Review

A systematic review on the optimum management of the use of methotrexate in rheumatoid arthritis patients in the perioperative period to minimize perioperative morbidity and maintain disease control

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ABSTRACT

Objective. *To examine the use of methotrexate (MTX) in rheumatoid arthritis (RA) patients during the perioperative period.*

Methods. *Systematic review of studies retrieved by a sensitive search strategy in Medline (1961–July 2007), Embase (1961–July 2007), Cochrane Library (up to July 2007), and from the abstracts of the ACR (2005, 2006) and EULAR (2005–2007) annual scientific meetings. Selection criteria: (population) studies had to include patients with RA undergoing surgery; (intervention and control) studies had to test continuing MTX* versus *stopping MTX; and (outcomes), studies had to report complications within a year after the surgery including infections, wound morbidity, surgery complications, and RA flares. Only randomized controlled trials (RCT) or high quality cohort studies with a control group were included.*

Results. *Patients from the four included studies were mostly women with mean ages around 60. All of them underwent elective orthopaedic surgery and were taking MTX doses mainly from 5 mg/week to 10 mg/week. By order of level of evidence, we found two RCTs, in which continuing on MTX was not associated with increasing risk of surgery complications, but it was statistically associated with less RA flares. In a prospective cohort study, four infections were observed in the MTX group while none were observed in the control group. No disease flare was reported in any group. A retrospective study showed that patients on MTX reported fewer cases of wound morbitity (p=0.038), RA flares (p=0.050), and no differences related to infections compared to those who stopped MTX.*

Conclusions. *Continuing with low doses of MTX seems to be a safe option during the perioperative period in RA patients without relevant comorbidities and/or risk factors of infections, undergoing elective orthopaedic surgery, while maintaining disease control.*

Introduction

Methotrexate (MTX) is a drug widely used on patients with rheumatoid arthritis (RA). Nowadays, there is controversy over whether or not to stop MTX in patients who are undergoing surgery in order to balance concerns over risk of infection or other complications and risk of increased disease activity (1, 2).

Steuer (3) reported, in a questionnaire sent to 200 randomly selected rheumatologists, the common opinion on this issue. Firstly, 35% of rheumatologists were concerned that MTX may increase post-operative complications. However, significantly fewer rheumatologists "always" advised stopping MTX both pre- and postoperatively (14%). Many advocated "sometimes" stopping the drug perioperatively (48%), depending on blood count, drug dose, previous postoperative complications and other factors. Finally, the timing of stopping treatment preoperatively and restarting after surgery also significantly differ among rheumatologists (from a week to even more than four weeks).

To date, there is, therefore, evidence of great variability in clinical practice related to the use of MTX perioperatively, probably reflecting the little evidence on whether or not to continue MTX and on the optimal time to stop the drug or optimal dosage if maintaining MTX. Given that the amount of RA patients undergoing surgery in daily practice is high (4, 5), the international experts of

the 3E Initiative (6) formulated the following question: "What is the optimum management of usual dose MTX in RA patients in the perioperative period to minimize perioperative morbidity, while maintaining RA control?".

The aim of this study was therefore to systematically review the literature available on the above question. This information was afterwards examined and used by the experts to generate clinical practice recommendations for rheumatologists regarding the use of MTX in the perioperative period.

Methods

A systematic review was performed to address the experts' question on the use of MTX in RA patients undergoing surgery during the perioperative period. The question was not rephrased because it was not necessary. The reviewer (EL) and the mentor (LC) established the protocol of the review and obtained further advice from the complete team of the 3E Initiative, including the program convenor, other mentors and other reviewers.

Search strategy

The studies were identified by sensitive search strategies in the main bibliographic databases (Table I). For this purpose, an expert librarian collaborated and checked the search strategies. The following bibliographic databases were screened: Medline and Embase from 1961 to July 11, 2007, and the Cochrane Central register of Controlled Trials (CENTRAL) up to July 11, 2007. The abstracts of the annual scientific meetings of the American College of Rheumatology (ACR) (2005, 2006), and The European League Against Rheumatism (EULAR) (2005, 2006, 2007) were also examined. There were no language limitations. All the retrieved references were managed in Procite 5.1 (Thomson ResearchSoft). Finally, a hand search was completed by reviewing the references of the included studies, and all the publications or other information provided by the experts related to the systematic review were also examined.

Selection criteria

The studies retrieved by the above strategies were included if they met the following pre-established criteria:

The patients studied had to be RA patients aged 18 or older who had started taking MTX more than four weeks before the surgery. The subjects should clearly take MTX (and no other DMARDs concomitantly when possible, and irrespectively of the use of steroids) at least one week before the surgery. No restrictions related to the type of surgery were considered.

In the intervention group, the patients should continue on MTX. The control group ought to include patients stopping MTX at least a week before the surgery.

The following outcomes within a year after the surgery were considered: infections, wound morbidity, surgery complications, and RA flares.

Only randomized controlled trials

Table I. Search strategies in the different bibliographic databases and hits.

Line	Terms	Result
	Medline (July 11 2007)	
1	"Arthritis, Rheumatoid" [mh]	84,747
2	rheumatoid arthritis [tiab]	53,961
3	1 OR 2	95,833
4	"Methotrexate" [mh]	25,380
5	methotrexate [tiab]	22,698
6	4 OR 5	32,604
7	3 AND 6	3,695
8	"Perioperative Care"[mh] OR "Surgery"[mh] OR "surgery "[sh] OR "Surgical Procedures, Operative"[mh]	2,176,486
9	perioperative [tiab] or surger* [tiab] OR surgic* [tiab]	850,917
10	8 OR 9	2,423,474
11	7 AND 10	274
12	"complications" [sh] OR "Intraoperative Complications" [mh] OR "Postoperative Complications" [mh] OR "Infection" [mh] OR "Cross Infection" [mh] OR "Surgical Wound Infection" [mh] OR "Wounds and Injuries" [mh] OR "injuries" [sh]	2,257,640
13	complication* [tiab] OR infection* [tiab] OR injuri* [tiab] OR wound [tiab]	1,090,981
14	12 OR 13	2,864,822
15	11 AND 14	118
	Embase (July 11 2007)	
1	RHEUMATOID ARTHRITIS/ or rheumatoid arthritis.mp.	34,960
2	METHOTREXATE/ or methotrexate.mp.	39,292
3	1 and 2	6,922
4	PERIOPERATIVE PERIOD/ or perioperative care.mp. or SURGERY/ or surgery.mp. or SURGICAL TECHNIQUE/ or surgical procedures.mp. or PEROPERATIVE CARE/ or preoperative care.mp. or intraoperative care.mp. or surger$.mp. or surgic$.mp.	539,385
5	3 and 4	309
6	COMPLICATION/ or INFECTION COMPLICATION/ or INFECTIOUS COMPLICATION/ or INJURY/ or PEROPERATIVE COMPLICATION/ or POSTOPERATIVE COMPLICATION/ or POSTOPERATIVE INFECTION/ or SURGICAL INFECTION/ or SURGICAL INJURY/ or SURGICAL MORTALITY/ or SURGICAL RISK/ or SURGICAL WOUND/ or WOUND COMPLICATION/ or WOUND INFECTION/ or complication$.mp. or infection$.mp. or injury$.mp. or wound$.mp.	889,656
7	5 and 6	151
	Cochrane Central Register of Controlled Trials (July 11 2007)	
1	rheumatoid arthritis.mp.	3,966
2	methotrexate.mp.	3,671
3	1 and 2	529
4	(perioperative or intraoperative or peroperative or postoperative or surgery).mp.	74,826
5	3 and 4	11
	ACR 2005, 2006	
1	"rheumatoid arthritis" AND "methotrexate" AND "surgery"	8
	EULAR 2005, 2006, 2007	
1	rheumatoid arthritis AND methotrexate AND surgery	15

(RCT) or high quality cohort studies with a control group were included.

Screening of studies, data collection and analysis

Two reviewers (EL and JAM) screened the titles and abstracts of the retrieved articles for selection criteria independently. This process was done in 20 minutes sessions. The two reviewers collected the data from the studies included by using *ad hoc* standard forms. All collection was double by article and independent. One of the reviewers (EL) entered the data from the forms into spreadsheets. If, while doing this, the reviewer found any discrepancy between her information and that of the other reviewer's, then a consensus was reached by looking at the original article or by asking the mentor. Articles that did not fulfil all the inclusion criteria or that had insufficient data were excluded. To grade the quality, we used a modification of the Oxford Centre for Evidence-based Medicine Levels of Evidence in its May 2001 update (7), in which: 1a) Systematic reviews of RCT with homogeneity; 1b) Individual RCT with narrow confidence intervals; 1c) Trials in which all patients get harm or none does; 2a) Systematic reviews of cohort studies with homogeneity; 2b) Individual cohort study, or low quality randomized controlled trials; 2c) "Outcomes" Research and Ecological studies; 3a) Systematic reviews of case-control studies with homogeneity; 3b) Individual Case-Control study; 4) Case-series and poor quality cohort and case-control studies; and 5) Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles".

Evidence tables were produced. Meta-analysis was only planned in case enough homogeneity was present among the included studies.

Results

The result of the search strategies is presented in Table I by specific terms, and in total in Figure 1. We found 39 articles that were studied in detail because by title or abstract they seemed to be related to the study, or because they had no abstract to review. Table II shows the studies that were excluded after detailed review and the reasons for exclusion.

Finally, four studies were included in the present systematic review and their data retrieved (all of them were available in Medline and Embase searches). Table III shows the main characteristics of the included studies. We selected 2 RCT (8, 9) (quality level Ib) and 2 cohort studies (10, 11) (quality level 2b). Related to the population of the studies, all patients underwent orthopaedic surgery and they were mostly women with mean ages around 60. For patients who continued on MTX, the mean doses were mainly from 5 mg/week to 10 mg/week and they were not modified before surgery. Finally, all studies included information on perioperative complications.

In the first study, Grennan (8) showed the results of a randomized unblinded prospective 1-year follow-up study (Oxford Level of Evidence 1b). A total of 338 RA patients underwent orthopaedic surgery, 88 continued on MTX (mean dose 10 mg/week) and 72 stopped the drug 2 weeks before surgery (mean doses 7.5 mg/week). Most of the patients

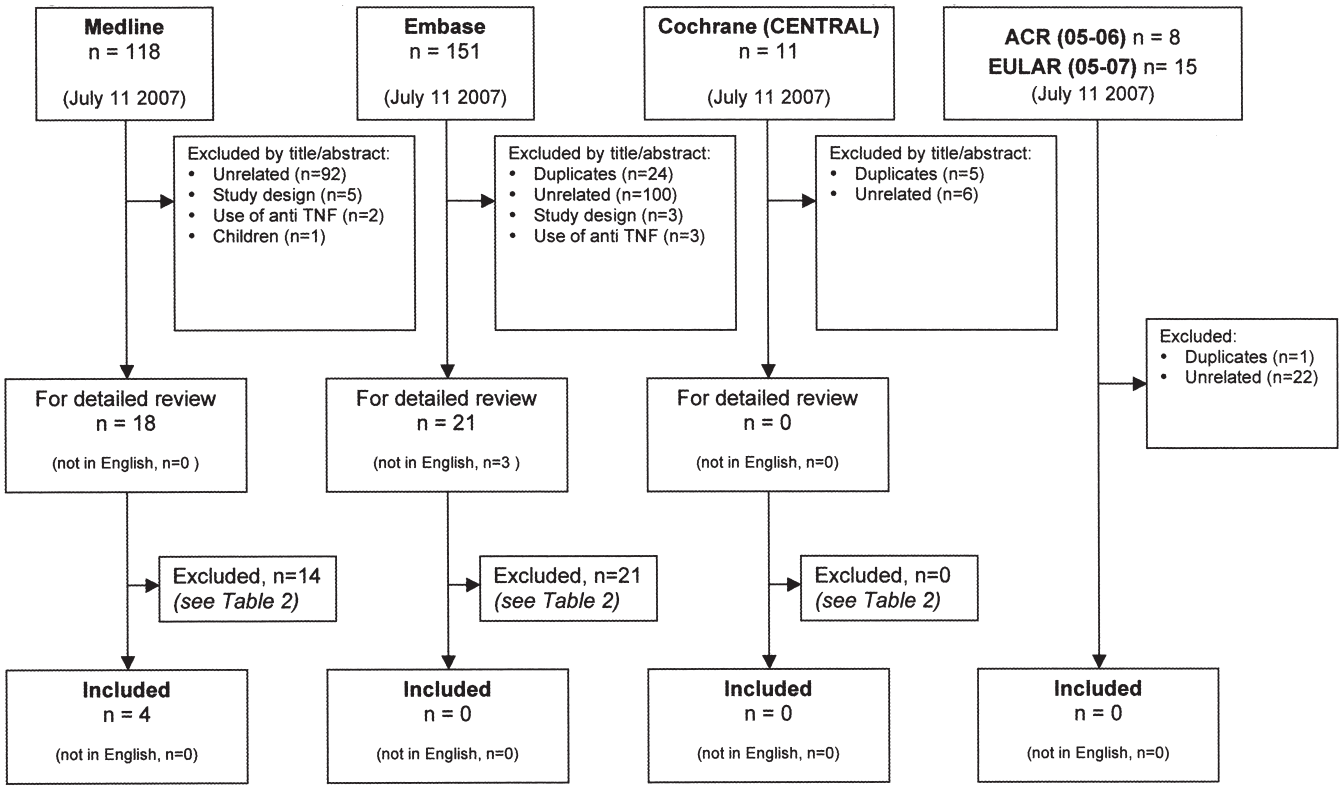

Fig. 1. Articles retrieved by the different search strategies and result of selection and appraisal process.

Table II. Excluded studies and reason for exclusion.

Study	Reason for exclusion
Alarcon[16], 1996	Case series
Bibbo[17], 2003	No control group
Bongartz[18], 200	Review article
Bridges[19], 1991	No control group
Bridges[20], 1997	Review article
Brooks[21], 1992	Review article
Busti[22], 2005	Review article
Coughlin[23], 2006	Unrelated
Den Broeder[24], 2007	Related to anti-TNF
Dias[25], 2001	Letter to editor
Escalante[26], 1995	No control group
Fuerst[27], 2006	No control group
Furst[28], 1994	Unrelated review article
Haynie[29], 1996	Review article
Howe[30], 2006	Review article
Howland[31], 1988	Case series
Hudson[32], 2006	Review article
Hurowitz[33], 2007	No control group
Jain[34], 2002	No control group
Jain[35], 2004	Review article
Kasdan[36], 1993	No control group
Katz[12], 1991	Letter to editor
Kelley[37], 2002	Review article
Keystone[38], 1996	Review article
Lidgren[39], 2003	Review article
Loehr[40], 1999	Incomplete data
Lyssy[2], 1996	Review article
Perhala[1], 1991	No control group
Petrozza[41], 2002	Review article
Raikin[42], 2006	Review article
Rehart[43], 2005	Review article
Rehart[44], 2006	Unrelated
Rehart[45], 2007	No control group
Steuer[3], 1997	Randomized interview to physicians asking on the use of perioperative methotrexate
Wilkinson[46], 2004	Review article

(80%) were women with a mean age of 62. The incidence of any complication was lower in the patients who continued with MTX compared to those who had stopped the drug (p=0.003). There were not any RA flares in the MTX group, while 8% of those who had stopped MTX presented at least one. In the multivariate analysis, MTX in any dose, whether continued or discontinued before surgery, did not increase the risk of surgical complications.

Sanny (9) included 64 RA patients who underwent orthopaedic surgery in a randomized unblinded prospective 8-month follow-up study (Oxford Level of Evidence 1b). A total of 32 patients continued MTX and 32 stopped it more than a week before surgery. All the study patients were on MTX mean doses of 10 mg/week. No differences were found relating to the occurrence of wound morbidity (19% in the group that stopped and 13% in the group that did not; p=0.500). No infections were registered in any group.

We also included an observational prospective one-year follow-up study (Carpenter (10), 1996), corresponding to the Oxford Level of Evidence 2b. In this study, 13 RA patients undergoing orthopaedic surgery continued on MTX (mean dose 13.1 mg/week) and 19 discontinued it two weeks before (mean dose 12.5 mg/w). Four infections occurred postoperatively among the patients on MTX while none occurred in the control group. No patient in either group experienced a postoperative flare of RA.

After the detailed review, the paper by Murata (6) was also included in this systematic review. It is a retrospective 1-year follow-up study (Oxford Level of Evidence 2b) in which 116 RA patients were analyzed. A total of 48 patients continued on MTX (mean doses 4.3 mg/week) and 12 stopped it (mean dose 4.9 mg/week) more than a week before surgery. Relating to wound morbidity, 10% presented it in the control group while just 1.3% of the RA patients continued on MTX (p=0.038). Moreover, there were fewer infections (4% *vs*. 5%; *p=0.601*) and RA flares (1% *vs*. 14%; *p=0.050*) in the MTX group.

Discussion

Currently there is evidence of great variability in clinical practice relating to the use of MTX perioperatively, probably due to the lack of evidence on whether or not to continue MTX and on the optimal time to stop the drug or optimal dosage if maintaining MTX (3).

In the present study we have analyzed the effect of MTX in RA patients undergoing surgery during the perioperative period. For the purpose of the present systematic review, we decided to include randomized and cohort controlled studies, in which there were control groups (a group of patients continuing on MTX and a control group stopping MTX). We considered this as the most appropriate way to answer the research question.

Overall, the evidence does not contraindicate the use of MTX during the perioperative period in RA patients undergoing elective orthopaedic surgery. MTX is not clearly associated with an increasing risk of surgery complications, and maintains disease control.

The largest amount of evidence comes from two RCTs (8, 9) of excellent quality (1b). Additionally, we analyzed two cohort studies (10, 11) quality 2b, with adequate follow-up (without any drop-out) who met our inclusion criteria.

According to the RCTs (8, 9) and to one of the cohort studies (11), MTX was not associated with an increasing risk of surgery complications, includ-

Table III. Main characteristics of the included studies.

Study	Participants	Intervention	Outcomes measured	Quality
Grennan[8], 2001 Randomised unblinded prospective study 1-y follow-up	n=338 (group A n=88, group B n=72) Mean age (group A 61, group B 63); women (group A 82%, group B 79%) RA, orthopaedic surgery	-Group A: MTX > 6 w (mean dose 10 mg/w) before surgery, not discontinued, same dose. -Group B: stopped MTX (mean dose 7.5 mg/w) 2 w before, restarted 2 w after surgery	% wound morbidity % systemic infections % total infections % surgery complications % RA flares	1b
Sany[9], 1993 Randomised unblinded prospective study 8-m follow-up	n=64 (group A n=32, group B n=32) Mean age (group A 52, group B 49); women (group A 94%, group B 88%) RA, orthopaedic surgery	-Group A: MTX (mean dose 10 mg/w) > 6 w before surgery, not discontinued, same dose. -Group B: stopped MTX (mean dose 10 mg/w) > 1 w before	% wound morbidity % total infections % RA flares	1b
Carpenter[10], 1996 Observational prospective 1-y follow-up	n=32 (group A n=13, group B n=19) Mean age (group A 59, group B 61); women (group A 77%, group B 79%) RA, orthopaedic surgery, MTX before surgery. No concurrent AZA	-Group A: MTX (mean dose 13.1 mg/w) > 6 w before surgery, not discontinued, same dose. -Group B: stopped MTX (mean dose 12.5 mg/w) 2 w before	% wound infections % prosthesis infection % total infections % RA flares	2b
Murata[11], 2006 Observational retrospective	n=116 (group A n=48, group B n=12) Mean age (group A 62 years, group B 59 years); mostly women in both groups RA, orthopaedic surgery. No concurrent etanercept, leflunomide, surgeries for infection	-Group A: MTX (mean dose 4.3 mg/w) > 6 w before surgery, not discontinued, same dose. -Group B: stopped MTX (mean dose 4.9 mg/w) 2 w before.	% wound morbidity % total infections % RA flares	2b

y: year; RA; rheumatoid arthritis; MTX: methotrexate; mg: milligram; w: week; m: month; AZA: azathioprine.

ing wound morbidity and infections. However, in the study by Carpenter (10) there were more infections in the RA patients who continued MTX perioperatively.

Regarding the part of the question "while maintaining RA control", there were no RA flares in the MTX continuation group and 8% in the discontinuation group in the Grennan study (8) and also there was a difference in the cohort study by Murata (11). No differences were found in the study of Carpenter (10), and the remaining RCT (9) did not properly report the RA flares .

However, the sample sizes from the four studies are probably too small to detect differences in risks between groups with an adequate statistical power. In fact, Katz (12) suggested that assuming a significance level of 0.05 and a power of 0.80, 160 patients should be enrolled in each group to detect a relative risk of 3 (15% *vs*. 5%).

Related to the studies population characteristics, most of the patients included were women, a gender distribution similar to those of most cohorts of patients undergoing orthopaedic surgery (4). Nevertheless, their mean ages were around sixty, and most patients did not report important comorbid conditions. Therefore, they may not properly represent the whole spectrum of RA patients who are being followed up in daily practice and who eventually undergo orthopaedic surgery. On the other hand, it is well known that orthopaedic surgery complications are associated with several factors including increasing age, the use of steroids and comorbidity (6, 13-15).

Regarding the reason to stop or continue MTX, in two of the studies (8, 9) the patients were randomly allocated to each group. In the study of Carpenter (10), patients continued or stopped according to orthopedist or rheumatologist preferences but no significant differences were found between groups in patient demographic and disease features. Finally, in the retrospective study of Murata (11), no clear information was provided on the reason to continue or stop MTX. Therefore, it is not possible to completely dismiss the possibility of a referral bias.

Moreover, the mean doses of patients continuing on MTX perioperatively were mostly from 5 up to 10 mg weekly. This systematic review could not address the perioperative effect of increased doses of MTX. This is very important because, as it has been shown, many RA patients who undergo orthopaedic surgery have active and aggressive diseases (4, 5), thus they are probably taking MTX at higher doses or combined therapy. Regarding the management of MTX after surgery, only one study (Grennan (8)) reported clearly when MTX was restarted, *i.e*. a week after surgery. This information is not present, or not in a clear way, in the other three studies included.

As presented, all patients underwent elective orthopaedic surgeries. Although these interventions are rather prevalent among RA patients, other major surgeries need to be analyzed, such as digestive procedures or minor but "dirty" procedures, such as dental procedures, in order to better decide the management of MTX in each surgery.

Authors defined surgery complications and RA control using very similar criteria. However, connected to the outcomes, and specifically to the disease activity in the included studies, the criteria used for RA flare were not based

on the disease activity measures currently used, such us the ACR criteria or DAS. Changes in DAS, HAQ and other similar accepted measures would probably be better to assess the effect of continuing or stopping MTX on disease activity and progression.

In conclusion, despite the limitations of the available data, MTX (low doses) seems to be a safe drug during the perioperative period, and it maintains disease control, at least in uncomplicated RA patients. Nevertheless larger studies of more representative patients are needed to answer this question more definitively. These studies should also determine the appropriate dosing of MTX perioperatively, or the timing for stopping and restarting MTX if this drug is discontinued.

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