# 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.

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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-

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 study[1], 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 study[2] found no differences in toxicity 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). One[3] 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 other[4] 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 study[5] and in 17 case reports[6-19]. 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 *Pnemocystis 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.

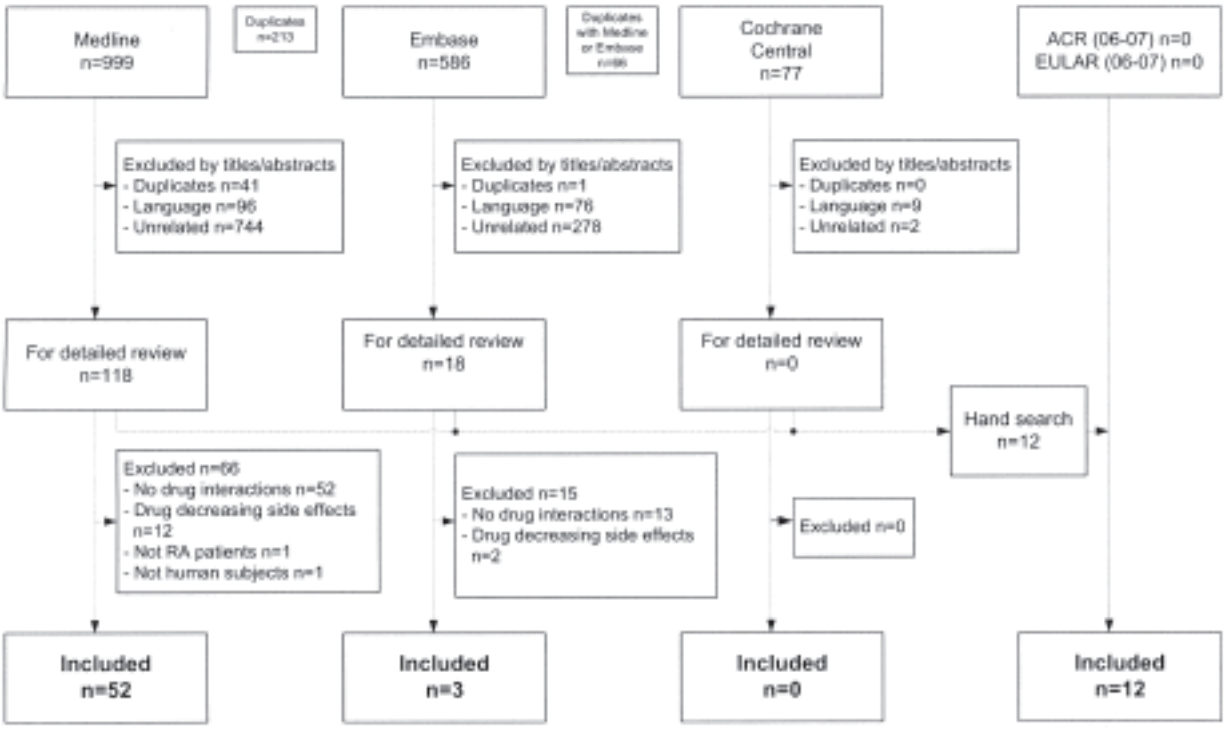


*Figure 1*. The process of study selection.

*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<br>N = ~ 2600 RA patients<br>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<br>N = 34 RA patients on MTX<br>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<br>N = 44 RA pts on MTX and INH for latent TB<br>Objective: to investigate the toxicity of INH and MTX treatment | 11% of pts demonstrated transient LFT elevations (< 2 × 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<br>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<br>N = 12 cases of pancytopenia<br>Controls = 144 without cytopenia<br>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 lanzoprazole has been thought to play a role in one case of cytopenia, and the $H_2$-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 2[47-67]. 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 ASA[50-54] (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<br>7-OH: Y |
| Kremer[54] | Various NSAID | 46 | MTX 7.5 mg: 61.8 (30 pts)<br>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<br>7-OH: N |
| Hartmann[56] | Lumiracoxib | 18 | 49.1 | 7 | 11 | MTX: N<br>7-OH: Y* |
| Hamilton[57] | Ferrous sulfate | 10 | 58.4 | 7 | 7.5 | N |
| Schwartz[58] | Rofecoxib | 25 | 59 | 21 | 13.9 | MTX: N<br>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<br>7-OH: Y |
| Combe[64] | Piroxicam | 20 | 49.1 | Min 15 | 10 | Y** |
| Anaya[65] | Etodolac | 19 | 48.7 | 7 | 10 | MTX: Y**<br>7-OH: N |
| Ahern[66] | Various NSAID | 14 | 66.3 | Min 5 | 15 | N |
| Svendsen[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 pharmacokinetics 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 patients[68]. 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 recommended[68] and caution is still advised in patients such as the elderly with potential for impaired renal function.

## REFERENCES


1. Fries J, Singh G, Lenert L, Furst D. Aspirin, hydroxychloroquine, and hepatic enzyme abnormalities with methotrexate in rheumatoid arthritis. Arthritis Rheum 1990;33:1611-9.
2. Rooney T, Furst D, Koehnke R, Burmeister L. Aspirin is not associated with more toxicity than other nonsteroidal antiinflammatory drugs in patients with rheumatoid arthritis treated with methotrexate. J Rheumatol 1993;20:1297-302.
3. Mor A, Ahn S, Izmirly P, Reddy S, Greenberg J, Bingham C, et al. Methotrexate combined with INH anti-tuberculous prophylaxis is well tolerated in RA patients. Ann Rheum Dis 2008;67:462-5.
4. Vanhoof J, Landewe S, Van Wijngaerden E, Geusens P. High incidence of hepatotoxicity of isoniazid treatment for tuberculosis chemoprophylaxis in patients with rheumatoid arthritis treated with methotrexate or sulfasalazine and anti-tumour necrosis factor inhibitors. Ann Rheum Dis 2003;62:1241-2.
5. Al-Awadhi A, Dale P, McKendry R. Pancytopenia associated with low dose methotrexate therapy. A regional survey. J Rheumatol 1993;20:1121-5.
6. Kaneko Y, Suwa A, Ikeda Y, Hirakata M. Pneumocystis jiroveci pneumonia associated with low-dose methotrexate treatment for rheumatoid arthritis: report of two cases and review of the literature. Mod Rheumatol 2006;16:36-8.
7. Sosin M, Handa S. Low dose methotrexate and bone marrow suppression. BMJ 2003;326:266-7.
8. Saravana S, Lalukotta K. Myelotoxicity due to methotrexate — an iatrogenic cause [letter]. Eur J Haematol 2003;71:315-6.
9. Chevrel G, Brantus JF, Sainte-Laudy J, Miossec P. Allergic pancytopenia to trimethoprim-sulphamethoxazole for pneumocystis carinii pneumonia following methotrexate treatment for rheumatoid arthritis [letter]. Rheumatology 1999;38:475-6.
10. Steuer A, Gumpel JM. Methotrexate and trimethoprim: a fatal interaction [letter]. Br J Rheumatol 1998;37:105-6.
11. Nygaard H. Pancytopenia secondary to methotrexate therapy in rheumatoid arthritis [letter]: comment on the article by Gutierrez-Urena, et al. Arthritis Rheum 1997;40:194-5.
12. Franck H, Rau R, Herborn G. Thrombocytopenia in patients with rheumatoid arthritis on long-term treatment with low dose methotrexate. Clin Rheumatol 1996;15:266-70.
13. Govert J, Patton S, Fine R. Pancytopenia from using trimethoprim and methotrexate [letter]. Ann Intern Med 1992;117:877-8.
14. Groenendal H, Rampen FH. Methotrexate and trimethoprim-sulphamethoxazole — a potentially hazardous combination. Clin Exp Dermatol 1990;15:358-60.
15. Jeurissen M, Boerbooms A, van de Putte L. Pancytopenia and methotrexate with trimethoprim-sulfamethoxazole [letter]. Ann Intern Med 1989;111:261.
16. Buchbinder R, Hall S, Ryan PFJ, Littlejohn GO, Harkness JG. Severe bone marrow failure due to low dose oral methotrexate [letter]. J Rheumatol 1988;15:1586-8.
17. Thevenet JP, Ristori JM, Cure H, Mizony MH, Bussiere JL. Pancytopenia during treatment of rheumatoid arthritis with methotrexate after administration of trimethoprim-sulfamethoxazole. Presse Med 1987;16:1487.
18. Thomas MH, Gutterman LA. Methotrexate toxicity in a patient receiving trimethoprim-sulfamethoxazole. J Rheumatol 1986;13:440-1.
19. Maricic M, Davis M, Gall E. Megaloblastic pancytopenia in a patient receiving concurrent methotrexate and trimethoprim-sulfamethoxazole treatment. Arthritis Rheum 1986;29:133-5.
20. Singh RR, Malaviya AN, Pandey JN, Guleria JS. Fatal interaction between methotrexate and naproxen [letter]. Lancet 1986;i:1390.
21. Kraus A, Alarcon-Segovia D. Low dose MTX and NSAID induced "mild" renal insufficiency and severe neutropenia [letter]. J Rheumatol 1991;18:1274.
22. Ohosone Y, Okano Y, Kameda H, Hama N, Mimori T, Akizuki M, et al. Clinical characteristics related to methotrexate-induced pancytopenia [letter]. Clin Rheumatol 1997;16:321-3.
23. Calvo-Romero JM. Severe pancytopenia associated with low-dose methotrexate therapy for rheumatoid arthritis. Ann Pharmacother 2001;35:1575-7.
24. Basin KS, Escalante A, Beardmore TD. Severe pancytopenia in a patient taking low dose methotrexate and probenecid. J Rheumatol 1991;18:609-10.
25. Frenia ML, Long KS. Methotrexate and nonsteroidal antiinflammatory drug interactions. Ann Pharmacother 1992;26:234-7.
26. Thonofer R, Kriessmayr M, Thonofer U, Wipfler E, Uitz E, Bahadori B, et al. Rheumatoid arthritis patients with therapy-induced myelodysplastic syndrome present with long-term remission after recovery. Scand J Rheumatol 2007;36:149-50.
27. Berthelot JM, Maugars Y, Hamidou M, Chiffoleau A, Barrier J, Grolleau J, et al. Pancytopenia and severe cytopenia induced by low-dose methotrexate. Eight case-reports and a review of one hundred cases from the literature (with twenty-four deaths). Rev Rhum (Engl Ed) 1995;62:477-86.
28. Tanaka Y, Shiozawa K, Nishibayashi Y, Imura S. Methotrexate induced early onset pancytopenia in rheumatoid arthritis: drug allergy? Idiosyncrasy? [letter]. J Rheumatol 1992;19:1320-1.
29. Laroche F, Perrot S, Menkes CJ. Pancytopenia in rheumatoid arthritis patients receiving methotrexate. Presse Med 1996;25:1144-6.
30. Serraj K, Federici L, Maloisel F, Alt M, Andres E. Pancytopenia related to low-dose methotrexate: study of five cases and review of the literature. Rev Med Interne 2007;28:584-8.
31. Maier WP, Leon-Perez R, Miller SB. Pneumonitis during low-dose methotrexate therapy. Arch Intern Med 1986;146:602-3.
32. Doolittle GC, Simpson KM, Lindsley HB. Methotrexate-associated, early-onset pancytopenia in rheumatoid arthritis. Arch Intern Med 1989;149:1430-1.
33. Mayall B, Poggi G, Parkin JD. Neutropenia due to low-dose methotrexate therapy for psoriasis and rheumatoid arthritis may be fatal. Med J Aust 1991;155:480-4.
34. Herrick AL, Grennan DM, Aarons L. Lack of interaction between methotrexate and penicillins [letter]. Rheumatology 1999;38:284-5.
35. Nanke Y, Kotake S, Akama H, Tomii M, Kamatani N. Pancytopenia and colitis with clostridium difficile in a rheumatoid arthritis patient taking methotrexate, antibiotics and non-steroidal anti-inflammatory drugs. Clin Rheumatol 2001;20:73-5.

36. Blackburn W Jr, Alarcon G. Toxic response to topical fluorouracil in two rheumatoid arthritis patients receiving low-dose, weekly methotrexate. Arthritis Rheum 1990;33:303-4.
37. Gutierrez-Urena S, Molina J, Garcia C, Cuellar M, Espinoza L. Pancytopenia secondary to methotrexate therapy in rheumatoid arthritis. Arthritis Rheum 1996;39:272-6.
38. Marshall RW, Marshall VJ, Hull R. Disease-modifying anti-rheumatic drugs are only one of a number of potential causes of myelosuppression: a careful drug history is necessary to elucidate the cause of an adverse event [letter]. Rheumatology 2006;45:362-3.
39. Sichere P, Maudhuit F, Hatem-Schliacowsky N. Pancytopenia during the treatment of rheumatoid polyarthritis by low doses of methotrexate. A new case that can question its combination with ranitidine. Rev Rhum 1990;57:593.
40. Richmond R, Microrie E, Ogden D, Lambert M. Methotrexate and triamterene — a potentially fatal combination? [letter]. Ann Rheum Dis 1997;56:209-10.
41. Dubost J, Sauvezie B. Fatal bone marrow toxicity in a patient treated with methotrexate and glafenine for rheumatoid arthritis [letter]. Clin Exp Rheumatol 1988;6:97-9.
42. Vincent S, Slease R, Rocca P. Epstein-Barr virus-associated lymphoproliferative disorder in a patient with rheumatoid arthritis on methotrexate and rofecoxib: idiosyncratic reaction or pharmacogenetics? Delaware Med J 2002;74:469-73.
43. Omdal R, Goransson L, Bergrem H. Fatal outcome of low-dose methotrexate therapy in rheumatoid arthritis [letter]. Clin Rheumatol 1993;12:283-4.
44. Alexandre C, Chaffanjon C, Tavan P, Thomas T, Pallot-Prades B, Prallet B, et al. Bone marrow aplasia in rheumatoid polyarthritis treated with low-dose methotrexate [letter]. Rev Rhum 1990;57:233-4.
45. MacKinnon S, Starkebaum G, Wilkens R. Pancytopenia associated with low dose pulse methotrexate in the treatment of rheumatoid arthritis. Semin Arthritis Rheum 1985;15:119-26.
46. McArthur G, Cole-sinclair M, Van der Weyden M. Haemopoietic toxicity and low-dose methotrexate [letter]. Med J Aus 1992;156:296.
47. Tracy TS, Krohn K, Jones DR, Bradley JD, Hall SD, Brater DC. The effects of a salicylate, ibuprofen, and naproxen on the disposition of methotrexate in patients with rheumatoid arthritis. Eur J Clin Pharmacol 1992;42:121-5.
48. Stewart CF, Fleming RA, Arkin CR, Evans WE. Coadministration of naproxen and low-dose methotrexate in patients with rheumatoid arthritis. Clin Pharmacol Ther 1990;47:540-6.
49. Skeith KJ, Russell AS, Jamali F, Coates J, Friedman H. Lack of significant interaction between low dose methotrexate and ibuprofen or flurbiprofen in patients with arthritis. J Rheumatol 1990;17:1008-10.
50. Stewart CF, Fleming RA, Germain BF, Seleznick MJ, Evans WE. Aspirin alters methotrexate disposition in rheumatoid arthritis patients. Arthritis Rheum 1991;34:1514-20.
51. Seideman P, Muller-Suur R. Renal effects of aspirin and low dose methotrexate in rheumatoid arthritis. Ann Rheum Dis 1993;52:613-5.
52. Tracy TS, Worster T, Bradley JD, Greene PK, Brater DC. Methotrexate disposition following concomitant administration of ketoprofen, piroxicam and flurbiprofen in patients with rheumatoid arthritis. Br J Clin Pharmacol 1994;37:453-6.
53. Furst DE, Herman RA, Koehnke R, Ericksen N, Hash L, Riggs CE, et al. Effect of aspirin and sulindac on methotrexate clearance. J Pharm Sci 1990;79:782-6.
54. Kremer J, Hamilton R. The effects of nonsteroidal anti-inflammatory drugs on methotrexate pharmacokinetics: impairment of renal clearance of MTX at weekly maintenance doses but not at 7.5 mg. J Rheumatol 1995;22:2072-7.
55. Vakily M, Amer F, Kukulka MJ, Andhivarothai N. Coadministration of lansoprazole and naproxen does not affect the pharmacokinetic profile of methotrexate in adult patients with rheumatoid arthritis. J Clin Pharmacol 2005;45:1179-86.
56. Hartmann SN, Rordorf CM, Milosavljev S, Branson JM, Chales GH, Juvin RR, et al. Lumiracoxib does not affect methotrexate pharmacokinetics in rheumatoid arthritis patients. Ann Pharmacother 2004;38:1582-7.
57. Hamilton SF, Campbell NR, Kara M, Watson J, Connors M. The effect of ingestion of ferrous sulfate on the absorption of oral methotrexate in patients with rheumatoid arthritis. J Rheumatol 2003;30:1948-50.
58. Schwartz JI, Agrawal NG, Wong PH, Bachmann KA, Porras AG, Miller JL, et al. Lack of pharmacokinetic interaction between rofecoxib and methotrexate in rheumatoid arthritis patients. J Clin Pharmacol 2001;41:1120-30.
59. Karim A, Tolbert DS, Hunt TL, Hubbard RC, Harper KM, Geis GS. Celecoxib, a specific cox-2 inhibitor, has no significant effect on methotrexate pharmacokinetics in patients with rheumatoid arthritis. J Rheumatol 1999;26:2539-43.
60. Iqbal MP, Baig JA, Ali AA, Niazi SK, Mehboobali N, Hussain MA. The effects of non-steroidal anti-inflammatory drugs on the disposition of methotrexate in patients with rheumatoid arthritis. Biopharm Drug Dispos 1998;19:163-7.
61. Hubner G, Sander O, Degner FL, Turck D, Rau R. Lack of pharmacokinetic interaction of meloxicam with methotrexate in patients with rheumatoid arthritis. J Rheumatol 1997;24:845-51.
62. Herrick AL, Grennan DM, Griffen K, Aarons L, Gifford LA. Lack of interaction between flucloxacillin and methotrexate in patients with rheumatoid arthritis. Br J Clin Pharmacol 1996;41:223-7.
63. Gumbhir-Shah K, Cevallos WH, DeCleene SA, Korth-Bradley JM. Lack of interaction between bromfenac and methotrexate in patients with rheumatoid arthritis. J Rheumatol 1996;23:984-9.
64. Combe B, Edno L, Lafforgue P, Bologne C, Bernard JC, Acquaviva P, et al. Total and free methotrexate pharmacokinetics, with and without piroxicam, in rheumatoid arthritis patients. Br J Rheumatol 1995;34:421-8.
65. Anaya JM, Fabre D, Bressolle F, Bologna C, Alric R, Cocciglio M, et al. Effect of etodolac on methotrexate pharmacokinetics in patients with rheumatoid arthritis. J Rheumatol 1994;21:203-8.
66. Ahern M, Booth J, Loxton A, McCarthy P, Meffin P, Kevat S. Methotrexate kinetics in rheumatoid arthritis: is there an interaction with nonsteroidal antiinflammatory drugs? J Rheumatol 1988;15:1356-60.
67. Svendsen KB, Bech JN, Pfeiffer-Jensen M, Stengaard-Pederson K, Pederson EB. Urinary excretion of alpha-GST and albumin in rheumatoid arthritis patients treated with methotrexate or other DMARDs alone or in combination with NSAIDs. Scand J Rheumatol 2005;34:34-9.
68. Visser K, Katchamart W, Loza E, Martinez-Lopez JA, Salliot C, Trudeau J, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. Ann Rheum Dis 2008;68:1086-93; E-pub Nov 25.