Review

Risk and management of liver toxicity during methotrexate treatment in rheumatoid and psoriatic arthritis: a systematic review of the literature

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The 3E Initiative, including this work, was supported by Abbott with an unrestricted educational grant.

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Received on December 3, 2008; accepted in revised form on April 29, 2009.

Clin Exp Rheumatol 2009: 27: 1017-1025.

Key words: Methotrexate, rheumatoid arthritis, hepatotoxicity, liver, systematic literature review.

Competing interests: none declared.

ABSTRACT

Objectives. *To systematically review the literature on liver toxicity in rheumatoid arthritis (RA) and psoriatic arthritis (PsA) patients treated with methotrexate (MTX), as an evidence base for generating clinical practice recommendations for the management of MTX and the indication for a liver biopsy (LB) in case of elevated liver enzymes (LE).*

Methods. *A systematic literature search was carried out in MEDLINE, EMBASE, Cochrane Library and ACR/EULAR meeting abstracts. Data on the incidence of elevated LE, subsequent adjustments in MTX therapy and the prevalence of fibrosis/cirrhosis in pre-MTX and post-MTX LB were pooled.*

Results. *Forty-seven out of 426 identified references were included in the systematic review. For RA, the incidence rate of elevated LE in the first three years of MTX use was 13/100 patient-years with a cumulative incidence of 31%. MTX was permanently discontinued in 7%, paused or reduced in 26% and continued without any adjustment in 67% of patients with an abnormal test. After 4 years of MTX use, LB showed in 15.3% of the (unrelated) cases mild fibrosis, in 1.3% severe fibrosis and in 0.5% cirrhosis, while pre-MTX biopsies showed 9%, 0.3% and 0.3% abnormalities, respectively. For PsA, evidence is limited. Additional studies suggest that cumulative MTX dose and serial LE elevations among other risk factors are related to liver pathology.*

Conclusion. *This review suggests that LE elevations during MTX therapy are a frequent but transient problem, that serial abnormal LE tests might be associated with liver pathology, but that cirrhosis is relatively rare. It is, however, not clear from the literature how therapy should be adjusted in case of elevated LE and to what extent MTX independently attributes to liver toxicity.*

Introduction

Methotrexate (MTX) is widely used as the disease modifying anti-rheumatic drug (DMARD) of first choice in the treatment of rheumatoid arthritis (RA) and is effective for psoriatic disease as well (1-3). Although the efficacy and tolerability profile of MTX is well established, liver toxicity has always remained a concern (4-6).

In several historical psoriasis cohorts in the seventies, prevalences of liver fibrosis/cirrhosis up to 26% were found in patients treated with MTX (7, 8). In addition, these studies suggested that higher cumulative doses of MTX were associated with liver pathology. This formed the basis for the recommendations of the Dermatology society to perform surveillance liver biopsies (LB) at baseline and after every 1.5 g of MTX (9, 10).

Rheumatologists initially followed the dermatology guidelines for MTX treatment of RA patients, but as emerging evidence and experience suggested a lower incidence of liver toxicity in RA, the American College of Rheumatology (ACR) suggested new guidelines (11). The '94 ACR guidelines only recommend a LB at baseline in RA patients with pre-existent risk factors for liver pathology and a LB during MTX therapy in case of persistent elevated aspartate aminotransferase (AST) or decreased albumin, as studies suggested a relation with liver pathology.

As a result of these discrepancies, clinical practice varies widely. Specifically, the management of psoriatic arthritis (PsA), often treated by both specialties, can create difficulties, as

the risk of liver toxicity in this subset of psoriatic patients is not clear (12). Furthermore, more recent studies have reported much lower incidences of liver pathology also in psoriasis, which led to a renewed discussion about the usefulness of surveillance LB (13-15). In summary, more consensus is needed on how to monitor liver toxicity during MTX therapy, including the need for multiple LE tests, LB, and subsequent treatment adjustments.

This manuscript is part of the 3E Initiative of '07-'08, a multinational effort that recently developed clinical practice recommendations for the use of MTX in rheumatology (16). As part of the 3E, the objective of the current work was to systematically review the literature on MTX-associated liver toxicity in RA and PsA, as an evidence base for generating the recommendations. The following question was addressed: 'What are indications for pausing, stopping or restarting MTX in case of elevated liver enzymes and when is a liver biopsy indicated?'

Methods

A detailed description of the methodology of the 3E Initiative can be found elsewhere (16). The systematic literature review was carried out in several steps following the updated guidelines for Cochrane systematic reviews (17).

Rephrasing research question

The clinical question as formulated by the rheumatologists in the 3E Initiative (16) was translated into an epidemiological research question according to the PICO method (18). *Patients* were defined as adults with RA according to the ACR criteria, or PsA, on MTX therapy, who had increased LE (AST or alanine aminotransferase (ALT)) (19). The *Intervention* was defined as any adjustment of MTX therapy (dose paused, reduced or permanently discontinued) with no adjustment of MTX as the *Comparator.* The anticipated *Outcome* was liver pathology, defined as either histological fibrosis/cirrhosis on a LB or persistently elevated LE. Odds ratios (OR) and relative risks (RR) were anticipated effect parameters. The final search question was thus rephrased as: 'What is the risk for liver pathology when adjusting MTX therapy or not in case of elevated LE in RA and PsA patients and what is the indication for a liver biopsy?'

Systematic literature search

A systematic literature search for articles published between 1950 and September 2007 was carried out in MEDLINE, EMBASE and the Cochrane Library, using a comprehensive search strategy, in collaboration with an experienced librarian (Table I) (20). The EULAR 2005-2007 and ACR 2005-2006 meeting abstracts were also searched. The search was not limited to study design or language.

Relevant articles were selected by title/abstract screening and reviewed in full paper, applying the following inclusion criteria: RA or PsA (not psoriasis) patients ≥18 years old on monotherapy MTX, not limited to any route of administration, with available data on elevated LE or LB. Articles that did not fulfil the inclusion criteria or had insufficient data for analysis were excluded. During the selection process, it became apparent that randomised controlled trials (RCTs) investigating different management strategies of MTX in case of elevated LE were not found. Therefore, only observational studies (prospective and retrospective cohort studies, case-control studies) were included. Letters, case reports, case series and reviews were also excluded, although they were used for hand searching additional references.

Data extraction and quality appraisal

Publication and study population characteristics, duration and (cumulative) dose of MTX, and data on LE and LB were extracted from the included articles using standard forms. The methodological quality of each study was graded by the 'Newcastle Ottawa Scale' for non-randomised observational studies(21), which was translated into the final Level of Evidence according to the Oxford Centre for Evidence-based Medicine (http://www.cebm.net/index.aspx?o=1025, accessed July 2008).

Data analysis

The retrieved articles contained insufficient information to precisely address the research question as defined in the PICO. No studies were found that compared the (hepatic) outcome of adjusting MTX or not in case of elevated LE. The included cohort studies, however, did assess the magnitude of the problem of liver toxicity, either as the incidence of abnormal LE tests or as the prevalence of fibrosis/cirrhosis in RA or PsA patients on MTX. Therefore, these available data were summarised and pooled.

A pooled cumulative incidence of elevated LE was calculated as the number of patients with at least one increased AST/ALT test (=cases) divided by the total number of patients initially at risk (at baseline) from the pooled studies. The 95% confidence interval (CI) was calculated as: $p \pm 2x\sqrt{(p(1-p)/N)}$ in which p=probability and N=total number of patients. In a second analysis, to account for the various follow-up periods, incidence rates were calculated per study as the number of cases divided by the total number of patient-years. Subsequently, the pooled mean incidence rate, weighted by the sample sizes of the studies, was calculated. A caveat of the calculation in patient-years is the fact that time is in the denominator, which might dilute the true incidence in studies with longer follow-up if LE elevations predominantly occur early. To explore this, a stratified analysis for patients with less than two years of follow-up and for patients with more than two years of follow-up was performed.

A pooled prevalence and 95% CI of fibrosis/cirrhosis was calculated as the number of patients with fibrosis/cirrhosis divided by the total number of patients who underwent a LB in the pooled studies. LB were graded according to the Roenigk scale in which: Grade I and II represent relatively normal histology, with mild to severe fatty infiltration, nuclear variability, and portal inflammation; Grade IIIA is mild fibrosis with or without formation of fibrotic septa extending into the lobules; Grade IIIB is moderate to severe fibrosis and Grade IV is cirrhosis (22).

Table I. Systematic search strategy Medline.

1. **Population**
   "Arthritis"[Majr:NoExp] OR "rheumatoid arthritis"[ti] OR "Arthritis, Rheumatoid"[Majr:NoExp] OR "arthritis, psoriatic"[Majr] OR psoriatic arthritis[ti]

2. **Intervention**
   "Methotrexate"[majr] OR mtx[ti] OR Amethopterin[ti] OR Methotrexate*[ti] OR Mexate*[ti] OR abitrexate*[ti] OR amethopterin*[ti] OR a-methopterin*[ti] OR ametopterin*[ti] OR antifolan*[ti] OR emtexate*[ti] OR emthexate*[ti] OR emtrexate*[ti] OR enthexate*[ti] OR farmitrexate*[ti] OR folex[ti] OR ledertrexate*[ti] OR methoblastin*[ti] OR methohexate*[ti] OR methotrate*[ti] OR methylaminopterin*[ti] OR metotrexat*[ti] OR novatrex*[ti] OR rheumatrex[ti]

3. **Outcome**
   hepatotoxic*[ti] OR liver enzymes[ti] OR liver enzyme[ti] OR cirrhosis[ti] OR Liver[ti] OR "Liver"[Majr] OR hepatic[ti] OR "Liver Diseases"[Majr] OR "Liver Cirrhosis"[Majr] OR "Liver Function Tests"[Majr] OR "Hepatic Insufficiency"[Majr:NoExp] OR alanine aminotransferase[ti] OR "Alanine Transaminase"[majr] OR aspartate aminotransferase[ti] OR "Aspartate Aminotransferases"[majr] OR alkaline phosphatase[ti] OR albumin[ti] OR "alkaline phosphatase"[majr] OR "albumins"[majr] OR "Hepatitis"[Majr] OR "Liver enzyme elevation"[ti] OR "hepatic enzyme"[ti] OR "hepatic enzymes"[ti]

4. 1 AND 2 AND 3

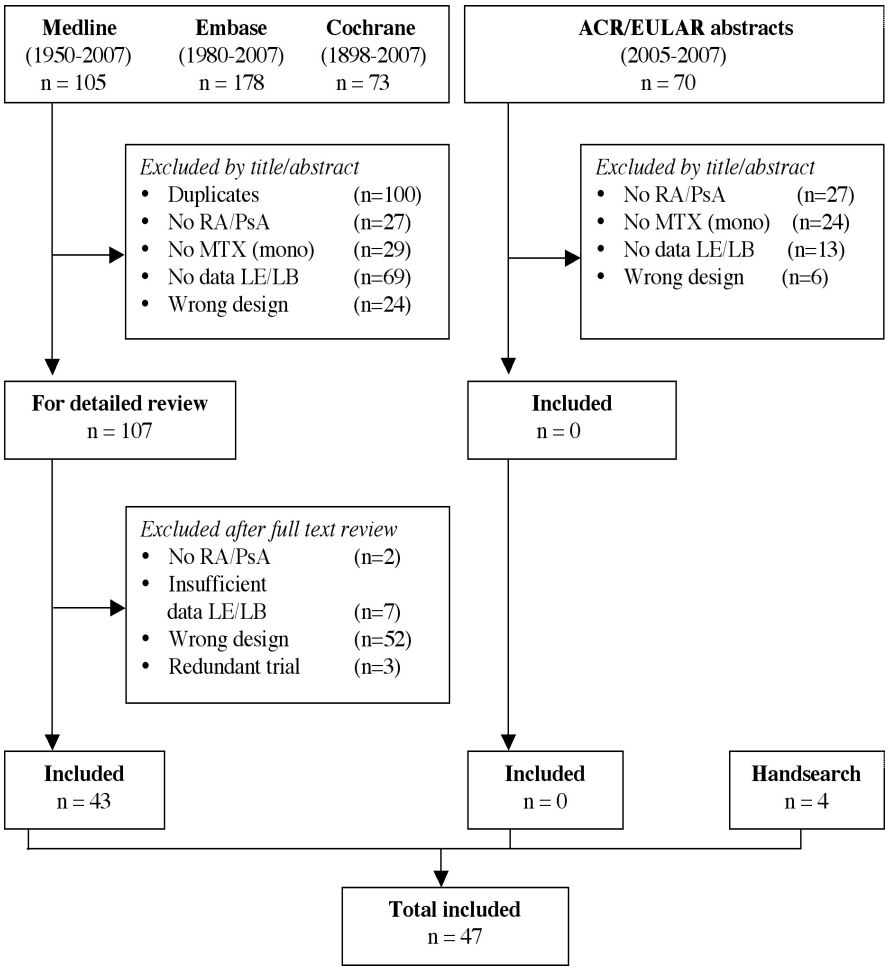

Fig. 1. Flowchart results systematic literature search.

When either a baseline and follow-up biopsy or several follow-up biopsies were available, the percentage of patients with progression was calculated, defined as an increase from Grade I/II to III/IV. Data from the first and the last LB were analysed.

Results

A total of 426 references were identified with the systematic search strategy, of which 107 articles were retrieved for full paper review and 43 fulfilled the inclusion criteria (Table I, Fig. 1). Four additional papers from the hand search were included. The final 47 references included prospective and retrospective cohort studies and 2 case-control studies. Only 5 studies on PsA were found. A list of excluded studies after full paper review with the reason for exclusion is available as supplementary material.

Elevated liver enzymes

Of the 47 references, 23 studies contained data on LE elevations during MTX use in RA patients (23-45). Patient characteristics of 2199 patients from 18 studies that contained sufficient data to be pooled, are shown in Table II (23-26, 28, 29, 31-33, 35-39, 42-45) The patients had established RA, with a mean disease duration of 9.2 years and 3.5 years of MTX use with a mean dose of 12.5mg/wk. Most risk factors for hepatic disease, including pre-existing liver disease, alcohol intake, diabetes and obesity were insufficiently reported.

The pooled cumulative incidence of elevated LE in these patients was 31% (Table IIIA). Stratified by the AST/ALT cut-off, defined in 14/18 studies, the cumulative incidence was 49% > the upper limit of normal (ULN) and 17% >2-3 times the ULN. The overall incidence rate of elevated LE was 13/100 patient-years. However, after stratification for follow-up time, it appeared that the incidence rate was highest in the first two years of MTX use (Table IIIB). Pooled data from 12/18 studies showed that MTX was frequently continued without any dose adjustment in 67%, the dose was reduced or paused in 26% and MTX was permanently discontinued in 7% of the patients with elevated LE (Table IIIA). These adjustments were

not standardised, but a decision of the rheumatologist. Whether LE spontaneously normalised was not sufficiently reported.

The remaining 5 studies included 4 prospective cohorts and 1 case-control study. Kremer *et al*. prospectively followed a cohort of longstanding RA patients for a mean of 7.5 years on MTX and found that elevated LE were most frequent during the first years of therapy.(30) Rau *et al*. reported that elevated LE were most frequent during the first months of therapy.(34) Ujfalussy *et al*. and Weinblatt *et al*. reported that only 5% and 2% of RA patients, respectively, permanently discontinued MTX due to serial LE elevations after 5-6 years (40, 41). Hoekstra *et al*. compared the MTX treated RA patients with and without elevated LE (ALT >3 times ULN) from a randomised placebo controlled trial of folic acid versus placebo and found lack of folic acid and high body mass index as predictors for elevated LE (27).

Liver biopsy abnormalities

Of the 47 references, 34 studies contained data on LB performed in RA patients during MTX therapy.(23-26, 28, 29, 34-36, 42, 43, 45-69) Walker *et al*. is a case-control study which will be described separately.(67) Characteristics of 2179 patients from the 33 cohort studies which were pooled are shown in Table II. They had established RA, with a mean disease duration of 9.9 years and 4.0 years of MTX use with a mean cumulative dose of 2.4 g. Risk factors for hepatic disease were insufficiently reported.

Pooled LB data of 1154 RA patients from these cohorts, showed a prevalence of 15.3% mild fibrosis (Roenigk Grade IIIa), 1.3% moderate to severe fibrosis (Grade IIIb) and 0.5% cirrhosis (Grade IV) (Table IVA). The LB were systematically taken after various cumulative doses of MTX for surveillance of treatment. Results did not change if the four studies in which LB were performed on indication were left out. MTX was discontinued as a result of the biopsy outcome in 2.9% of the patients. In pre-treatment LB from 372 patients, mild fibrosis was already present in 9.1%, severe fibrosis in 0% and cirrhosis in 0.3% (Table V).

Table II. Characteristics of RA patients, weighted by study sample size, from 18 studies assessing liver enzyme (LE) elevations and 33 studies assessing liver biopsy (LB) abnormalities.

Patient characteristics weighted mean (range)	LE studies (n=18)	LB studies (n=33)
Total no. patients	2199	2179
Age (yrs)	56 (43–62)	55 (44–66)
Females %	66 (46–95)	68 (20–100)
Disease duration (yrs)	9.2 (3.2–13.2)	9.9 (3.2–18.5)
Duration MTX therapy (yrs)	3.5 (0.3–5.0)	4.0 (1.0–12.5)
Dose MTX (mg/wk)	12.5 (5.0–15.0)	12 (7.5–15.9)
Cumulative dose MTX (g)	1.7 (0.2–3.1)	2.4 (0.4–8.8)
Prior DMARDs (% studies)	50	52
Folic acid use (% studies)	24	9
NSAID use (% studies)	56	67

MTX: methotrexate; DMARDs: disease modifying anti-rheumatic drugs; NSAID: non-steroidal anti-inflammatory drug.

Table III. A. Cumulative incidence ± 95% confidence interval of abnormal liver enzymes (LE) and subsequent MTX adjustments, pooled from 18 studies in 2199 RA patients on MTX for a mean of 3.5 years (cumulative dose 1.7 g)
B. Pooled incidence rates of abnormal LE, stratified by MTX duration and LE cut-off.

A

Elevated LE	Cumulative incidence	Permanent stop MTX	Pause/dose reduction	MTX unchanged
All cut-offs (n=18)	31% ± 2	7% ± 2	26% ± 4	67% ± 4
>ULN (n=7)	49% ± 3	7% ± 2	19% ± 4	74% ± 4
>2-3 x ULN (n=7)	17% ± 2	12% ± 10	42% ± 15	46% ± 16

B

Incidence rate (per 100 patient-years)	< 2 yrs MTX	≥ 2 yrs MTX
>ULN (n=7)	40	12
>2-3 x ULN (n=7)	17	5

LE: liver enzymes; MTX: methotrexate; ULN: upper limit of normal.

Pooled data on serial biopsies in 689 patients, who underwent either a pre-MTX plus a post-MTX LB or several post-MTX LB, showed progression from a normal liver to fibrosis in 43 patients (6.2%). All patients progressed to Grade IIIa, except one who progressed to Grade IIIb. No progression to cirrhosis was found. The mean duration of MTX therapy in these patients was 4.6 years.

Of the 15 identified patients with severe fibrosis, only 2 baseline LB were available which did not show signs of fibrosis. In addition, in 7/15 patients other risk factors for hepatic disease were present, in 1/15 no other risk factors were present and in 7/15 this information was not available. Of the 6 identified patients with cirrhosis, only one had a baseline LB, which already showed cirrhosis. In 4/6 patients other risk factors were present and in 2/6 not. Risk factors included diabetes, obesity, viral hepatitis, congestive heart failure, alcohol, autoimmune hepatitis and toxic drug use.

In four studies risk factors for histological fibrosis/cirrhosis were investigated using multivariable analyses. Ros *et al*. reported that age, alcohol, RA duration and albumin (at the time of LB) were independently associated with the Roenigk score, but cumulative MTX dose was not (35). Philips *et al*. identified obesity and pre-existent pulmonary

Table IV. A. Prevalence ± 95% confidence interval of fibrosis and cirrhosis in liver biopsies (LB) during MTX therapy per study and pooled over 1154 RA patients. Data from the last biopsies are given. **B.** Stratified by cumulative dose of MTX in grams.

A

Study (ref)	Number of patients with ≥ 1 LB	Grade IIIa (mild fibrosis)	Grade IIIb (severe fibrosis)	Grade IV (cirrhosis)
Kent (29)	5	1 (20%)	0	0
Fathi (52)	32	4 (13%)	0	0
Ros (35)	24	3 (13%)	0	0
Richard (62)	36	10 (28%)	0	0
Weinblatt (69)	17	2 (12%)	0	0
Beyeler (47)	16	1 (6%)	1 (6%)	0
Kremer (58)	94	7 (7%)	0	0
Erickson (50)	66	14 (21%)	3 (5%)	2 (3%)
Arias (23)	16	1 (6%)	0	0
Bjorkman (49)	15	10 (67%)	1 (7%)	0
Carvallo (26)	16	1 (6%)	0	0
Minocha (60)	24	0	1 (4%)	2 (8%)
Philips (61)	45	7 (16%)	2 (4%)	1 (2%)
Tishler (65)	10	1 (10%)	0	0
Hall (55)	18	13 (72%)	2 (11%)	0
Scully (36)	40	12 (30%)	0	0
Willkens (43)	52	15 (29%)	0	0
Brick (25)	69	8 (12%)	1 (1%)	1 (1%)
Kremer (56)	27	14 (52%)	0	0
Rau (34)	30	9 (30%)	1 (3%)	0
Aponte (46)	21	3 (14%)	2 (10%)	0
Bjorkman (48)	26	4 (15%)	0	0
Shergy (63)	210	6 (3%)	0	0
Szanto (64)	17	1 (6%)	0	0
Boh (24)	21	0	0	0
McKenzie (59)	60	1 (2%)	0	0
Tolman (66)	29	9 (31%)	1 (3%)	0
Weinstein (42)	17	6 (35%)	0	0
Groff (54)	3	0	0	0
Hoffmeister (28)	57	7 (12%)	0	0
Drosos (45)	41	6 (15%)	0	0
Total	1154	176	15	6
Pooled prevalence	-	15.3 % ± 2.1	1.3 % ± 0.7	0.5 % ± 0.4

B

Cumulative dose MTX (g)	Number of patients	Grade IIIa (mild fibrosis)	Grade IIIb (severe fibrosis)	Grade IV (cirrhosis)
<1.5	144	12.5% ± 5.5	0.7% ± 1.4	0%
1.5-3	500	17.4% ± 3.4	1.4% ± 1.1	0.8% ± 0.8
>3	154	30.5% ± 7.4	4.6% ± 3.4	1.3% ± 1.8

fibrosis as statistically significant predictors for fibrosis/cirrhosis, corrected for several clinical variables (61). In contrast, the cumulative dose/duration of MTX was a significant predictor of serious liver disease, together with age, in a case-control study by Walker *et al*. (67). Similarly, Kremer *et al*. found that the cumulative dose/duration of MTX was significantly related to fibrotic changes on LB. The multivariable analysis, however, only included weight, gender and alcohol, and revealed only weight as a predictor (56). Our pooled data, in a stratified analysis, showed a trend for more histological abnormalities with higher cumulative MTX dose (Table IVB). However, the analysis could not be corrected for other confounding risk factors as these were insufficiently reported.

Association LE and LB

The evidence on the relation between elevated LE and LB abnormalities is conflicting. Some studies reported that serial measurements of abnormal LE are related to LB abnormalities (43, 50, 56, 58, 66, 67), but others found no such association (25, 36, 42, 45, 48, 56) Walker *et al*. showed in a case-control study that LE were more often elevated in the preceding year in MTX treated RA patients with clinically significant liver disease, than in patients without liver disease.(67) Erickson *et al*. retrospectively applied the '94 ACR guidelines, which recommend a LB if 5/9 AST tests are >ULN, on a cohort of 66 RA patients who underwent a surveillance LB after every 1.5 g MTX.(50) Only one diabetic patient with significant LB abnormalities would have been missed. The sensitivity and specificity of the guidelines were 80% and 82%, respectively, but the positive predictive value for severe fibrosis/cirrhosis was low. Finally, Kremer *et al*. prospectively studied 3 cohorts of 94 RA patients, who underwent a total of 354 surveillance LB during 5 years of MTX therapy (56, 58). The mean AST level and the percentage of abnormal AST tests (>ULN) were correlated with the Roenigk biopsy grades. If <50% of the LE tests was normal, the specificity for a normal LB was 97%. However, the positive predictive value of serial elevated LE remained low, as most of the biopsy results were normal.

PsA

For PsA only 5 studies were identified (39, 40, 51, 53, 63) Tilling *et al*. reported a higher incidence of elevated LE (>3xULN) after 3 years of MTX in PsA than in RA patients (14.5% versus 7.5%, respectively), with more frequent discontinuation of MTX in PsA (40% versus 17%, respectively) (39). The incidence was higher in male PsA than in male RA patients, not explained by alcohol intake. Espinoza *et al*. reported an incidence of elevated LE of 27.5% (>ULN) after 3 years MTX therapy (51).

Pooled data on LB from 71 PsA patients showed an incidence of 9.9%±7.1 mild fibrosis, 1.4%±2.8 moderate fibrosis and 1.4%±2.8 cirrhosis (51, 53, 63). Only Espinoza *et al*. reported the MTX duration of 3 years with a cumulative dose of 1.6 g. Sufficient data on pre-MTX LB and progression were not available.

Discussion

This systematic review summarises the available evidence on MTX-associated liver toxicity in RA and PsA. Within the limitations of what was available in the literature, the results formed the phramework of discussions in the 3E Initiative, resulting in the development of clinical practice recommendations for the management of MTX therapy (16).

The results showed that LE elevations above the ULN are frequent with an incidence rate of 40/100 patient-years in the first two years of MTX use and a cumulative incidence of 49% after three years. Despite the frequent occurrence of elevated LE tests, the results suggest that MTX is continued without any adjustment in the majority of the patients. If we assume that rheumatologists would eventually adjust MTX therapy in patients with sustained abnormal tests, it seems that spontaneous normalization occurred frequently, but this is not reported as such and therefore only assumption. Nevertheless, results from our review and two separate cohort studies suggest that LE elevations are often a transient problem, occurring more frequently in the early stages of treatment (30, 34). However, these observations might be biased by the fact that therapy is adjusted or even discontinued with the aim of lowering the liver enzymes and by the selection of well responding patients. The most intriguing question, however, whether reduction or (temporary) discontinuation of MTX reduces the risk of future liver pathology, could not be answered, as this has not been investigated in any study.

Our results showed that the prevalence of severe liver fibrosis and cirrhosis in RA patients after a mean of four years on MTX is relatively low (1.3% and 0.5% respectively). Walker estimated an even lower 5-year incidence of significant liver disease of 0.1% in RA patients treated with MTX, but this was based on a survey among American rheumatologists (67). Whiting-O'Keefe reported a prevalence of advanced histological changes (Grade IIIb/IV) of 2.7% after 4 years on MTX in a meta-analysis of 334 RA patients.(70) In our extended review including 1154 patients, the corresponding risk for Grade IIIb/IV was 1.9%. In addition, we found that 6.2% of the RA patients on MTX showed progression from normal to mild fibrosis (Grade IIIa) in serial LB, while Whiting-O'Keefe found that 24.3% of the RA patients showed histological progression. However, progression in the latter study was probably overestimated, as it was defined as an increase in 1 grade on the Roenigk scale with the assumption that baseline LB would be normal. As our data showed that 9.1% of pre-treatment LB already had Grade IIIa changes, this assumption probably does not hold. In summary, the risk for serious hepatic pathology with MTX is low, but mild fibrotic changes seem to occur more often.

The most important caveat of the observational evidence is the lack of correction for other risk factors associated with liver pathology. It is, therefore, difficult to assess the independent contribution of MTX to the development of liver disease. Looking closely at the data we found some indications, although these are not conclusive. Two of the four studies which investigated determinants of liver fibrosis/cirrhosis via solid statistical analyses, found that the cumulative dose and duration of MTX therapy were significant determinants (56, 67). We found a similar trend for such an association, but we could not correct the analysis for potential confounders. That other risk factors should be accounted for is emphasised by the finding that these were typically present in the cases of severe fibrosis/cirrhosis described in the literature, however not in all patients (34, 46, 47, 50, 51, 60, 61, 71, 72). Potential confounders include age, diabetes, alcohol, obesity, viral hepatitis, disease duration and other hepatotoxic drugs. In addition, our data on pre-treatment hepatic changes indicate that other factors than MTX might be involved early in the development of liver pathology. Moreover, the histological features of MTX-associated toxicity are non-specific and resemble those of non-alcoholic steatohepatitis (NASH), which is a common form of liver disease, associated with diabetes and obesity and with the propensity to develop into cirrhosis (73). Given all these potential confounders and their insufficient reporting in most studies, it remains difficult to assess the attributable risk of MTX for liver pathology independent of other risk factors.

The available evidence on the usefulness of performing serial LE tests for the detection of (future) liver pathology is controversial. The findings of Kremer *et al*. served as the basis for the '94 ACR guidelines, in which monitoring of AST/ALT every 4-8 weeks and a LB in case of 5 abnormal tests out of 9 during one year are recommended (11). Although repeatedly normal tests had high specificity for a normal biopsy, the

Table V. Prevalence ± 95% confidence interval of fibrosis and cirrhosis in pre-MTX liver biopsies (LB) per study and pooled over 372 RA patients.

Study (ref)	Number of patients with pre-MTX LB	Grade IIIa (mild fibrosis)	Grade IIIb (severe fibrosis)	Grade IV (cirrhosis)
Fathi (52)	10	0	0	0
Ros (35)	42	6 (14%)	0	0
Richard (62)	38	15 (39%)	0	0
Erickson (50)	10	1 (10%)	0	0
Carvallo (26)	21	0	0	0
Philips (61)	34	0	0	0
Tishler (65)	10	1 (10%)	0	0
Brick (25)	62	2 (3%)	0	1 (2%)
Kremer (56)	27	0	0	0
Rau (34)	60	9 (15%)	0	0
Boh (24)	20	0	0	0
McKenzie (59)	25	0	0	0
Groff (54)	3	0	0	0
Hoffmeister (28)	10	0	0	0
Total	372	34	0	1
Pooled prevalence	–	9.1% ± 3.0	0 %	0.3% ± 0.6

positive predictive value of serial abnormal tests was low.(50) In addition, the risks associated with performing a LB are substantial. Therefore, we are in need of more sensitive non-invasive tests for the prediction and diagnosis of liver pathology. New promising non-invasive methods for quantitative testing of fibrosis are currently emerging in the field of hepatology (74, 75).

For PsA the evidence suggests a somewhat higher incidence of elevated LE and fibrosis/cirrhosis compared with RA patients, but the evidence is limited. Whiting O'Keefe's meta-analysis also included psoriatic patients and reported a higher prevalence of severe fibrosis/cirrhosis (7.7% *vs*. 2.7%) and a higher progression rate (33.1% *vs*. 24.3%) than in RA, but a separate analysis for PsA was not performed due to insufficient data on this subgroup (70). Potential reasons for the higher frequencies observed in psoriasis patients are a different distribution of confounding risk factors, an inherently higher susceptibility, and more regular testing of LE with treatment adjustments in RA. Nevertheless, the risk for PsA patients and the question whether they are more like RA or psoriasis, remains unclear.

This review summarised and pooled evidence from a large number of studies, which were systematically identified following a strict methodology. However, pooling data might have introduced bias, due to heterogeneity of the included studies. Therefore, stratified analyses for clinically relevant subgroups were also performed. Another limitation is the lack of more recent studies including early diagnosed RA patients treated with higher dosages of MTX plus folic acid, which would better reflect current practice. As investigated concurrently in the 3E Initiative, and reported in several well-designed studies, folic acid significantly reduces the incidence of elevated LE, but whether this protects the liver in the long-term is not known (27, 76, 77). Most importantly, trials comparing different management strategies of MTX in case of elevated LE are completely lacking. Therefore, future studies might address these unanswered questions, while also taking into account correction for confounding factors.

In conclusion, this review suggests that hepatotoxicity during MTX therapy for RA is a relatively mild problem. Serial abnormal LE might be associated with liver pathology, but there is no evidence on how therapy should be adjusted in case of elevated LE in order to prevent future liver disease. Moreover, the contribution of MTX independent from other risk factors has not been well established. Therefore, for the monitoring of liver toxicity, control of these factors seems equally important, as they are often involved concomitantly. Given the low prevalence of cirrhosis and the risks of complications, liver biopsy only seems justifiable as an ultimate measure for histological confirmation of liver disease.

Acknowledgements

We wish to thank J.W. Schoones, Walaeus Library, Leiden University Medical Center, The Netherlands, for participating in the elaboration of the systematic search strategy; all the participants of 3E, and especially the bibliographic team who participated in rephrasing the research question, developing the search strategy and planning the analyses.

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