid arthritis?

2. What are the clinical practice guideline recommendations on the use of parenteral versus oral methotrexate in adults with rheumatoid arthritis?

KEY MESSAGE

One randomized controlled trial suggests that the subcutaneous form of methotrexate may be more effective than the oral form for the treatment of early rheumatoid arthritis; however, guidelines recommend a preference for the oral route with a switch to parenteral administration for patients who experience inadequate response or intolerance.

METHODS

A limited literature search was conducted on key resources including Ovid MEDLINE, PubMed, The Cochrane Library (2011, Issue 3), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and guidelines (the grey literature search for guidelines was limited to 5 years). Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2001 and April 8, 2011. The selection criteria are provided in Table 1.

Table 1: Selection criteria

Population	Adults (≥18 years) with rheumatoid arthritis
Interventions	Parenteral methotrexate
Comparator	Oral methotrexate
Outcome	Relevant clinical outcomes specific to rheumatoid arthritis Guidelines and recommendations
Study design	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and evidence-based guidelines

Rapid response reports are organized so that the higher quality evidence is presented first. In this report, systematic reviews are presented first, followed by randomized controlled trials and then evidence-based guidelines.

The AGREE (Appraisal of Guidelines for Research and Evaluation) instrument was used to evaluate the quality of the guidelines identified in the literature search.[10] The AMSTAR (Assessment of Multiple Systematic Reviews) instrument was used to assess the methodological quality of systematic reviews.[11]

SUMMARY OF FINDINGS

Two systematic reviews, one randomized controlled trial and three guidelines were identified. No health technology assessments or meta-analyses were identified.

Systematic reviews

Two systematic reviews were identified that included comparisons of parenteral and oral administration of methotrexate.[12,13] Both systematic reviews found a single relevant randomized controlled trial, Braun et al, 2008.[14]

In 2009, Visser and van der Heijde published a systematic review of the literature on the optimal dosage and route of administration of methotrexate in rheumatoid arthritis.[12] Eligibility criteria for the review included adults with rheumatoid arthritis according to American College of Rheumatology (ACR) criteria, an intervention of methotrexate in a certain dosage and a certain route of administration, with a different dosage or route as the comparator. Outcomes were predefined and included multiple clinical efficacy measures [e.g., swollen joint count (SJC), tender joint count (TJC), disease activity score (DAS), ACR20/50/70 response], radiological progression, and toxicity. The search was limited to randomized controlled trials (RCTs).

A total of eight RCTs were identified that directly compared different dosages or routes of methotrexate administration. Of these, only one study compared different routes of administration for methotrexate. Braun et al. 2008 published a randomized, controlled, double blind study in 375 adults with early rheumatoid arthritis (less than one year).[14] All subjects were methotrexate-naïve. Treatment groups were initiated on methotrexate 15 mg per week, given either orally or subcutaneously. If a patient did not reach ACR20 at 16 weeks, subjects either a) had their SC dose escalated or b) were switched from oral methotrexate to subcutaneous methotrexate at the same dose of 15 mg per week. Total follow up was 24 weeks. This study was assigned an evidence level of 1b (Individual RCT; with narrow confidence interval). A definition of the ACR criteria is provided in Appendix 1.

The systematic review presented the study results as odds ratios (OR). The original study presented percentages reaching defined outcomes and corresponding statistical significance (p value) for the difference between treatment groups. Statistically significantly more patients who started SC methotrexate achieved an ACR20 response at 16 weeks than those who started oral methotrexate (85% versus 77%, $p<0.05$), which corresponds to an odds ratio (OR) of 1.7 [95% confidence interval (CI) 1.01 to 2.9]. The review reports that there was a trend towards more patients achieving an ACR20 (OR 1.5, 95% CI 0.96 to 2.4) and ACR70 (OR 1.4; 95% CI 0.9 to 2.1) after 24 weeks, although the original study publication reports these treatment differences to be statistically significant ($p<0.05$). It was also reported that patients on SC methotrexate discontinued therapy more often due to toxicity, although the difference was not statistically significant (OR 2.3; 95% CI 0.98 to 5.5). There were no differences observed between treatment groups in the number of patients experiencing adverse events (OR1.2, 95% CI 0.8 to 1.9) or in the type of adverse event, including gastrointestinal toxicity. [12]

Considering all of the evidence reviewed on the optimal dosages and routes of administration, the authors concluded that the preferred route of methotrexate seemed to be oral, but a switch to subcutaneous was suggested in the case of an insufficient response at the highest tolerable dose.

Strengths of the systematic review include a well-defined clinical question and methods, a comprehensive literature search, clear inclusion criteria and an assessment of the scientific quality of the included studies. The literature search included articles in any language published from 1950 to September 2007. The authors did not provide an explanation about the inclusion of the study by Braun et al. which was published in 2008. Keywords used in the literature search were provided in an appendix. Databases searched included: Medline, Embase, and the Cochrane library. In addition, the authors reviewed reference lists of relevant articles and abstracts of recent international conferences. Data were extracted using a standard form and the authors were contacted to provide additional information, if required. Limitations of the methods include the lack of independent study selection and data extraction by more than one person and the lack of an assessment of publication bias. The results of the studies were not combined, which was appropriate due to different study designs.

In 2011, Mouterde et al. published a systematic literature review on optimizing methotrexate therapy in rheumatoid arthritis.[13] The review was conducted by a group of French rheumatologists who selected four topics on methotrexate in rheumatoid arthritis by consensus. One of the four topics was "route of administration at treatment initiation and during maintenance treatment." Specific inclusion criteria included adults (over 18 years) with rheumatoid arthritis meeting ACR criteria, an intervention of methotrexate given orally, subcutaneously or intramuscularly once a week for at least six weeks, and a comparison of treatment strategies, dosages or routes of administration. No specific outcomes were pre-defined. All study types were included in the search except case reports, systematic reviews and expert opinion.

A total of 11 articles were selected for the four methotrexate topics, and five of the articles were considered relevant to the discussion of route of administration of methotrexate. The results section of the review provided a narrative review of these five studies. A meta-analysis was not performed since the outcomes were not considered appropriate to combine. A single study, by Braun et al. (2008), was identified that compared different routes of administration for methotrexate in a randomized controlled trial.[14] The other four studies found in the systematic review switched all patients from oral to IM methotrexate and therefore did not compare efficacy of different routes of administration. [15-18]

The authors assigned the RCT by Braun et al (2008) a Jadad score of 5/5 and a level of evidence of 1b, since it was a randomized controlled trial.[14] The study design was described above in the discussion of the systematic review by Visser (2009). This review presented additional data not presented in the review by Visser. In patients with early RA, more patients treated with SC methotrexate achieved an ACR20 response at 24 weeks than those on oral methotrexate (78% versus 70%, $p<0.05$). After 16 weeks, patients in the oral treatment group who had not reached ACR20 (n=30) were switched to the subcutaneous route of administration at the same dose, resulting in a response in an additional 30% of patients. More patients in the subcutaneous group compared to the oral group withdrew due to serious adverse events (9.3% versus 4.3%), although fewer patients in the subcutaneous group experienced diarrhea (2.6% versus 6.9%) and elevation of transaminase (1.6% versus 4.6%). No p values were provided to indicate if these differences were statistically significant.

Based on the results of the study by Braun et al., the authors concluded that the subcutaneous route was more effective than the oral route for methotrexate administration and that if standard oral dosages were not effective, switching to parenteral methotrexate improved the therapeutic effect in patients with early RA.[13]

Strengths of the systematic review include well defined methods, a comprehensive literature search, clear inclusion criteria and an assessment of the scientific quality of the included studies. The literature search included articles in English or French published up to May 2009. Keywords used in the literature search were provided. Databases searched included: Medline, Embase and Cochrane Central database. In addition, the authors reviewed reference lists of relevant articles and abstracts of recent international conferences. Limitations of the methods include no clear clinical question, the lack of independent study selection and data extraction by more than one person and the lack of an assessment of publication bias. The results of the studies were not combined, which was appropriate due to different study designs.

Randomized controlled trials

A single randomized controlled trial was found that compared subcutaneous and oral methotrexate in the treatment of adults with early rheumatoid arthritis.[14] This study was described previously in the discussion of the systematic reviews; however since this is the only comparative trial that was found in the systematic reviews, complete study details are found in Appendix 2.

Guidelines and recommendations

In 2009 Visser et al.[19] published evidence based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis. It was targeted for clinicians involved in the treatment of patients with rheumatic disorders. Recommendations were based on systematically generated evidence and expert opinion and were formulated by consensus. They were developed using the 3E initiative (evidence, expertise, exchange) which is a multinational effort, aimed at promoting evidence based medicine by formulating detailed recommendations addressing clinical problems. This process involved a total of 751 rheumatologists from 17 different countries. Ten clinical questions were selected by consensus, with one addressing the optimal dosage and route of administration of methotrexate in rheumatic disorders. A systematic review of the evidence was conducted and recommendations were merged and formulated by consensus. This systematic review was discussed previously.[12] For each recommendation the level of evidence and the grade of recommendation were assessed using the Oxford levels of evidence and the level of agreement by experts was determined.

Recommendation for optimal dosage and route of administration for methotrexate:[19]

Oral methotrexate should be started at 10-15 mg/week, with escalation of 5 mg every 2-4 weeks up to 20-30 mg/week, depending on clinical response and tolerability; parenteral administration should be considered in the case of inadequate clinical response or intolerance. (pg.1087)

- Level of evidence 2b (Individual cohort study (including low quality RCT; e.g., <80% follow-up)
- Strength of recommendations B (consistent level 2 or 3 studies).
- Agreement among experts: 7.8/10 (standard deviation: 2.6)

This particular recommendation addresses both the dosage and route of administration. The complete recommendation was assigned a level of evidence of 2b, although the individual RCT by Braun (2008) was assigned a level 1b in the systematic review by Visser (2009). Specifically regarding the route of administration, the evidence considered included expert opinion, retrospective studies, pharmacokinetic studies, a single RCT (Braun et al 2008) and a study that involved switching patients who failed on oral methotrexate to the parenteral route. [14,15]

Strengths of this guideline include the clearly stated objective and described methods, the systematic review of the literature and the grading of evidence. Limitations include the lack of involvement of professional groups other than rheumatologists, no conflicts of interests were declared for the authors or the scientific committee of experts, and patient views and preferences were not specifically considered.

In 2010, a group of 26 Canadian rheumatologists who participated in the international 3E initiative developed nine recommendations for five additional Canadian questions regarding the use of methotrexate in rheumatoid arthritis.[20] The Canadian expert committee reviewed evidence from systematic reviews prepared by a bibliographic team and formulated practice recommendations by consensus. Methods were similar to the international initiative, although on a smaller scale.

Specific to this review, one recommendation addressed the management of non-serious side effects of methotrexate:[20]

To minimize non-serious gastrointestinal side effects of MTX one could try to switch from oral to parenteral (subcutaneous or intramuscular) MTX (pg.1426)

- Level of evidence 4 (case series and poor quality cohort and case-control studies)
- Strength of recommendations D (expert opinion or inconsistent or inconclusive studies)
- Agreement among experts: 97%

The systematic review on which this recommendation is based has not yet been published, but included a literature search up to September 2007. Therefore, this review would not include the randomized controlled trial by Braun et al (2008). This recommendation is based on extrapolation of results from cohort studies using the intramuscular route of administration for methotrexate.[20]

In 2006, Pavy et al.[21] published a clinical practice guideline for the use of methotrexate in patients with RA, with the goal of optimizing everyday clinical practice. The guideline was developed by an expert scientific committee of French rheumatologists "with extensive experience in the management of RA". Five broad clinical questions were selected by consensus, one of which addressed which dosages and routes of administration should be used for methotrexate in RA. Part of this question addressed the question of the appropriate route of administration for methotrexate and when different routes should be used.

This guideline was targeted for clinicians involved in the treatment of patients with RA. A systematic literature review was conducted and presented to the experts at a conference. Recommendations were based on a literature review and expert opinion, and were formulated by consensus. Methods were clearly described. Levels of evidence and strength of recommendation were assigned for each recommendation. "The strength of a recommendation depends not only on the level of evidence used to develop the recommendation but also on the treatment effect, adverse effects, applicability of the recommendation to the target population, ease of administration, and economic considerations."[21]

Recommendations about the use of methotrexate in rheumatoid arthritis are easily identified in the publication. Related to the route of administration, one recommendation states:[21]

"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.(pg.390)

- Level of evidence 2/3 (evidence from controlled study without randomization or quasi-experimental study or non-experimental descriptive studies).
- Strength of recommendations D (expert opinion or based on extrapolated evidence).
- Agreement among experts: 91.7%.

There were a number of limitations to this guideline that were identified. Patient views and preferences were not specifically considered. The guideline was not externally reviewed prior to publication. The guideline was funded by Abbott France, although their role is not clearly defined. No conflicts of interest statements are provided for the authors or the scientific committee. Overall, this recommendation is based on expert opinion, open-label and retrospective studies as well as extrapolated pharmacokinetic data comparing the bioavailability of oral and parenteral routes of administration for methotrexate. This recommendation was made before the publication of the comparative study by Braun et al.

Limitations

Published evidence comparing parenteral and oral methotrexate for patients with rheumatoid arthritis is limited to a single good quality randomized controlled trial using the SC route of administration. Therefore, results can be generalized only to the study population that included adults with early rheumatoid arthritis who had not previously taken methotrexate.

Two systematic reviews[12,13] and one guideline[19] included the study by Braun et al.[14] Two additional guidelines [20,21] did not include the study by Braun since it was not published at the time of the literature search.

All conclusions and recommendations from the systematic reviews and guidelines are based on the single randomized controlled trial and expert opinion as well as non-comparative, cohort and pharmacokinetic studies.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

One randomized controlled trial suggests that the subcutaneous form of methotrexate may be more effective than the oral form for the treatment of early rheumatoid arthritis. Although more patients in the SC treatment group discontinued therapy due to toxicity, there were no differences observed between treatment groups in the number of patients experiencing adverse events or in the type of adverse event, including gastrointestinal toxicity. It is not known if increasing the dose of oral methotrexate beyond 15 mg would have had similar efficacy to SC methotrexate at a dose of 15 mg.

Guidelines recommend a preference for the oral route, with a switch to parenteral for inadequate response or intolerance. This recommendation was formulated by consensus of experts, and is based on one comparative trial using the subcutaneous route, as well as pharmacokinetic, non-comparative and cohort studies. There is no evidence directly comparing the intramuscular and oral routes of administration in patients with rheumatoid arthritis.

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APPENDIX 1

American College of Rheumatology (ACR) criteria:

A composite measure of response rated according to its percentage change from baseline; 20% (ACR 20), 50% (ACR 50) and 70% (ACR 70).

ACR 20% response

≥ 20% reduction in the tender joint count (TJC) and the swollen joint count (SJC) plus an improvement of at least 20% in at least 3 of the following 5 criteria:

[I] patient's assessment of pain
[ii] patient global assessment
[iii] physician global assessment
[iv] function/disability measure Health Assessment Questionnaire (HAQ) or modified HAQ (MHAQ)
[v] erythrocyte sedimentation rate (ESR) or C-reactive protein (CPR).

Criteria I to iv are assessed with the use of visual analog scales (range 0-10 cm).

ACR 50% and 70% responses

≥ 50% and ≥70% reduction, respectively, in the numbers of both tender and swollen joints plus an improvement of ≥ 50% and ≥70%, respectively in the degree of improvement in at least 3 of the above 5 criteria.

APPENDIX 2

Table 2: Study Details of Braun et al (2008)[14]				
Study Design and Treatment Groups	**Patient Population**	**Outcomes**	**Authors' Conclusions**	**Limitations**
Multi-centre, randomized, double-blind, controlled, phase IV trial (Germany) Treatment goups MTX SC 15 mg/wk, n=194 MTX PO 15 mg/wk, n=190 Treatment duration 24 weeks At week 16 – patients not meeting ACR20 switched from oral to SC 15 mg/wk or increased SC dose to 20 mg/week (dependent on treatment group)	Adults aged 18 to 75 years with RA according to ACR 1987 criteria Disease Activity Score in 28 joints (DAS28) ≥4 MTX-naïve Exclusion criteria: intraarticular injections of corticosteroids during the study, impaired renal function, pulmonary disease,,history of severe liver disease, among others. **Demographics** age (median): 58-59 years female: 74-79% Time since RA diagnosis (median): 2.1-2.5 months DAS28 median: 6.1-6.3	*Efficacy* ACR20 at 24 wks (primary outcome) ACR50/70 Physician's global assessment of disease activity Patient's global assessment of disease activity Patient assessment of pain Patient assessment of disability *Safety* AEs, SAEs, discontinuation due to AEs and lab tests. *Results are found in Table 3*	This trial is the first to examine oral versus SC administration of MTX. They found that SC administration was significantly more effective than oral administration of the same MTX dosage. There was no difference in tolerability. The results of our study support the use of MTX as monotherapy in patients with RA, being the best of the currently available monotherapies for this condition.	Challenges associated with blinding an oral/SC study were handled appropriately. Research is required to determine if the same level of improvement could have been reached by increasing the oral dose, and whether the oral dose could be maximized before switching to SC.

ACR20: at least 20% improvement from baseline values in swollen joint count and tender joint count, as well as 5 other disease activity measures that are part of the ACR improvement criteria.
DAS28: disease activity severity; includes an assessment of 28 joints and includes ESR and disease activity VAS

abbrevations: ACR=American College of Rheumatology; DAS=Disease Activity Score; ESR= erythrocyte sedimentation rate; MTX=methotrexate; PO=oral administration; RA=rheumatoid arthritis; SC=subcutaneous administration

Table 3: Efficacy and Safety Results from Braun et al (2008)[14]				
Efficacy				
Total study population		**MTX SC N=188**	**MTX oral N=187**	**P values**
ACR20	16 weeks	85%	77%	P<0.05
	24 weeks	78%	70%	P<0.05
ACR50	24 weeks	62%	59%	ns
ACR70	24 weeks	41%	33%	P<0.05
# swollen joints	24 weeks	2	2	P=0.04
# tender joints	24 weeks	3.5	6	P=0.08
DAS28	24 weeks	3.3	3.7	ns
Patient with a time between diagnosis and study entry ≥1 year		MTX SC N=52	MTX oral N=46	
ACR20	24 weeks	89%	63%	P<0.05
Patients who did not reach ACR20 at week 16 (treatment strategy dependent on initial treatment group)		MTX 15 mg SC to MTX 20 mg SC N=22	MTX oral to MTX SC 15mg N=30	
ACR 20	24 weeks	23%	30%	
Safety				
Total study population		MTX SC N=193	MTX oral N=188	P values
Withdrew due to AE		9.3%	4.3%	nr
≥1 adverse event		66%	62%	nr
≥1 moderate AE		41%	41%	nr
SAE		5.7%	4.3%	nr
Abdominal pain		8.8%	10.6%	nr
Diarrhea		2.6%	6.9%	nr
Dyspepsia		6.7%	5.9%	nr
Loss of appetite		7.3%	3.2%	nr
Nausea		16.6%	12.2%	nr
Stomatitis		3.1%	3.7%	nr
Vomiting		3.6%	3.2%	nr
Increase liver enzymes		1.6%	4.3%	nr

abbreviations: ACR=American College of Rheumatology; AE=adverse event; DAS=Disease Activity Score; MTX=methotrexate; nr=not reported; ns=no statistically significant difference; PO=oral administration; SAE=serious adverse event; SC=subcutaneous administration