Benefit and risk of methotrexate treatment in rheumatoid arthritis

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ABSTRACT

This is a literature review on the efficacy and toxicity of low dose weekly methotrexate treatment in rheumatoid arthritis. Personal recommendations on dosing and monitoring (of) the drug are given.

Introduction

The last two decades have seen important achievements in the treatment of rheumatoid arthritis.

1. There is general agreement now that disease modifying anti-rheumatic drug (DMARD) treatment should be introduced as early as possible in the course of the disease, to suppress disease activity and thereby provide the possibility of avoiding joint damage and disability.
2. An improved understanding of the pathophysiology of rheumatoid arthritis has facilitated the development of new drugs specifically targeted at cytokines, which play a well defined role in the inflammatory process. These "biologic agents" have been proven to be effective and well tolerated, but are very expensive.
3. The broad introduction of methotrexate (MTX) for the treatment of rheumatoid arthritis (RA) some 20 years ago had even larger consequences from a practical and economic point of view. This drug proved to be very effective, had a relatively rapid onset of action, was well tolerated in most cases, and could be prescribed in a wide dose range taking into account the needs of each individual patient. These features led to MTX becoming the most widely used DMARD worldwide. Moreover, MTX adds to the efficacy of tumor necrosis factor alpha (TNF-α) biologic agents, which appear to be indicated in only a minority of patients suffering from severe RA despite conventional DMARDs (1). MTX remains the "anchor drug" in the treatment of the majority of patients with RA (2).

This article presents an overview of our present knowledge of the benefits and risks of low dose MTX treatment.

Beneficial pharmacologic properties and mechanisms of action

MTX is generally taken weekly by the oral or parenteral (iv, im, sc) route. Oral absorption of doses between 10 and 25 mg may be as low as 25% and as high as 100% (mean 70%) (3-6). With the higher doses of 25-40 mg (median 30 mg) weekly, the bio-availability in RA patients ranged from 21% - 96% (mean 64%) when compared to subcutaneous application (7). If efficacy is insufficient, parenteral dosing may be tried. The absorption rate remains constant over time in the same individual at the low dose of 7.5 mg/week (8), but decreases by 13.5% at a maintenance dose of 17 mg (9). Renal function is critical for drug elimination and thereby to prevent toxicity, as 50-80% of the drug is eliminated unchanged through glomerular filtration with a half-life of 2 - 4 hours, the mean renal clearance being 110 ml/min/m^2 (3). Impaired renal function (10) or advanced age (11) may decrease clearance and increase toxicity.

The short total half-life of 6-7 hours (12) has practical advantages in the clinical "handling" of MTX when compared with other DMARDs such as parenteral gold and leflunomide. Normally, after 24 hours no MTX can be detected in the serum. However, MTX (and its oxidation product 7-hydroxy-MTX) can be found in the polyglutamated form after more than one week within the cells of RA patients being treated with low dose weekly MTX (13), allowing for a once-weekly dosage.

MTX may have different mechanisms of action. The classical mechanism in the treatment of neoplasia involves the inhibition of dihydrofolate reductase (DHFR) and other folate dependent enzymes, thereby interfering with the syn-

thesis of pyrimidine and purines (14). The inhibitory effect of MTX on cytokine production can be reversed by the addition of folinic acid or thymidine and hypoxanthine (15).
The rapid onset of the clinical effect of MTX in RA – the CRP decreases significantly within days after a single injection (16) – indicates strong anti-inflammatory properties (14). The occurrence of opportunistic infections may point to additional immunosuppressive effects.

Interactions of MTX with other drugs have to be considered

Some NSAIDs, including ibuprofen, naproxen, ketoprofen or salicylates, may significantly reduce the clearance of creatinine and MTX, while other nonsteroidal anti-inflammatory drugs (NSAIDs), including etodolac, piroxicam and meloxicam, do not interact with MTX. In general, these interactions are not clinically important, although substantial individual variation regarding drug interactions may be seen, and single cases with severe side effects have been reported (17-19).
NSAIDs did not affect the pharmacokinetic variables of MTX at weekly MTX doses of 7.5 mg, but reduced the renal clearance by 20% at a mean maintenance dose of 17 mg (20). There was also a 20% reduction in MTX clearance in patients receiving long-term corticosteroid treatment (21). Probenecid increases the 24 hour MTX plasma levels up to 400% (22). Chloroquine was found to reduce the bio-availability of MTX by approximately 50% (23). However, hydroxychloroquine significantly increased the mean area under the curve for MTX by approximately 65% ($p = 0.005$) and at the same time the peak MTX concentration was reached later and was lower (24). Cyclosporine A (CSA) may reduce creatinine as well as MTX clearance, thereby increasing the effective MTX dose. Furthermore, the co-administration of CSA led to a significant increase in the MTX plasma concentration and an 80% decrease in the plasma-7-OH-MTX concentration in the area under the curve, indicating that CSA may block the oxidation of MTX to its relatively inactive metabolite, 7-OH-MTX, thus potentiating MTX efficacy (and toxicity) (25). These drug interactions may have few practical implications, since the MTX dose can easily be adapted according to tolerability.

Beneficial effects of MTX on clinical outcome parameters

The first observation of the successful treatment of 7 RA patients with aminopterin in 1951 (26) was forgotten because of the dramatically positive effects of corticosteroids in the treatment of RA and the fear of MTX toxicity. Between 1951 and 1980 only a few reports on the treatment of RA with MTX with weekly i.v. doses of 15 mg (27) and oral weekly doses of 10-15 mg (28) appeared. In 1979, the authors approached the manufacturers of MTX to study its use in patients with RA, and were told that MTX was designed for the treatment of malignancies and was far too toxic for treating RA patients.
In the early 1980s, open pilot studies indicated effectiveness of 7.5–15 mg MTX weekly in RA patients not responsive to conventional DMARDs (29-32). Between 1984 and 1989, several randomized placebo-controlled trials over 6-26 weeks with weekly MTX doses of 7.5–25 mg demonstrated a significant improvement in the patients' clinical status (33-36). A significant dose-response relationship of MTX was documented (37), in terms of a rapid and excellent response to weekly i.v. doses of 25 mg (38) and 50 mg (39).

Long-term observational studies demonstrate superior effectiveness and tolerability

Multiple, carefully monitored, long-term observational studies have documented lasting clinical effectiveness and good tolerability of MTX with low discontinuation rates (40-52). These studies had follow-up periods of up to 11 years and included between 26 and 453 patients, most of them suffering from long-lasting disease unresponsive to previous DMARD treatment. MTX resulted in a significant improvement of all clinical measures, including acute phase reactants, with a peak effect reached after 6 months. The beneficial effect usually appeared to be sustained during the entire follow-up period. Marked improvement (>50% decrease) in the number of swollen joints occurred in > 50% (51), and 69% (45) of patients. Clinical remissions, according to the definition of Pinals (53), however, were infrequent and are difficult to achieve in patients with severe destructive disease.
A long adherence to a treatment can serve as a surrogate for both good tolerability and effectiveness. In long-term studies, drug survival rates of more than 5 years occur in more than 50% of patients. In routine clinical care, MTX treatment was continued substantially longer than treatment with other DMARDs (54-58) – e.g. a treatment continuation rate of 57% for MTX was seen after 5 years compared to 20% and 25% for other DMARDs ($p < 0.01$) (58). In 460 patients from 7 private practices in Melbourne, Australia 75.4% of patients were still taking MTX after 6 years (56) and 53% of patients were continuing at 12 years (59). However, in two other studies the continuation rate after 4 years was not different between MTX and other DMARDs (60, 61).
One reason for the long continuation rate of MTX may be the possibility to adapt the dose in a wide range to the needs of the individual patient, which is more difficult with other DMARDs. The patient must be observed carefully and the dose may be increased in cases of increasing disease activity. In a follow-up of 437 patients starting MTX between 1988 and 1996, health assessment questionnaire (HAQ) disability index values improved up to month 30, but after 42 months re-progressed again, reaching baseline values after approximately 8 years (62). There is the need for a more rapid upward dosage titration and the longer maintenance of an optimal or highest tolerated dosage (62). Although MTX was equally or even more effective in patients older than 65 years (63, 64), withdrawal occurred more frequently in these patients (52, 56).

MTX is a potent inhibitor of radiographic progression

The primary consequences of RA are

functional disability and joint destruction, which are correlated significantly in the later stages of the disease (65). Therefore, the most important goals of treatment are to prevent the progression of joint damage and functional disability by early aggressive treatment aimed at remission.

The capacity to retard radiographic signs of disease progression is regarded as the most important criterion for disease modification. In long-term studies documenting radiographic outcomes, most patients usually demonstrated ongoing progression under MTX treatment (41, 43, 51, 66, 67). In contrast, patients who had remission of disease activity displayed an arrest of damage progression (41, 43, 51, 67). Two studies found a significant inhibition of progression during MTX treatment, compared to radiological progression during prior treatment with DMARDs which were clinically insufficient (68, 69), while no significant difference was seen in one study (70). In patients with early erosive RA, radiographic progression was clearly inhibited in patients treated with either parenteral gold or intramuscular MTX, with no significant difference between the groups (71, 72). Other studies comparing MTX with other DMARDs also demonstrated a flattening of the progression curve over time (73). A meta-analysis stated that disease progression with MTX treatment was comparable to that seen with parenteral gold (74), but it was less than under treatment with other DMARDs (73-75). Based on these results, it is reasonable to conclude that MTX delays radiological progression in patients who also respond favorably in terms of clinical effectiveness.

MTX compares favorably with other DMARDs

The relative efficacy and toxicity of MTX has been investigated in several studies. In one study, a dose of 7.5–15 mg MTX weekly was superior to 6-9 mg Auranofin per day in terms of improving disease activity as well as withdrawal rates (76), while another study indicated non-significant differences in the efficacy of 7.5 mg MTX weekly versus 6 mg auranofin per day (77).

Three clinical trials found no significant differences in clinical improvement between parenteral gold and MTX, while MTX appeared to be slightly less toxic (78-80). In a two-center, double-blind comparison between parenteral gold (50 mg per week) and parenteral MTX (15 mg per week) in 174 patients with early erosive RA (median disease duration 11 months), all of the clinical parameters and acute phase reactants were improved significantly by > 50% after 1 and 3 years without significant inter-group differences. Marked improvement (> 50%) occurred in 68% of MTX-treated patients and 76% of patients treated with gold. Tolerability was significantly better with MTX (81, 82). In a randomized, but open study in 141 patients, all efficacy parameters were improved significantly with parenteral gold or MTX treatment by 24 weeks ($p < 0.001$); inter-group differences were not seen for efficacy, but gold caused significantly more withdrawals for toxicity ($p = 0.0026$) (83).

In 42 patients treated over 24 weeks, no significant difference was seen between 100 mg azathioprine (AZA)/day and 10 mg MTX/week, with a trend towards earlier and more marked improvement with MTX (84). In another study, 7.5 – 15 mg MTX/week (n = 33) was significantly better than 100-150 mg AZA/day (n = 31) over a period of 48 weeks (73); after 48 weeks, only 36% of patients remained on AZA, while 91% continued on MTX. A meta-analysis of clinical trials in 3957 patients found MTX to be more effective than auranofin and comparable to D-penicillamine and parenteral gold (85).

In a large American study the ACR20/50/70 response rates were 72/56/26% for leflunomide and 67/43/20% for MTX, with supplementation of 1-2 mg/day folic acid. The CRP improved significantly in both groups, while the ESR declined only marginally (86). The ACR response rates were maintained over 24 months (87). In a European study comparing leflunomide with MTX, in which only 10% of patients had folate supplementation, improvement of all efficacy parameters was significantly greater with MTX than with leflunomide. However, more patients on MTX were withdrawn due to liver enzyme elevations (88).

The new biologic agents have been celebrated as a "breakthrough" in the treatment of RA and have already changed treatment habits, more in the United States than in Europe. Only one study compared MTX with one of the TNF-inhibitors, etanercept, in patients with early RA. In that study a clinical response was seen earlier with etanercept than with MTX. This difference may have resulted in part from the low initial dose adopted of 7.5 mg MTX per week (with folate supplementation), which was increased to 15 mg after 4 weeks and to 20 mg after 8 weeks in many patients. The difference in ACR 20 response after one year was small: 72% responders with etanercept, 65% with MTX ($p = 0.16$) (89). At 24 months, the difference was great, 72% with etanercept, 59% with MTX, and statistically significant; fewer patients completed the study with MTX (59% versus 74%) (90). Radiographic progression was 1.59 Sharp units with MTX and 1.0 with etanercept, corresponding to 0.25% and 0.385% of the maximum total Sharp score. After 2 years, the progression in the total Sharp score was 3.2 units with MTX and 1.3 with etanercept.

Direct comparisons of results with biologic agents and conventional DMARDs in different studies are difficult, since there are differences in patient selection, methodology, dosing, concomitant steroid treatment, outcome parameters, etc. However, such comparisons have been made for the step-up combination of MTX with different TNF-alpha blocking agents (91). In a similar comparison, conventional DMARDs performed very well when compared with the biologic agents based on outcome in composite scores (ACR, EULAR), ESR, CRP, swollen joint count and radiographic progression (92).

MTX is an ideal combination partner

Combinations of different DMARDs provide additional, or even potentiating, effects, and therefore have become widely used (92a, 93). Early meta-analyses did not find evidence for a superiority of combination treatment over

monotherapy in parallel comparisons (94, 95). The various designs of combination studies – parallel design, step-down design, add-on step-up design – have to be considered when judging the results. For example, the comparison of placebo or infliximab added to ongoing MTX treatment in patients with insufficient response to MTX is more a comparison between placebo and infliximab than combination versus monotherapy.

MTX has emerged as the optimal anchor drug to be used in combination with other DMARDs, and has been so studied in several trials (2). In one, a combination of MTX with auranofin was not more effective than the individual drugs (77). A combination with azathioprine was not superior to MTX alone regarding outcome parameters. However, fewer patients in the combination group required a dose increase than patients in the single drug arms (96,97). The combination of MTX with chloroquine was clearly more effective than MTX alone (98), although in a pharmacokinetic study chloroquine was found to reduce the bioavailibility of MTX by approximately 50% (23).

The combination of MTX with sulfasalazine (SAS) was only marginally superior to the individual drugs (99, 100). Triple combination treatment including MTX + SAS + hydroxychloroquine demonstrated high effectiveness in one study (101). In a parallel design the triple combination MTX + HCQ + SAS was more effective than the combination MTX + SAS and the combination MTX + HCQ after 2 years (ACR20 78%, 60% and 49%, respectively). Similar trends were seen for the ACR50 response (102).

The addition of 2.5 – 5.0 mg of cyclosporine/day to ongoing MTX treatment in patients with only a partial response to MTX improved efficacy significantly over 1 and 2 years, while creatinine levels increased only marginally (103, 104). Also, in two studies with a parallel design the combination MTX + CSA was more effective than MTX monotherapy in improving clinical measures and radiographic progression (105, 106). When leflunomide was added to an ongoing MTX treatment in patients with an incomplete response to MTX, leflunomide was significantly more effective than placebo (ACR20 46.2% and 19.5%; $p < 0.001$), while discontinuation rates were similar in both treatment groups (107).

The combination of infliximab with MTX appeared to reduce antibody formation and improve the tolerability of infliximab. Infliximab serum concentrations tended to be higher when combined with MTX than with infliximab monotherapy. At this time, all TNF inhibitors are combined with MTX because study results and general experience have demonstrated a better efficacy of the combinations. In the case of adalimumab, this may be due to a prolongation of the half-life and increased serum levels when combined with MTX (108). To the best knowledge of the authors, a formal interaction study of etanercept + MTX has not been performed.

MTX may have favorable and unfavorable effects on the extra-articular manifestations of RA

In two case reports (109, 110) and two case series of 4 (111) and 7 patients (112) with Felty's syndrome, an increase in the number of neutrophils, and an improvement in the ESR and number of swollen joints was observed, accompanied by a reduction in the corticosteroid dose when treated with MTX.

Rheumatic vasculitis may respond favorably to MTX, resulting in the healing of vasculitic ulcerations and digital infarctions (113, 114). On the other hand, MTX therapy can also induce vasculitic lesions, which may disappear when treatment is continued (115).

An accelerated nodulosis has been estimated to occur in approximately 8% of RA patients treated with MTX (116). Multiple small nodules, histologically indistinguishable from the "usual" rheumatoid nodules, may develop in the hands and feet. The nodules may heal with the discontinuation of MTX and reappear with its reintroduction. Nodules may also develop in the heart or the lungs (117).

Risks of MTX treatment in RA

A superior "drug survival rate" indicates a favorable tolerability with presumptive effectiveness and limited toxicity of MTX in RA patients. However, a drug with desirable effects on multiple organ systems must have undesirable effects as well. Some adverse events appear to be related to the antifolate activity of MTX and mimic the symptoms of folate deficiency. Fortunately, clinically relevant side effects are rare. In prospective long-term studies in which patients were seen frequently (41, 43, 46-49, 51, 118), as well as in studies with the i.v. application of higher MTX doses (39), 60–85% of patients reported adverse events and 10-30% discontinued MTX due to toxicity. Elevated creatinine serum levels (119), advanced age (56,120) and low folic acid levels (121) predisposed to adverse events. The creatinine elevations are generally reversible when MTX is discontinued.

A post-dosing reaction characterized by arthralgias/myalgias or fatigue/malaise or both is seen in approximately 10% of patients within hours after dosing (122).

Gastrointestinal side effects

Nausea, malaise and vomiting were observed in prospective studies in 10-50% of patients, starting 1-8 hours after medication and continuing for a few hours up to one week. Some patients are unable to work after dosing and take MTX only on weekends. MTX polyglutamate is accumulated in cells of the intestinal mucosa (123), which may explain in part the gastrointestinal side effects in some patients. Healing of peptic ulcers caused by concomitant NSAID medication may be delayed (124). Hence, an active peptic ulcer should be regarded as a relative contraindication for MTX.

Skin and mucous membranes

Stomatitis has been observed in long-term studies in 12-37% of patients (42, 48, 120, 125) and was the reason for discontinuation in 6% (51). Mild alopecia occurs in up to 27% of patients (40, 48, 120, 125), but prompted discontinuation in only 4% (51). Urticaria (126), small vessel vasculitis, and granulomatous vasculitis are rare.

Hematopoetic system

Hematologic complications of weekly MTX treatment for RA are seen infrequently. In short term studies, even with higher doses, they occurred in 2-3% in some reports (38,39,124), and in 11% in another report (127). In long-term studies, bone marrow side effects occurred in up to 24% of patients (42, 48, 125). The most frequent abnormality is mild to moderate leucopenia (41). In one long-term follow up, mild leucopenia was observed in only 8 and mild thrombocytopenia in 7 out of 271 RA patients (51). Pancytopenia occurred in 7 of 511 patients (1.4%) included in prospective trials (128). The number of withdrawals due to cytopenia ranged from 0 to 5.9% (42, 48, 125). Impaired renal function (119,129), folic acid depletion (121), advanced age, current infection, multiple co-medication (128), and treatment with trimetoprim-sulfametoxazol (128) have been identified as risk factors for bone marrow toxicity. Usually, blood counts are normalized within 2 weeks after the withdrawal of MTX, but some patients may require supplementation with folic acid (121,130) or even treatment with colony stimulating factors (131).

Central nervous system

Central nervous disturbances, including headache, dizziness, vertigo, lightheadedness, and mood alterations were reported in up to 36% of patients in long-term studies (41, 48, 118). Again, advanced age and elevated serum creatinine are predisposing risk factors (132). In 2 patients with a history of epilepsy, seizures reappeared within 6 weeks of starting MTX treatment and disappeared when MTX was discontinued.

Respiratory system

MTX-induced lung disease is a rare, but potentially life-threatening complication, and the rapid evaluation of pulmonary symptoms in patients receiving MTX is crucial (133). The predominant symptoms of MTX pulmonitis are the subacute development of dyspnea and dry non-productive cough and fever, accompanied by headache, malaise, cyanosis, hypoxemia and restrictive pulmonary function changes (134). Rales may be present on physical examination, and interstitial infiltrates may be seen on chest radiographs. Lung biopsy may reveal hypersensitivity pneumonitis characterized by massive interstitial and alveolar infiltration with inflammatory cells, predominantly lymphocytes, and granuloma formation with giant cells (135). Other causes of pulmonary disease, e.g. nosocomial infections (136-138), must be excluded before a diagnosis of MTX-induced pneumonitis can be established.

Pulmonary complications occurred in 2.1% to 6.8% of patients (140-142), but some clinical studies did not encounter any pulmonary complications (96, 143). Between 1981 and 1993, 27 patients with MTX pneumonitis were identified in 6 clinical centers, and reports on 68 patients were found in the medical literature (134). The mortality rate in these patients was approximately 17.5% (134). Pre-existing lung disease does not seem to pre-dispose to MTX pulmonary adverse events (139, 140). Furthermore, there is no evidence to suggest that low-dose MTX is associated with chronic interstitial lung disease (144).

Liver toxicity

Among patients with psoriasis, liver fibrosis and cirrhosis developed with increasing cumulative doses in up to 24% of patients treated with daily MTX. Risk factors for liver toxicity, in addition to daily dosing, included high alcohol consumption, obesity, and diabetes. Weekly dosing was found to be better tolerated than daily dosing. Awareness of potential liver side effects in the long-term treatment with MTX is necessary, although hepatotoxicity has not been a substantial problem with weekly low-dose MTX in patients with RA. There are proposals to change the guidelines for monitoring liver function tests (145).

Transient slight elevations in liver enzymes were observed in up to 48% of patients in one study (146), and in 53% in a more recent study (147). These elevated levels returned to normal after dose reduction, a change in the concurrent NSAID therapy, folic acid supplementation or even the unchanged continuation of treatment (41,51,148). Frequent elevations of aminotransferases indicate structural liver abnormalities (149-152) and were correlated significantly with liver biopsy grades (153, 154). Galactose elimination capacity and the aminopyrine breath test declined significantly during MTX treatment over 3.8 years (155).

A high prevalence of minor histologic changes in the liver of patients with RA is seen (156, 157), which may be classified as mild reactive hepatitis in one-third of patients (157). Some of these changes may be related to the underlying disease, as they can be observed before any drug treatment has taken place. Comparative liver biopsy studies did not show differences in a number of histologic parameters, among them "necrosis", "inflammation" and "fibrosis", between biopsies taken before and during MTX treatment (158,159), even in cumulative doses of up to 8,400 mg (160). Minor fibrosis was present in approximately 25% of patients before and during MTX treatment (158). Only 5 of 25 liver biopsies demonstrated minor fibrosis in patients who received MTX for more than 10 years (161). However, Kremer observed a significant increase of fibrosis in 29 patients with baseline and yearly follow-up biopsies over 4 years (162), and a significant increase of the Roenigk score after 6 years (163).

Baseline electron microscopy showed collagen deposits in the space of Disse and lysosomal changes not seen in controls (164), but these did not increase after a mean follow-up period of 8.2 years (163). In several overviews, the frequency of fibrosis among MTX-treated RA patients was estimated to be between 3% and 11%. Among RA patients treated with MTX for more than 5 years, the incidence of cirrhosis was estimated to be 1:1000 (165). At these levels, the risk of complications of liver biopsy are greater than the risk of cirrhosis, and liver biopsy is rarely indicated.

Infections

Infections occur more often in patients treated with MTX than with other

DMARDs (166, 167), especially in patients with severe RA (168) and during the first years of treatment. In prospective studies, they were observed in up to 25% of patients (42). This phenomenon may be confounded by a higher rate of infections in patients with RA, particularly severe RA, and the fact that patients treated with MTX have more severe RA. Opportunistic infections (136, 137, 169), serious fungal infections (61, 170), increased frequency of herpes zoster (167, 171), as well as re-activation of hepatitis B (172) and tuberculosis (173,174) have been reported. Some patients must discontinue MTX permanently because of recurrent infections, mostly affecting the small airways or the urinary tract.

Perioperative complications, i.e. wound infections or wound healing disturbances, were increased after orthopedic surgery in some studies, but in others they were not. Some authors withhold MTX for 2 weeks prior to surgery (133), but others continue treatment through a surgical intervention (175).

Kidneys and the reproductive system

The excretion of MTX and its metabolites is delayed in patients with impaired renal function, leading to potentially increased toxicity (10). MTX treatment may also impair renal function, at least in elderly patients; in one study the glomerular filtration rate and tubular excretion was reduced by 10% during oral MTX treatment with 15 mg weekly without any co-medication (176). MTX clearance and creatinine clearance also decreased with a stable MTX dose of 7.5 mg/week (177). These observations emphasize the need to monitor creatinine levels during MTX treatment.

Oligospermia, impotence, and gynecomastia have been reported with MTX use in 11 cases. No malformations were detected among 10 pregnancies during low-dose MTX treatment in RA patients (179). However, a case with multiple congenital abnormalities has been described, after the mother had been treated with weekly low-dose MTX during the first trimester of pregnancy (180). Furthermore, malformations have been reported after MTX was used to induce abortion (178).

Oncogenicity

Large studies of cancer and psoriasis did not establish an association between MTX and malignancy. RA patients have a disease-related increased risk of developing certain lymphoid malignancies. Cases of Hodgkin's disease (182, 183) and leukemia (184) have been reported in RA patients treated with MTX. The majority – more than 50 (185) – of cases with malignancy were non-Hodgkin-lymphomas (185), most of which were associated with Epstein-Barr-virus (EBV) infection (186, 187).

Whether MTX plays a role in the development of lymphoma in RA patients remains unclear (186). RA patients are known to have a defect in HBV-directed suppressor T-cell-function (187). It is not established that MTX augments (or may correct) this T-cell-suppressor defect, although opportunistic infections are clearly associated with MTX use (perhaps in patients with severe RA) (188). The risk for RA patients to develop lymphoma while taking MTX is increased in those with severe disease activity, intense immunosuppression, genetic predisposition, and latent infections with EBV virus (185, 189). Some lymphomas associated with EBV infection remit after the discontinuation of MTX (185, 189, 191) or with treatment with rituximab (192). However, in 16,263 patients with RA, no increase in lymphoma was observed in patients taking MTX (190).

Bone

Active RA is associated with osteoporosis, especially in patients taking corticosteroids (193). In rats treated with MTX, the osteoid volume decreased significantly, bone formation was reduced markedly (194), and significant osteopenia developed through the suppression of osteoblast activity (195). However, in RA patients there was no difference in bone mineral density between those treated with and those not treated with MTX (196, 197). However, when patients who were taking prednisone in doses ≥ 5 mg/day were additionally treated with MTX, they showed significantly greater bone loss than patients treated with a similar dose of prednisone without MTX ($p = 0.004$) (196).

Folate supplementation does reduce MTX toxicity

The mode of action of MTX may be related in part to its antifolate activity (198), and several MTX adverse events mimic the clinical manifestations of folate deficiency. Folate supplementation has been shown to reduce MTX toxicity in several studies (199-203), although in two studies toxicity was unchanged (204, 205). In a large 48-week randomised study, 434 RA patients beginning MTX treatment were supplemented with folic acid (1 mg/day), folinic acid (2.5 mg/week), or placebo. Side effect-related withdrawals occurred in 38% in the placebo group, 17% in the folic acid group, and 12% in the folinic acid group. The difference was almost entirely accounted for by an elevation of hepatic transaminases (increased in 53% of all patients !). No differences were seen between the groups with respect to all the other adverse events (147). In one study, side effects were inversely related to red cell folate levels and occurred at levels < 800 nmol/L (206). Unfortunately, in all the other studies noted above the folate status was not documented.

Folate supplementation may reduce MTX efficacy

Although the mode of action of MTX is related in part to its antifolate activity (198), and the addition of folinic acid reverses the inhibitory effect of MTX on cytokine production (15), there is still much controversy about whether or not folate supplementation diminishes the efficacy of MTX. With the exception of one study (207), folate supplementation did not appear to interfere with MTX efficacy (208). However, the number of patients in these studies was small, and the outcome parameters were too insensitive to reliably recognize any effect on efficacy. In a Dutch study (147), the final MTX dose was higher in patients taking folic acid, compared with those receiving placebo (mean 18 and 14.5 mg/week, respectively), indicating an indirect reduction in the MTX dose with folate supple-

mentation. The MTX dose was adapted to achieve a sufficient response. In a large phase III trial in the United States, MTX with folate supplementation was less effective than leflunomide, compared to a corresponding European study in which MTX without folate supplementation was significantly more effective than leflunomide (86, 88).

It has been suggested that homocysteine is an independent risk factor for cardiovascular disease and mortality. Folic acid supplementation can prevent the increase in homocysteine concentration caused by MTX treatment (209, 210). However, there are no reports about increased cardiovascular mortality in RA patients treated with MTX. On the contrary, MTX treatment reduced the risk of all-cause mortality by 60% and reduced even more the risk of cardiovascular mortality (211). As inflammatory mechanisms seem to be important for the development of atherosclerosis, the reduction in cardiovascular mortality may be explained by the suppression of inflammation (212). An increase in life expectancy was clearly related to a good response to MTX (213). However, in RA patients with established cardiovascular disease and/or hypertension, MTX was associated with an increased risk of death by a factor of 3.4 (214). An intriguing observation indicated that homocysteine levels were correlated significantly with disease activity ($p < 0.001$) and with creatinine levels ($p < 0.001$). These data suggest that MTX may increase homocysteine levels in some patients by inducing mild renal insufficiency (215).

The improvement in MTX tolerability by folate supplementation may, at least in part, be due to a relative dose reduction of MTX, which in turn results in the need to increase the dose of MTX. Over the last 10-15 years the mean MTX dose in American long-term observational studies has been steadily increasing. Therefore, we have supplemented folic only temporarily in those patients who experienced side effects in the presence of folate deficiency, and had good experience with this strategy. However, most authors recommend folic acid supplementation in all patients.

Personal recommendations for administration and drug monitoring

MTX can be administered orally or by intra-muscular, intravenous, or subcutaneous injection with doses ranging from 7.5–30 mg once a week. The dose depends on body weight, gender, renal function, concomitant disease, general health status, and disease activity.

We usually start treatment with a relatively high dose of 15–25 mg given parenterally to exclude the individual differences in bioavailability of oral medication and to achieve a rapid response. After 6-12 weeks, most patients are converted to oral medication and the dose is adjusted according to efficacy and tolerability. Most rheumatologists prefer to begin with lower oral doses, and then increase the dosage. Tolerability can often be improved by administering the drug in the evening or in two equal doses in the morning and evening of the same day, by changing the route of administration (parenteral versus oral), reducing the dose, or by supplementation with folic acid. Nausea and vomiting frequently may indicate the presence of a peptic ulcer.

Possible interactions with NSAIDs should taken into consideration. We consider folate supplementation when side effects occur in the presence of concomitant folate deficiency. With 5 mg of folic acid 2 days after MTX application, folate levels usually normalize after several weeks and supplementation can be stopped. Most authors recommend folic supplementation with 1 mg per day.

Relative or absolute contraindications to MTX treatment are listed in Table I. If there is no alternative to MTX in a patient with renal impairment, we start with lower doses (i.e. 5 mg/week) and check the MTX serum level after 24 hours to ensure that it is below 0.05 mM/l. Regular monitoring of serum creatinine is necessary to avoid toxicity. Women with childbearing potential should practice adequate contraception. The safe amount of alcohol consumption while taking MTX is not known and may differ from patient to patient. Usually, we allow only one or two glasses of wine or beer per week.

During MTX treatment, we monitor full blood counts, including the differential white blood count and platelets, serum creatinine, and aminotransferases, weekly during the first month, every two weeks during months 2 and 3, and monthly thereafter.

Table I. Contraindications to MTX therapy.

1. Renal insufficiency (serum creatinine > upper limit)
2. Inadequate contraception
3. Active liver disease
4. Regular alcohol intake
5. Acute or chronic infection
6. Leucopenia or thrombocytopenia (exception: Felty's syndrome)
7. Serious underlying systemic disease
8. Non-compliance

MTX should be discontinued temporarily under the following conditions: serum creatinine exceeding normal values; aminotransferases exceeding 3-fold the normal values; leucopenia or thrombocytopenia; stomatitis; acute infections; severe concurrent illness; concomitant treatment with sulfonamides; or acute pulmonary symptoms.

Whether MTX should be discontinued before and after surgery should be decided in co-operation with the operating surgeon. Pre-treatment liver biopsies are recommended only in patients with significant alcohol consumption or a history of liver disease. Biopsies during MTX treatment are recommended only if over 50% of the ALT (alanine aminotransferase) level readings within 1 year – measured every 4-8 weeks – are elevated to more than twice the normal level, or if the serum albumin concentration falls below normal. Treatment can be continued if liver biopsies reveal a Roenigk-class I, II or IIIa. In patients with moderate to severe fibrosis or cirrhosis (class IIIb or IV), MTX should be permanently discontinued (152, 216).

Parameters of disease activity, radiographic progression, the development of deformities, and functional capacity should be monitored regularly. In the case of unsatisfactory response we increase the dose or, if this is impossible, combine MTX with another conventional DMARD or a biologic agent.

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