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# Side effects and management of side effects of methotrexate in rheumatoid arthritis

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## ABSTRACT

*Low-dose methotrexate (MTX) remains the first-line treatment option among the disease-modifying antirheumatic drugs in patients with rheumatoid arthritis. However, diverse side effects are the major reason for MTX withdrawal and change of treatment. The following article reviews the published data on general and organ-specific side effects and outlines the current recommendations addressing prevention and management of MTX-associated adverse effects.*

## Introduction

Methotrexate (MTX) is considered as first choice therapy among the disease modifying antirheumatic drugs (DMARDs) for the treatment of rheumatoid arthritis (RA) (1). Its favourable efficacy and toxicity profile results in a comparatively low withdrawal rate. As high-dose MTX may cause many and severe side effects while low-dose treatment is well tolerated in the majority of patients, it needs to be emphasised that low-dose MTX treatment in RA patients is substantially different from high-dose therapy used in neoplastic diseases. Nevertheless, the toxicity spectrum in RA patients is widespread with respect to symptoms and intensity, including serious and sometimes fatal cytopenia, pneumonitis and liver disease. Careful patient selection and regular monitoring as well as doses adapted to the actual needs of the patients are essential to reduce the toxicity of MTX in RA.

In the following article, general and organ specific adverse effects of low-dose MTX therapy (10–25mg/week) in RA patients will be discussed. Recommendations addressing prevention and management of side effects are assorted. The estimated risk of specific side effects, is very difficult to obtain as clinical trials, retrospective collection of patient data and case reports dif-

fer considerably in their duration and treatment doses. Small patient cohorts and concomitant treatment as well as incomplete documentation of folate supplementation further complicate exact assessments. Subsequently, the variation of the reported incidences is high. Approximate incidence ranges of attributed adverse reactions to MTX in patients with RA are outlined in Table I.

## General toxicity

Comparing the potency of different DMARDs, MTX is one of the most efficacious drugs and has a comparatively low toxicity. This property explains why patients with RA stay significantly longer on MTX than on other DMARDs (2). However, incidence and severity of acute side effects during MTX therapy are related to dose and frequency of administration. Patients with an initial dose of 25mg/week had a higher rate of gastrointestinal side effects (28% vs. 17%) and of liver enzyme elevation (47% vs. 39%) compared to a dose of 15mg/week (3). In contrast, the age of the patient at initiation of MTX treatment does not seem to influence its efficacy and toxicity in RA except for underlying renal impairment (4).

In a pooled meta-analysis of 21 prospective studies, with mean treatment duration of three years, 72.9% of MTX treated patients had at least one adverse effect, the most common being gastrointestinal and elevation of liver enzymes (5). Minor adverse reactions that resolved with temporary drug discontinuation occurred in up to 62% of RA patients. Major side effects such as cytopenia, severe infections or respiratory failure were present in 10% of MTX treated patient cohorts (6, 7). Discontinuation of MTX treatment due to adverse effects is reported in 10–37% of patients depending on the study cohort and duration of administration

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**Table I.** Incidences of methotrexate-associated adverse effects in patients with rheumatoid arthritis.

| Organ System              | Adverse effects                                                                                                                                                                |
|---------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cardiovascular            | Serositis                                                                                                                                                                      |
| Dermatologic              | Oral ulcers (37%)<br>Alopecia (0.4–4%)<br>Rash (1.4%)<br>Anaphylactic reactions<br>Photosensitivity<br>Vasculitis<br>Nodulosis (8%)                                            |
| Gastrointestinal (20–65%) | Nausea<br>Vomiting<br>Diarrhoea<br>Gastrointestinal bleeding<br>Complication of ulcers                                                                                         |
| Hematologic               | Mild leucopenia (12%)<br>Thrombocytopenia (12%)<br>Cytopenia (4–7%)<br>Pancytopenia (0.8%)                                                                                     |
| Hepatic                   | Elevation of liver enzymes (10–43%)<br>Mild fibrosis (15.3%)<br>Severe fibrosis (1.3%)<br>Cirrhosis (0.5–0.8%)                                                                 |
| Immunologic               | Opportunistic infections                                                                                                                                                       |
| Musculoskeletal           | Osteopathy                                                                                                                                                                     |
| Nervous (21–38%)          | Headache<br>Dizziness<br>Vertigo<br>Fatigue<br>Mood alteration<br>Memory impairment                                                                                            |
| Renal                     | Renal insufficiency (only in pre-existing, severely impaired renal function)                                                                                                   |
| Respiratory               | Dry cough (10%)<br>Interstitial pneumonitis (2.1–8%)<br>Pneumocystis carinii pneumonia                                                                                         |
| Urogenital                | Abortion (23%)<br>Malformation (5%)<br>Decreased libido<br>Menstrual dysfunction<br>Vaginal discharge<br>Defective oogenesis and spermatogenesis<br>Impotence<br>Gynaecomastia |
| Other                     | Application reaction (10%)                                                                                                                                                     |

(5). A meta-analysis of 159 studies revealed that 65% of patients continued MTX treatment over a period of 60 months (2). MTX withdrawal based on side effects and major toxicity occurred predominantly during the first year of treatment while the frequency of minor toxic events remained stable throughout 5-year observations (8–10). Cases

of death due to severe adverse effects have been reported, especially associated with severe cytopenia, infection and pneumonitis (7, 11–13).

A general application reaction consisting of arthralgia, myalgia, fatigue and/or malaise is reported in 10% of MTX treated patients (n=356) with a dropout rate of 4%. In this study, the application

reaction was the second most common side effect after gastrointestinal leading to MTX withdrawal (14).

### Organ specific side effects and management

#### – Cardiovascular

Pericardial serositis is a rare complication of MTX treatment in RA patients. Case reports have described the development of pericarditis and pericardial tamponade that have not recurred after withdrawal of MTX therapy (15, 16). Vice versa, MTX seems to have a beneficial impact on cardiovascular mortality in patients with RA. It is being discussed whether direct atheroprotective effects, as well as inflammatory suppression, may be responsible for this effect (17, 18).

#### – Dermatologic

The prevalence of stomatitis during MTX treatment was found in 37% in a controlled study (n=51) (19). Symptoms can be controlled and reduced by temporary dosage reduction or treatment termination. In some patients with mild stomatitis, increase of folate supplementation can be efficient. Uncommonly, MTX-associated lymphoproliferative disorders can present as ulcers in the oral cavity (20). Similarly, crural ulcers can be triggered or show a prolonged healing. In low dose treatment, alopecia is rare and generally resolves several months after discontinuation. The occurrence of anaphylactic reactions, rash and photosensitivity has also been described; here, a withdrawal of MTX is the only therapeutic option.

The manifestation of cutaneous vasculitis is reported despite a good clinical response to MTX (21). Accelerated subcutaneous rheumatoid nodules occur with an estimated incidence of up to 8% (22). Rheumatoid factor positivity is not a prerequisite for this side effect. New nodules are preferentially located over the extensor surfaces of finger joints, rarely also in the heart and the lung. After MTX withdrawal, nodulosis might regress, but can also reappear after reapplication of MTX. In a small number of patients, regression of nodulosis and vasculitis lesions has been observed during additional treatment with

D-penicillamine in a moderate dosage (500mg/d). Therefore, application of D-penicillamine can be considered as a possible alternative therapeutic option to MTX withdrawal (23).

### – Gastrointestinal

The incidence of gastrointestinal side effects ranges from 20% to 65% (8, 9, 24). They seem to occur irrespective of treatment duration (8). Nausea, vomiting and malaise are the most frequent adverse effects of MTX treatment. Symptoms can be controlled by dosage reduction, distribution over a 12-hour period or splitting the weekly dose to a daily dose, change to evening/parenteral application or symptomatic treatment with metoclopramide. As the healing of gastrointestinal ulcers is thought to be delayed during MTX treatment, an active gastric ulcer should be a relative contraindication for MTX.

### – Haematologic

One of the primary toxic effects of MTX is a potential myelosuppression. Mild leucopenia and thrombocytopenia are reported in up to 12% of MTX treated patients and might resolve with temporary drug discontinuation (6). Moderate bone marrow suppression recovers within two weeks after the withdrawal of MTX. Cytopenia occurs in 4.2–7% of patients with RA and MTX treatment (9, 24, 25). The occurrence is abrupt and in 25% of cases develops within one month of treatment initiation (12, 13). Macrocytosis might precede the appearance of cytopenia. Risk factors include renal dysfunction, hypoalbuminaemia, concomitant use of other antifolate medications such as trimethoprim-sulfamethoxazole, and concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid (1, 26). A preexisting folate deficiency and an increased mean corpuscular volume value (>94fl) are discussed to be a predictor of haematologic toxicity, but with contradictory study results (25, 27). Severe pancytopenia is rarely observed (0.8%), but in 24–44% of the reported cases resulting in fatal outcome with the most frequent cause of death being infections (11–13).

- A pre-existing myelosuppression or

low haematologic cell counts are contraindications for using MTX.

- Complete blood cell counts should be obtained before MTX treatment and at least once a month for the first 3 months; then every 4–12 weeks during MTX therapy (31).

### – Hepatic

MTX can cause transient elevated liver enzymes in 10–43% of RA patients that can resolve with temporary drug discontinuation (6, 9, 24, 29). Seventy-three percent of patients with at least one liver function test abnormality continued MTX treatment despite the elevation and without further evaluation or change in therapy. Subsequent liver function test assessments were within normal limits (29). Elevations higher than two-fold above the upper limit of normal occurred in 1–2% of patients on MTX (30).

Chronic hepatotoxicity is a rare and dose-related complication of MTX treatment in RA patients. After four years of MTX use, liver biopsies showed mild fibrosis in 15.3% of patients, severe fibrosis in 1.3% and cirrhosis in 0.5% (28). Risk factors for the development of chronic hepatotoxicity are alcohol consumption, higher age, obesity, chronic renal insufficiency, hypoalbuminaemia, diabetes and viral or alcoholic hepatitis (1). Since a correlation between aspartate aminotransferase (AST) levels and histological grades of liver disease has been reported, and serial abnormal AST tests have shown an 80% sensitivity and 82% specificity for the detection of fibrosis and cirrhosis, they are preferred to liver biopsy (1, 32). Screening of patients to be treated includes complete liver blood tests (alanine aminotransferase (ALT), AST, albumin, alkaline phosphatase, bilirubin), baseline serum creatinine and complete blood count. Hepatitis B and C serology should be performed in patients with abnormal liver function tests. However, a pretreatment liver biopsy should be considered only for patients with a history of excessive alcohol consumption, persistently abnormal baseline AST values, or chronic hepatitis B or C infections (32). Hepatic enzymes need to be monitored every 1 to

3 months, initially every 1 to 1.5 months until a stable dose is reached. A withdrawal of MTX is necessary if serum transaminase levels exceed three times the upper limit of normal, but may be reinitiated with a dose adjustment. Further diagnostics should be performed if elevated AST/ALT levels persist three times above the upper limit of normal after MTX withdrawal (1).

- ALT/AST levels are mandatory before starting MTX therapy and at least once a month for the first 3 months, then every 4–12 weeks.
- Serology for hepatitis B and C and a serum albumin measurement are recommended (31, 32).

### – Immunologic

A recent review has summarised the literature on risk of infection associated with low-dose MTX use in patients with RA (33). It has been shown that patients with RA do have an increased rate of infections. This risk is particularly increased in patients with comorbidities (diabetes, chronic lung disease and alcoholism), the use of corticosteroids and increased disease activity. In contrast to suggestions from earlier clinical studies, low dose MTX does not appear to increase the risk of infection in RA patients. Although multiple case reports have described major opportunistic infections during low-dose MTX therapy, a direct MTX-induced increase has not been confirmed. Concomitant corticosteroid therapy and underlying RA itself may solely be responsible for the predisposition to opportunistic infections. The literature review also concluded that, counteracting previous considerations, MTX appears not to be an additional risk factor for a reactivation of varicella zoster virus causing herpes zoster beyond the increased risk in RA itself.

- In case of mild viral infections MTX therapy can be continued.
- In the occurrence of bacterial infections that require antibiotic therapy, MTX should be discontinued until the antibiotic course has been completed, inflammatory markers have returned to baseline levels and clinical symptoms have resolved (33).

If opportunistic infections during MTX

treatment occur, they can be severe and sometimes life threatening. Pneumocystis carinii pneumonia is the most common opportunistic infection. There are other reports of nocardiosis, histoplasmosis, aspergillum, cryptococcosis, herpes zoster, herpes simplex and listeria-meningitis.

- MTX should be contraindicated in patients with immunodeficiency syndromes; a serology for HIV has to be considered in case of risk patients.

#### *Immunisation*

Low-dose MTX does not affect the responsiveness to influenza vaccination in patients with RA. Responsiveness to pneumococcal vaccination might be impaired (33). It is not reported whether the more recent conjugated pneumococcal vaccines might be more efficacious in RA patients. Immunisation with live virus vaccines is not recommended. There have been reports of disseminated vaccine infections after smallpox immunisation in patients receiving MTX therapy.

#### *Perioperative management*

There is no evidence that temporary discontinuation of MTX prior to and during elective surgery minimises the risk of infectious complications. A prolonged wound healing was also noticed in RA patients with temporary discontinuation of MTX treatment (34). A review of the published data on the perioperative management of MTX in patients with RA undergoing elective orthopaedic surgery concludes that continued MTX therapy appears to be safe perioperatively and seems also to be associated with a reduced risk of flares (35).

- MTX can be continued perioperatively in RA patients undergoing elective orthopaedic surgery (1, 33).

#### **– Musculoskeletal system**

MTX osteopathy was first reported in children with leukaemia treated with high doses of MTX. In animal studies, even low doses of MTX exerted an adverse effect on bone metabolism. The long-term use of low-dose MTX in RA patients might also be associated with decreased bone density by osteoblast inhibition. MTX may therefore be an

additional risk factor for the development of osteoporosis and fractures in RA. Several case reports describe the incidence of stress fractures and histological changes consistent with osteoblast inhibition (36, 37). Here, MTX withdrawal is the only treatment option. Therefore, MTX should be relatively contraindicated especially in postmenopausal women with multiple risk factors for osteoporosis.

#### **– Nervous system**

Central nervous system (CNS) toxicity induced by low-dose MTX has been reported in single cases, and it seems to be more common in older patients with mild renal insufficiency (38). The most common side effects include headache, dizziness, vertigo and fatigue (39). Irritating cranial sensations, mood alteration and memory impairment have been described as well (38). A complex pattern of neurological symptoms including fluctuant dysarthria, magnetic gait, weakness and dysmetria of the lower limbs has also been described in a case report (40).

- Since reinitiation with MTX led to recurrence of CNS symptoms, MTX withdrawal is recommended.

#### **– Renal**

Patients with renal impairment have a higher overall rate of toxicity for a variety of drugs. The risk of severe toxicity is increased about 4-fold in patients with renal impairment. Concomitant use of other potentially nephrotoxic drugs, including NSAIDs, and pre-existing renal insufficiency are additional risk factors. Therefore, although direct toxicity of low dose MTX has not been proven, the dosage regimen should be adjusted in patients with severe renal impairment.

- Before starting MTX therapy and for monitoring, investigation of serum creatinine with creatinine clearance and serum albumin assay should be obtained once a month for the first 3 months, then every 4–12 weeks (31).

#### **– Respiratory**

Interstitial pneumonitis is one of the rare life-threatening rheumatologic emergencies under treatment with MTX.

The reported incidence ranges from 2.1% to 8% (8, 24, 42, 43). In a review of 123 published cases, a mortality of 13% was reported (41). On the other hand, most of the patients recover completely without progression to pulmonary fibrosis. The occurrence of MTX-induced pneumonitis is independent from cumulative dose and duration of treatment. It can occur as early as four weeks after initiation of treatment with MTX and is most frequent within the first year, suggesting an idiosyncratic immune reaction rather than a dose-related toxic insult to the lung (41, 43). A pre-existing lung disease has been identified as a risk factor for the occurrence of interstitial pneumonitis and can be characterised by radiographic interstitial infiltrates prior to the initiation of treatment (42, 43). Patients present with a dry and non-productive cough, acute dyspnoea and fever, hypoxemia and potential respiratory failure. Diagnosis is often difficult as patients show very similar symptoms to that of an acute respiratory infection. Negative microbial cultures of blood and sputum have to be obtained. A decline in vital capacity and a low transfer factor for carbon monoxide are not specific (41). Chest radiographics may show bilateral diffuse interstitial and alveolar infiltration. High-resolution computed tomography of the lungs is more sensitive and might offer additional help to distinguish MTX pneumonitis from infection, hypersensitivity pneumonitis caused by other drugs and autoimmune alveolitis due to RA as underlying disorder. Diffuse homogeneous ground glass opacity with sharp demarcation by interlobular septa (type A of ground glass opacity) is a characteristic sign of MTX induced pneumonitis, but autoimmune pneumonitis in RA patients can also present either with or without interlobular septal boundaries (type B of ground glass opacity). An elevated lymphocyte count and an increased CD4/CD8 ratio in bronchoalveolar lavage at bronchoscopy are also observed in both conditions, which make the distinction of these two disorders difficult (44). Early diagnosis, immediate withdrawal of MTX therapy and treatment with corticosteroids are essential in the



management of MTX pneumonitis. MTX should not be rechallenged after recovery from pneumonitis.

There are several case reports of RA patients who develop *Pneumocystis carinii* pneumonia (PCP) infection during treatment with low-dose MTX. Although rare, PCP is a serious complication of low-dose MTX therapy and should be excluded when a patient presents with pulmonary symptoms.

Dry cough not accompanied by dyspnoea or constitutional symptoms and without evidence of parenchymal lung involvement is not uncommon during MTX treatment and can be controlled with symptomatic treatment or temporary discontinuation (9).

- A chest x-ray obtained within the previous year is mandatory before starting MTX therapy. In patients with a history of respiratory disease or current respiratory symptoms, lung function tests with determination of the diffusion capacity for carbon monoxide are recommended. In the event of serious respiratory symptoms possibly related to MTX toxicity, advice from a pulmonologist should be obtained (31).

### – Urogenital

Adverse genitourinary effects can affect either gender. Menstrual dysfunction, vaginal discharge, decreased libido and infertility have been described. Defective oogenesis and spermatogenesis are usually transient. The appearance of impotence and gynaecomastia has been reported, with symptoms improving after MTX withdrawal.

As MTX may cause abortion and malformation, it has to be discontinued at least 3 months before termination of contraceptive treatment. During MTX exposure and up to three months after MTX discontinuation, a safe contraception has to be assured in female and male patients. In case of pregnancy during MTX treatment, MTX has to be discontinued as early as possible. Among 28 cases with MTX exposure ending before 8 weeks of gestation, miscarriages occurred in 4 patients, 5 had elective termination of pregnancy and 19 live births with one minor anomaly (45). In a systematic review

with 101 MTX exposed pregnancies from conception to first trimester were 23% miscarriages, 66% live births, 5% of them with neonatal minor malformations. The rate of induced abortions was 18%. The rates of miscarriages and of birth defects are similar to the rates observed in healthy population. Besides, the data allow no sufficient evidence of whether MTX or the underlying RA is responsible for the rate of miscarriages (46).

There is no confirming data on the safety and risks in respect to MTX and lactation. Therefore, MTX should not be used during breastfeeding.

- In case of pregnancy or inadequate contraception, MTX is contraindicated. Patient education is mandatory in male and female. A pregnancy test has to be considered.

### Oncogenicity

RA is an independent risk factor for the development of non-Hodgkin's lymphoma. The relative risk of lymphoma associated with RA is about twofold higher than in the general population. However, no studies indicate that MTX increases the risk of cancer in RA patients (5, 47). A relationship between the cumulative dose or the duration of MTX therapy and the subsequent development of a haematologic malignancy could not be found. In addition, alternating DMARD treatment and additional therapy with NSAIDs in the course of RA leave a true risk association difficult to estimate.

Various case reports describe the incidence of lymphoproliferative disorders (LPD) during MTX treatment in RA patients. They are often associated with Epstein-Barr virus infection. A review of the literature identified 26 patients with MTX-associated LPD resulting spontaneous complete remission mostly within four weeks after withdrawal of MTX therapy. Remission appeared to be persistent during the further course of the disease. However, 8 patients showed only partial remission making a careful monitoring after discontinuation of MTX advisable (20, 48).

- Due to its acceptable safety profile, MTX can be used as long-term treatment (1).

### Efficacy of folic acid

Reports about the efficacy of folic acid and folinic acid in reducing side effects of low dose MTX in RA are still inconsistent. A meta-analysis surveying 307 patients showed a 79% reduction in mucosal and gastrointestinal side effects for folic acid without reduced efficacy (49). In a review with 6 randomised controlled trials including 648 patients, a significant reduction of hepatic side effects was found and a trend in favour of a reduction for gastrointestinal and mucosal side effects emerged (50). As folinic acid at doses higher than 5mg/week is associated with a significant increase in clinical signs of disease activity, folic acid is favoured as folate supplementation regime (1).

- Folate supplementation with a dose of 5mg folic acid per week, 24 hours apart from MTX, is highly recommended (1, 31).

### Intoxication

Intoxication during low dose MTX treatment may appear in case of misinterpretation of dose application (e.g. daily instead of weekly doses) or with increasing renal impairment. As MTX accumulates intracellularly with an intra-erythrocyte half-life period of about nine days, folinic acid (Leucovorin) should be applied as antidote for 2–3 weeks. Especially haematologic complications improve after application of leucovorin.

### Adverse effects in combination therapy

MTX combined with sulfasalazine and MTX combined with leflunomide each significantly increased the risk of gastrointestinal side effects and hepatotoxicity. MTX combined with sulfasalazine and hydroxychloroquine did not increase the risk of withdrawal due to toxicity (1). Regarding toxicity, MTX monotherapy is favoured over DMARD combination in DMARD naive patients, whereas the combination with prednisone or anti-tumour necrosis factor is not contradicted with regard to increased adverse effects.

### Summary

MTX is an effective DMARD for the

treatment of patients with RA and has a relatively safe side effect profile compared to other DMARDs. Minor gastrointestinal side effects, mild transaminase elevation, and stomatitis are frequent but reversible after dose reduction or discontinuation of treatment. Serious side effects include cytopenia, hepatotoxicity and interstitial pneumonitis; in all cases, MTX withdrawal is indispensable. MTX should be avoided in patients with risks of liver damage or pre-existing lung diseases. Patient monitoring prior to and during MTX treatment is essential to reduce the potential serious toxicities of MTX.

## References

- VISSER K, KATCHAMART W, LOZA E *et al.*: Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systemic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. *Ann Rheum Dis* 2009; 68: 1086-93.
- MAETZEL A, WONG A, STRAND V, TUGWELL P, WELLS G, BOMBARDIER C: Meta-analysis of treatment termination rates among rheumatoid arthritis patients receiving disease-modifying anti-rheumatic drugs. *Rheumatology* 2000; 39: 975-81.
- SCHNABEL A, REINHOLD-KELLER E, WILLMANN V, GROSS WL: Tolerability of methotrexate starting with 15 or 25mg/week for rheumatoid arthritis. *Rheumatol Int* 1994; 14: 33-8.
- RHEUMATOID ARTHRITIS CLINICAL TRIAL ARCHIVE GROUP: The effect of age and renal function on the efficacy and toxicity of methotrexate in rheumatoid arthritis. *J Rheumatol* 1995; 22: 218-23.
- SALLIOT C, VAN DER HEIJDE D: Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. *Ann Rheum Dis* 2009; 68: 1100-04.
- WEINBLATT ME, TRENTAM DE, FRASER PA *et al.*: Long-term prospective trial of low-dose methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 167-75.
- GISPEN JG, ALARCON GS, JOHNSON JJ, ACTON RT, BARGER BO, KOOPMAN WJ: Toxicity of methotrexate in rheumatoid arthritis. *J Rheumatol* 1987; 14: 74-9.
- KREMER JM, PHELPS CT: Long-term prospective study of the use of methotrexate in the treatment of rheumatoid arthritis. Update after a mean of 90 months. *Arthritis Rheum* 1992; 35: 138-45.
- SCHNABEL A, HERLYN K, BURCHARDI C, REINHOLD-KELLER E, GROSS WL: Long-term tolerability of methotrexate at doses exceeding 15mg per week in rheumatoid arthritis. *Rheumatol Int* 1996; 15: 195-200.
- RAU R, SCHLEUSSER B, HERBORN G, KARGER T: Long-term treatment of destructive rheumatoid arthritis with methotrexate. *J Rheumatol* 1997; 24: 1881-9.
- KINDER AJ, HASSELL AB, BRAND J, BROWNFIELD A, GROVE M, SHADFORTH MF: The treatment of inflammatory arthritis with methotrexate in clinical practice: treatment duration and incidence of adverse drug reactions. *Rheumatology* 2005; 44: 61-6.
- KUITUNEN T, MALMSTROM J, PALVA E, PETTERSON T: Pancytopenia induced by low-dose methotrexate. A study of the cases reported to the Finnish Adverse Drug Reaction Register From 1991 to 1999. *Scand J Rheumatol* 2005; 34: 238-41.
- BERTHELOT JM, MAUGARS Y, HAMIDOU M *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.
- HALLA JT, HARDIN JG: Underrecognized postdosing reactions to methotrexate in patients with rheumatoid arthritis. *J Rheumatol* 1994; 21: 1224-6.
- MOHYUDDIN T, ELYAN M, KUSHNER I: Pericarditis: a rare complication of methotrexate therapy. *Clin Rheumatol* 2007; 26: 2157-8.
- ABU-SHAKRA M, NICOL P, UROWITZ MB: Accelerated nodulosis, pleural effusion and pericardial tamponade during methotrexate therapy. *J Rheumatol* 1994; 21: 934-7.
- PHAM T, GOSSEC L, CONSTANTIN A *et al.*: Cardiovascular risk and rheumatoid arthritis: clinical practice guidelines based on published evidence and expert opinion. *Joint Bone Spine* 2006; 73: 379-87.
- REISS AB, CARSONS SE, ANWAR K *et al.*: Atheroprotective effects of methotrexate on reverse cholesterol transport proteins and foam cell transformation in human THP-1 monocyte/macrophages. *Arthritis Rheum* 2008; 58: 3675-83.
- INCE A, YAZICI Y, AMURYUDAN V, YAZICI H: The frequency and characteristics of methotrexate (MTX) oral toxicity in rheumatoid arthritis (RA): a masked and controlled study. *Clin Rheumatol* 1996; 15: 491-4.
- PASTOR-NIETO MA, KILMURRAY LG, LOPEZ-CHUMILLAS A *et al.*: Methotrexate-associated lymphoproliferative disorder presenting as oral ulcers in a patient with rheumatoid arthritis. *Actas Dermosifiliogr* 2009; 100: 142-6.
- SEGAL R, CASPI D, TISHLER M, FISHEL B, YARON M: Accelerated nodulosis and vasculitis during methotrexate therapy for rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 1182-5.
- KERSTENS PJ, BOERBOOMS AM, JEURISSEN ME, FAST JH, ASSMANN KJ, VAN DE PUTTE LB: Accelerated nodulosis during low dose methotrexate therapy for rheumatoid arthritis. An analysis of ten cases. *J Rheumatol* 1992; 19: 867-71.
- DASH S, SEIBOLD JR, TIKU ML: Successful treatment of methotrexate induced nodulosis with D-penicillamine. *J Rheumatol* 1999; 26: 1396-9.
- MCKENDRY RJ, DALE P: Adverse effects of low dose methotrexate therapy in rheumatoid arthritis. *J Rheumatol* 1993; 20: 1850-6.
- NAKAZAKI S, MURAYAMA T, KATOH S: Cytopenia associated with low dose pulse methotrexate in the treatment of rheumatoid arthritis. *Ryumachi* 2001; 41: 929-37.
- BOURRE-TESSIER J, HARAOU I B: Methotrexate Drug Interactions in the Treatment of Rheumatoid Arthritis: A Systematic Review. *J Rheumatol* 2010; Epub ahead of print.
- WHITE DH, CHAPMAN PT, O'DONNELL JL, JAMES J, FRAMPTON C, STAMP LK: Lack of association between elevated mean red cell volume and haematological toxicity in patients receiving long-term methotrexate for rheumatoid arthritis. *Intern Med J* 2009; epub ahead of print.
- VISSER K, VAN DER HEIJDE DM: Risk and management of liver toxicity during methotrexate treatment in rheumatoid and psoriatic arthritis: a systematic review of the literature. *Clin Exp Rheumatol* 2009; 27: 1017-25.
- YAZICI Y, ERKAND, HARRISON MJ, NIKOLOV NP, PAGET SA: Methotrexate use in rheumatoid arthritis is associated with few clinically significant liver function test abnormalities. *Clin Exp Rheumatol* 2005; 23: 517-20.
- CURTIS JR, BEUKELMANN T, ONOFREI A *et al.*: Elevated liver enzyme tests among patients with rheumatoid arthritis or psoriatic arthritis treated with methotrexate and/or leflunomide. *Ann Rheum Dis* 2010; 69: 43-7.
- PAVY S, CONSTANTIN A, PHAM T *et al.*: Methotrexate therapy for rheumatoid arthritis: clinical practice guidelines based on published evidence and expert opinion. *Joint Bone Spine* 2006; 73: 388-95.
- KREMER JM, ALARCON GS, LIGHTFOOT RW *et al.*: Methotrexate for rheumatoid arthritis. Suggested guidelines for monitoring liver toxicity. American College of Rheumatology. *Arthritis Rheum* 1994; 37: 316-28.
- MCLEAN-TOOKE A, ALDRIDGE C, WAUGH S, SPICKETT GP, KAY L: Methotrexate, rheumatoid arthritis and infection risk – what is the evidence? *Rheumatology* 2009; 48: 867-71.
- SANY J, ANAYA JM, CANOVAS F *et al.*: Influence of methotrexate on the frequency of postoperative infectious complications in patients with rheumatoid arthritis. *J Rheumatol* 1993; 20: 1129-32.
- PIERINGER H, STUBY U, BIESENBAACH G: The place of methotrexate perioperatively in the elective orthopedic surgeries in patients with rheumatoid arthritis. *Clin Rheumatol* 2008; 27: 1217-20.
- ZONNEVELD IM, BAKKER WK, DIJKSTRA PF, BOS JD, VAN SOESBERGEN RM, DINANT HJ: Methotrexate osteopathy in long-term, low-dose methotrexate treatment for psoriasis and rheumatoid arthritis. *Arch Dermatol* 1996; 132: 184-7.
- PRESTON SJ, DIAMOND T, SCOTT A, LAURENT MR: Methotrexate osteopathy in rheumatic disease. *Ann Rheum Dis* 1993; 52: 582-5.
- WERNICK R, SMITH DL: Central nervous system toxicity associated with weekly low-dose methotrexate treatment. *Arthritis Rheum* 1989; 32: 770-5.
- WEINSTOCK-GUTTMANN B, NAIR D, COHEN JA: Neurologic complications of immunosuppressive and anti-inflammatory therapy

- for rheumatic diseases. *J Clin Rheumatol* 1996; 2: 268-78.
40. SOMMER WH, GANIERE V, GACHOUD D *et al.*: Neurological and pulmonary adverse effects of subcutaneous methotrexate therapy. *Scand J Rheumatol* 2008; 37: 306-9.
  41. SARAVANAN V, KELLY CA: Reducing the risk of methotrexate pneumonitis in rheumatoid arthritis. *Rheumatology* 2004; 43: 143-7.
  42. GOLDEN MR, KATZ RS, BALK RA, GOLDEN HE: The relationship of preexisting lung disease to the development of methotrexate pneumonitis in patients with rheumatoid arthritis. *J Rheumatol* 1995; 22: 1043-7.
  43. OHOSONE Y, OKANO Y, KAMEDA H *et al.*: Clinical characteristics of patients with rheumatoid arthritis and methotrexate induced pneumonitis. *J Rheumatol* 1997; 24: 2299-303.
  44. TOKUDA H, SAKAI F, YAMADA H *et al.*: Clinical and radiological features of Pneumocystis pneumonia in patients with rheumatoid arthritis, in comparison with methotrexate pneumonitis and Pneumocystis pneumonia in acquired immunodeficiency syndrome: a multicenter study. *Intern Med* 2008; 47: 915-23.
  45. LEWDEN B, VIAL T, ELEFANT E, NELVA A, CARLIER P, DESCOTES J: Low dose methotrexate in the first trimester of pregnancy: results of a French collaborative study. *J Rheumatol* 2004; 31: 2360-5.
  46. MARTINEZ LOPEZ JA, LOZA E, CARMONA L: Systematic review on the safety of methotrexate in rheumatoid arthritis regarding the reproductive system (fertility, pregnancy, and breastfeeding). *Clin Exp Rheumatol* 2009; 27: 678-84.
  47. BEAUPARLANT P, PAPP K, HARAOUI B: The incidence of cancer associated with the treatment of rheumatoid arthritis. *Semin Arthritis Rheum* 1999; 29: 148-58.
  48. RIZZI R, CURCI P, DELIA M *et al.*: Spontaneous remission of "methotrexate-associated lymphoproliferative disorders" after discontinuation of immunosuppressive treatment for autoimmune disease. Review of the literature. *Med Oncol* 2009; 26: 1-9.
  49. ORTIZ Z, SHEA B, SUAREZ-ALMAZOR ME, MOHER D, WELLS GA, TUGWELL P: The efficacy of folic acid and folinic acid in reducing methotrexate gastrointestinal toxicity in rheumatoid arthritis. A metaanalysis of randomized controlled trials. *J Rheumatol* 1998; 25: 36-43.
  50. PREY S, PAUL C: Effect of folic or folinic acid supplementation on methotrexate-associated safety and efficacy in inflammatory disease: a systematic review. *Br J Dermatol* 2009; 160: 622-8.