

Methotrexate Drug Interactions in the Treatment of Rheumatoid Arthritis: A Systematic Review

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ABSTRACT. *Objective.* Patients with rheumatoid arthritis (RA) often have comorbidities that require multiple medications. Several of these medications may alter the efficacy or increase the toxicity of methotrexate (MTX). The purpose of our study was to determine which drugs used in combination with MTX (excluding disease modifying antirheumatic drugs, folic and folinic acid, corticosteroids, and biologic agents) enhance side effects or toxicity of MTX or lower its efficacy.

Methods. A systematic literature search was performed with Medline, Embase, Cochrane Register and Database, and abstracts from the 2006/2007 annual congresses of the American College of Rheumatology and the European League Against Rheumatism. A manual search of the citation lists of retrieved publications was performed.

Results. Of the 1172 articles identified, 67 were included: 21 pharmacokinetics studies, 5 observational studies, and 78 case reports. Most medications do not significantly affect the pharmacokinetics profile of MTX. Among the clinical studies, cytopenia and elevation of liver enzymes were the main reported toxicities. The use of trimethoprim-sulfamethoxazole (TMP-SMX) was mentioned as a risk factor for developing cytopenia in one observational study and in 17 case reports. Thirty case reports of cytopenia were attributed to the use of concomitant nonsteroidal antiinflammatory drugs, including acetylsalicylic acid. Two studies described mild abnormalities of liver enzymes with the use of isoniazid, and one study with the use of high-dose ASA.

Conclusion. Based on the published literature, MTX has limited drug interactions, with the exception of TMP-SMX and high-dose ASA, which can exacerbate toxicity of MTX. The clinical significance of these interactions has not been substantiated by extensive clinical observations. (First Release May 1 2010; J Rheumatol 2010;37:1416–21; doi:10.3899/jrheum.090153)

Key Indexing Terms:

METHOTREXATE

DRUG INTERACTIONS

RHEUMATOID ARTHRITIS

In recent years, the introduction of methotrexate (MTX) in the field of rheumatology has dramatically improved the clinical status and the outcome of many patients with rheumatoid arthritis (RA) and other inflammatory diseases. MTX is currently the recommended first-line therapy in RA, being used as monotherapy or in combination with traditional or biologic disease modifying antirheumatic drugs (DMARD). It is therefore not surprising that more than 70% of the patients in large RA cohorts are treated with MTX.

Patients with RA often have comorbidities that require multiple medications. The use of concomitant drugs might result in considerable variations in MTX pharmacokinetics, and this may alter the efficacy or increase the toxicity of MTX. Thus, it is important to investigate the potential for clinically significant drug interactions with MTX.

Our systematic review is part of the 3e Initiative (evidence, expertise, exchange) in Rheumatology, a multinational effort to promote evidence-based medicine by formulating recommendations addressing clinical problems. In our review we aimed to identify drugs that could affect the efficacy and/or toxicity of MTX in patients with RA.

MATERIALS AND METHODS

Our objective was to determine what drugs used in combination with MTX (excluding DMARD, folic and folinic acid, corticosteroids, and biologic agents) might increase side effects or toxicity of MTX, or lower its efficacy. Applying relevant keywords, we performed a systematic literature search using Medline (Ovid from 1950 to July week 5, 2008), Embase (from 1980 to 2008 week 32), Cochrane Central Register of Controlled Trials (until Quarter 3, 2008), Cochrane Database of Systematic Reviews (until Quarter 2, 2008), and abstracts from the 2006/2007 annual congresses of American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR). The strategy combined synonyms of MTX (methotrexat*, amethopterin*, methylamethopterin*, metotrexate*, mexate, mtx, rheumatrex) with different terms used for adverse events and efficacy (drug interaction, drug resistance, drug tolerance, drug toxicity, poisoning, chemically induced, contraindication, complication, adverse effect*, drug effect*, mortality, toxicity, effica*, effecti*, toxi*, side effect*, toler*, intoler*, discont*). DMARD, folic and folinic acid, corticosteroids, and biologic agents were deliberately excluded in the search strategy as MeSH terms (Medical Subject Headings). However, articles reporting the use of these medications concomitantly with MTX and another medication were analyzed. The methodological quality of the observa-

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tional studies was graded according to the levels of evidence of the Oxford Center for Evidence-Based Medicine (<http://www.cebm.net>; range 1–5, with lower value indicating higher quality). The methodology is summarized in Figure 1.

RESULTS

The search identified 1341 citations, excluding duplicates. Articles in English or French were selected, which represent 1160 papers. We supplemented the search by reviewing references from the selected articles and found 12 additional references, for a total of 1172. We screened each title and abstract for relevance and excluded 1024 articles that did not specifically report on MTX drug interaction in RA patients. After exclusions, based on abstract review, 148 full-text articles were retrieved and reviewed in detail. Eighty-one were excluded because they were not relevant (Figure 1). Finally, 67 papers were included in the analysis: 5 observational studies, 78 case reports, and 21 pharmacokinetics studies. Study characteristics were summarized in tabular format for each article included. The level of evidence was between 2b and 3b for the observational studies, and between 4 and 5 for the case reports. Characteristics of the 5 observational studies are described in Table 1. Among the clinical studies, cytopenia and elevation of liver enzymes were the main reported toxicities. In one observational study¹, the proportion of patients with abnormal liver enzymes was higher in the group “MTX plus high-dose acetylsalicylic acid (ASA)” compared to the group “MTX without ASA.” Another study² found no differences in toxic-

city between nonsteroidal antiinflammatory drugs (NSAID) and high-dose ASA. Two studies^{3,4} described mild abnormalities of liver enzymes with the use of isoniazid (INH). One³ found that 11% of the patients taking MTX and INH had transient increase in liver enzymes. These elevations were less than one-half the upper limit of normal and resolved spontaneously. The other⁴ found mildly abnormal liver enzymes in 2 of 5 patients taking MTX, INH, and infliximab concomitantly.

Use of trimethoprim-sulfamethoxazole (TMP-SMX) was mentioned as a risk factor for developing bone marrow suppression in a retrospective case-control study⁵ and in 17 case reports⁶⁻¹⁹. In the case reports, TMP-SMX was mostly used for the treatment of cystitis. There was no reported case of interaction with TMP-SMX 3 times weekly for *Pneumocystis jiroveci* prophylaxis. The duration of antibiotic treatment before discovery of cytopenia was between 2 days and 2 months, with the majority being within the first 2 weeks. MTX dose was usually low, between 5 and 15 mg per week. Folic acid was either not used or was not mentioned in the report.

Thirty case reports of cytopenia were attributed to use of concomitant NSAID^{12,20-32}. Indomethacin, diclofenac, and ibuprofen were each reported in 3 or more cases, but naproxen, probenecid, flurbiprofen, metamizole, ketoprofen, and piroxicam were rarely mentioned. Four cases were attributed to use of high-dose ASA (3.0–5.2 g/day)^{31,32}. There were no reported cases with use of low-dose ASA.

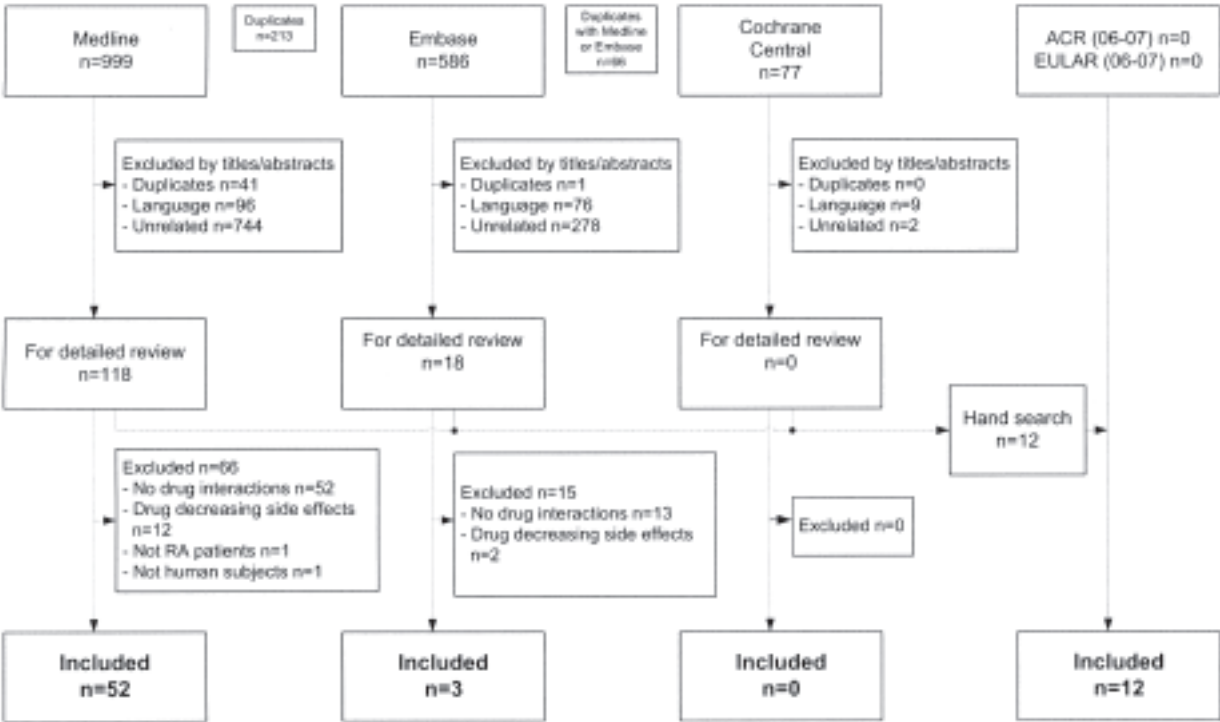


Figure 1. The process of study selection.

Table 1. Observational studies on methotrexate drug interactions.

Study	Study Characteristics	Results	Oxford Level of Evidence
Fries ¹	Retrospective study: review of data bank ARAMIS N = ~ 2600 RA patients Objective: to identify medications that are risk factors for elevated transaminase	MTX without ASA: N = 186; % abnormal LFT: AST/ALT: 2.69/7.86; MTX with ASA: N = 46; % abnormal LFT: AST/ALT = 15.22/16.67; Conclusion: Combination of: MTX and ASA increases frequency of abnormal liver enzymes	2b
Rooney ²	Retrospective study N = 34 RA patients on MTX Objective: to compare clinical toxicity of NSAID vs ASA, used with MTX	ASA: n = 12; Various NSAID: n = 22; Conclusion: No difference in toxicity between NSAID and ASA, when used with MTX	2b
Mor ³	Retrospective study N = 44 RA pts on MTX and INH for latent TB Objective: to investigate the toxicity of INH and MTX treatment	11% of pts demonstrated transient LFT elevations ($< 2 \times N$), spontaneously resolved; No cessation of treatment; Conclusion: Use of INH with MTX was well tolerated; follow LFT closely	3b
Vanhoof ⁴	Part of a RCT evaluating safety of TNF inhibitors N = 5 pts on MTX, infliximab, and INH	2/5 developed liver abnormalities; Mean AST/ALT = 50/82; Conclusion: Be aware during treatment with INH and MTX	2b
Al-Awadhi ⁵	Retrospective study N = 12 cases of pancytopenia Controls = 144 without cytopenia Objective: to determine which risk factors are associated with pancytopenia associated with MTX	2/12 pts with pancytopenia used TMP-SMX; 0/144 pts without pancytopenia used TMP-SMX; Conclusion: One of the identified risk factors was concomitant use of TMP-SMX and MTX	3b

ARAMIS: Arthritis, Rheumatism and Aging Medical Information System; TB: tuberculosis; INH: isoniazid; NSAID: nonsteroidal antiinflammatory drug; ASA: acetylsalicylic acid; TNF: tumor necrosis factor; LFT: liver function test; TMP-SMX: trimethoprim-sulfamethoxazole.

Other specific medications that have been implicated in case reports are amoxicillin, ofloxacin, flucloxacillin, cefotiam, penicillin, tetracycline, and erythromycin, reported in one case each, and fluorouracil cream, reported in 2 cases^{11,12,33-37}. The proton pump inhibitor lansoprazole has been thought to play a role in one case of cytopenia, and the H₂-antagonists cimetidine and ranitidine have been implicated in one and 4 cases of cytopenia, respectively^{27,29,38,39}. Triamterene, rofecoxib, nicotinic acid, glafenine, and angiotensin-converting enzyme inhibitors are other medications that have rarely been reported^{29,33,40-42}. The concomitant use of multiple medications was also mentioned as a factor precipitating cytopenia in a number of case reports^{27,30,37,43-46}.

Papers dealing with pharmacokinetics interactions are detailed in Table 2⁴⁷⁻⁶⁷. Nineteen of 21 reports evaluated NSAID. Cyclooxygenase-2 (COX-2) inhibitors were evaluated in 4 studies and ASA in 5. The number of patients in each study is generally small, with an average of 19 patients. The outcome was MTX pharmacokinetics in 19 studies, including 6 that evaluated both MTX and its metabolite, 7-OH-MTX. The majority looked at the area under the concentration-time curve (AUC) and the maximum concentration observed in plasma (C_{max}) as the outcomes.

Most medications (13/19) did not significantly alter the pharmacokinetics profile of MTX and 3/6 showed no change in its metabolite upon addition of another medication. Few studies reported variation in the pharmacokinetics variables, such as an increase in exposure to MTX or its

metabolite. On the other hand, 4 studies showed either a small reduction in the AUC, therefore decreasing the exposure to MTX, or a reduction in the C_{max} without changing the exposure. For ibuprofen and naproxen, conflicting results were observed. Tracy, *et al*⁴⁷ found that ibuprofen and naproxen, as well as trisalicylate, can decrease the systemic clearance of MTX. However, Stewart, *et al*⁴⁸ found no difference in the clearance of MTX with the use of naproxen, and Skeith, *et al*⁴⁹ showed that the pharmacokinetics indices were not significantly influenced by ibuprofen. Studies evaluating high-dose ASA⁵⁰⁻⁵⁴ (1.3–4.5 g/day) were more consistent, with 4/5 (80%) studies reporting an increase of the serum concentration of MTX. In general, clinical implications were not reported or discussed.

DISCUSSION

The objective of our study was to investigate the potential for clinically significant drug interactions with MTX in adult patients with RA. A systematic review of the literature revealed that studies were very heterogeneous in terms of design, quality, and details provided. Observational studies often lack a comparator group. Case reports provide anecdotal evidence that does not highlight patients who took concomitant medications without developing any side effects. The clinical influence and relevance of the pharmacokinetics studies is unknown. Therefore, although our systematic review of the literature included 67 papers, the paucity of high quality studies limits our ability to draw strong conclusions on the role of concomitant medications

Table 2. Pharmacokinetics studies on MTX interactions.

Study	Medication	No. Patients	Age, yrs [†]	Duration of Treatment Combination (days)	MTX dose (mg/wk) (mean if unspecified)	Pharmacokinetics Modification?
Herrick ³⁴	Flucloxacillin	20	54 (median)	3	7.5 (median)	Y*
Tracy ⁴⁷	ASA (2.2–4.5 g/day), ibuprofen, naproxen	9	46	Min 7	7.5 to 15	Y
Stewart ⁴⁸	Naproxen	15	34 to 78	38	15	N
Skeith ⁴⁹	Ibuprofen or flurbiprofen	6	61.7	7	20	N
Stewart ⁵⁰	ASA (3.9 g/day)	15	35 to 63	7	10	Y
Seideman ⁵¹	ASA (2 g)	11	55	One dose	15	Y
Tracy ⁵²	Ketoprofen, piroxicam, flurbiprofen	10	48	Min 6	7.5 to 17.5	N
Furst ⁵³	ASA (3.4 g/day), sulindac	12	—	16	17.8	MTX: Y 7-OH: Y
Kremer ⁵⁴	Various NSAID	46	MTX 7.5 mg: 61.8 (30 pts) Usual dose: 54.7 (16 pts)	Variable	7.5 (30 pts)	Y (pts receiving usual wkly maintenance doses)
Vakily ⁵⁵	Naproxen and lansoprazole	27	50.3	7	7.5 to 15	MTX: N 7-OH: N
Hartmann ⁵⁶	Lumiracoxib	18	49.1	7	11	MTX: N 7-OH: Y*
Hamilton ⁵⁷	Ferrous sulfate	10	58.4	7	7.5	N
Schwartz ⁵⁸	Rofecoxib	25	59	21	13.9	MTX: N 7-OH: Y
Karim ⁵⁹	Celecoxib	14	51.9	7	10.5	N
Iqbal ⁶⁰	Various NSAID	37	39	Min 6	7.5 to 10	N
Hubner ⁶¹	Meloxicam	13	59	7	15	N
Gumbhir-Shah ⁶³	Bromfenac	10	54.2	6	9.5	MTX: N 7-OH: Y
Combe ⁶⁴	Piroxicam	20	49.1	Min 15	10	Y**
Anaya ⁶⁵	Etodolac	19	48.7	7	10	MTX: Y** 7-OH: N
Ahern ⁶⁶	Various NSAID	14	66.3	Min 5	15	N
Svensen ⁶⁷	Various NSAID	44	60	—	—	N

* Small decrease in exposure (AUC) to MTX or 7-OH-MTX with the use of the comedication. ** Decrease in the C_{max} , but no change in exposure (AUC).

[†] Values are mean unless otherwise specified. Min: minimum; Y: yes; N: no; ASA: acetylsalicylic acid; NSAID: nonsteroidal antiinflammatory drugs.

as a risk factor for MTX toxicity. Prospective drug interaction studies would have brought a higher level of evidence and should be done in the future for drugs that are likely to be administered concomitantly with MTX in large numbers of patients. Nevertheless, based on the published literature, some data suggest that TMP-SMX and high-dose ASA could have an effect. Indeed, use of TMP-SMX was implicated in one case-control study and in 17 case reports. TMP is a structural analog of the pteridine portion of dihydrofolic acid and has the potential to inhibit dihydrofolate reductase. Since MTX also inhibits dihydrofolate reductase, it is not surprising that the use of these 2 medications can potentiate bone marrow toxicity. It is noteworthy that interactions with TMP-SMX occurred with relatively low dose of MTX, between 5 and 15 mg per week.

It is well known that salicylates can increase serum levels of MTX by several mechanisms. Four of 5 pharmacokinetic

studies and some observational studies suggest that there is a potential for high-dose ASA to interact with MTX. Nevertheless, there was no reported interaction with the use of low-dose ASA. The introduction of a large choice of NSAID in recent years has significantly decreased the use of high-dose ASA as the mainstay NSAID for treatment of RA. Despite some case reports incriminating NSAID as risk factors for MTX toxicity, no significant signals have emerged from the many clinical trials using MTX in RA, nor from the large observational cohorts. It is therefore appropriate to prescribe NSAID with reasonable confidence in RA patients taking MTX, while being cautious in patients with potential for impaired renal function.

The use of folic or folinic acid, which was not the norm at the time most of these observations were reported, could have reduced the incidence of toxicities in these patients⁶⁸. Our systematic review of the literature was purposely limit-

ed to adult RA patients and we cannot exclude that other interactions could potentially occur with the use of MTX in different populations or situations.

In conclusion, based on the published literature, MTX has limited drug interactions, with the exception of TMP-SMX and high-dose ASA, that can exacerbate toxicity of MTX. Despite some incriminating case reports, NSAID have been widely used without emerging signals of toxicity. Therefore, the often cited drug interactions, for example, with NSAID or the proton pump inhibitors, should not contraindicate their concomitant use with MTX in patients with RA. However, regular monitoring of blood counts and liver enzymes needs to be performed as recommended⁶⁸ and caution is still advised in patients such as the elderly with potential for impaired renal function.

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