REVIEWS

Adv Clin Exp Med 2007, **16**, 2, 287–295
ISSN 1230-025X

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Toxicity of Low Dose Methotrexate in Rheumatoid Arthritis

Działania niepożądane w czasie terapii metotreksatem u chorych na reumatoidalne zapalenie stawów

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Abstract

Methotrexate (MTX) has become in the last 15 years the "gold standard" in the treatment of rheumatoid arthritis. Low-dose MTX has shown to be an effective treatment for rheumatoid arthritis. However during the treatment with low doses MTX (7.5–25 mg weekly) adverse effects occurred frequently – by 37–96% of patients. This article reviews the most common adverse events (gastrointestinal, haematological, neurologic adverse events, cutaneous reactions, hepatotoxicity, pulmonary toxicity, MTX osteopathy, MTX-induced nodulosis) and methods minimizing them. In this review the role of folate supplementation during MTX therapy was described. The factors associated with toxicity, especially the genetic factors were analyzed (**Adv Clin Exp Med 2007, 16, 2, 287–295**).

Key words: methotrexate, polyarthritis rheumatoidea, adverse events.

Streszczenie

W ciągu ostatnich 15 lat metotreksat (MTX) stał się „złotym standardem" w leczeniu reumatoidalnego zapalenia stawów (r.z.s.). Skuteczność MTX w leczeniu r.z.s. została potwierdzona w wielu pracach. Często jednak, stosując nawet małe dawki MTX (7,5–25 mg raz w tygodniu), obserwuje się działania niepożądane. Odsetek wszystkich działań niepożądanych podczas długotrwałej terapii małymi dawkami MTX wynosi 37–96%. W artykule przedstawiono najczęstsze działania niepożądane (na przewód pokarmowy, oddechowy, skórę, powikłania hepatologiczne, hematologiczne, nefrologiczne, pochodzące z ośrodkowego układu nerwowego) i sposoby zapobiegania im. Omówiono rolę substytucji kwasu foliowego podczas leczenia MTX. Zwrócono także uwagę na czynniki predysponujące do wystąpienia działań niepożądanych ze szczególnym uwzględnieniem predyspozycji genetycznych (**Adv Clin Exp Med 2007, 16, 2, 287–295**).

Słowa kluczowe: metotreksat, reumatoidalne zapalenie stawów, objawy uboczne.

Methotrexate (MTX) has been used in the treatment of rheumatoid arthritis (RA) for 30 years. In the last 15 years it has become the "gold standard" in the treatment of RA, and most new modes of treatment are compared with MTX treatment. It is a basic element of many kinds of RA complex treatment. In the treatment of active RA, biological agents are more often combined with MTX. When evaluating a drug, one considers the effectiveness of the therapy and the potential adverse effects, which are the most common reasons for discontinuing the treatment. They arise as soon as within the first six months of the therapy. In the first year of the therapy, 20–30% of patients discontinue it. MTX therapy is continued after 2 years by 55–81.8%, after 5 years by 43–62%, and after 10 years 30–50% of patients still use the drug [1–3]. The purpose of this study was to present the most common adverse events (gastrointestinal, hematological, neurological adverse events, cutaneous reactions, hepatotoxicity, pulmonary toxicity, MTX osteopathy, and MTX-induced nodulosis) and methods for minimizing them (Tab. 1).

Table 1. Adverse effects of methotrexate in rheumatoid arthritis and methods to minimize them

Tabela 1. Działania niepożądane podczas terapii MTX u chorych na r.z.s. i sposoby ich minimalizacji

Adverse effects (Rodzaj działania niepożądanego)	Frequency – % (Częstość – %)	Prevention (Zapobieganie)
Gastroenterological (Gastroenterologiczne)	10–70	folic acid supplementation; dividing the dose into 2–3 parts to be taken every 12 hours; lowering the MTX dose; parenteral administration
Hepatotoxicity (Hepatotoksyczne)	15–70	lowering the MTX dose; folic acid supplementation; monitoring according to ACR recommendations
Cutaneous (Skórne)	5–10	folic acid supplementation; lowering the MTX dose
Interstitial pneumonitis (Śródmiąższowe zapalenie płuc)	2.5–7.5	annual chest X-ray*; regular spirometry**
Hematological (Hematologiczne)	5–25	monitoring MCV, creatinine (at first every 4, later every 8 weeks); folic acid supplementation
Nephrotoxicity (Nefrotoksyczne)	case studies	monitoring creatinine every 8–12 weeks**
Infections (Zakażenia)	17/1000 cases/year	influenza and pneumococcus vaccination
Carcinogenicity (Rakotwórczość)	not definitely proven, largely lymphoma	
Central nervous system disorders (Zaburzenia o.u.n.)	1–30	aminiphiline (< adenosine in CSF)
MTX-induced nodulosis (Guzki pometotreksatowe)	8–11	colchicine, hydroxichlorochine
Postdosing reactions (Reakcja po podaniu leku)	1–10	lower MTX dose; change from parenteral to oral route; divide the dose into two parts

* In patients with undiagnosed pulmonary diseases (this recommendation is not widely accepted).
** This recommendation is not widely accepted.

* U pacjentów z niewyjaśnionymi chorobami płuc (zalecenie nieakceptowane przez wszystkich).
** Nieakceptowane przez wszystkich.

Gastrointestinal Adverse Effects

The most common adverse effects while using MTX are gastrointestinal disorders. They arise in 10–70% of patients during the first two years of therapy. They emerge mainly in obese persons, those not supplemented with folic acid, in women, and in patients who already had gastrointestinal disorders [4]. It is supposed that frequent adverse gastrointestinal effects are due to an inadequate influence of MTX on rapidly proliferating mucosa cells. It has been demonstrated that the MTX levels in plasma necessary for inhibiting DNA synthesis in individual cells differ (10 nM for bone marrow and 5 nM for gastrointestinal endothelium). This is why adverse effects due to gastrointestinal mucosal damage are more common than myelosuppresive activity during treatment with low doses of MTX [5]. The most common are nausea, dyspeptic ailments, loss of appetite, and, less commonly, diarrhea and vomiting. Diarrhea and vomiting occur 1–8 hours after administration of the drug and abate after a few hours, though sometimes they occur for up to two days. They are frequently diminished when the dose is lowered, when the drug is administered in 8- to 12-hour intervals, or when folic acid is supplemented. Reduction in nausea is observed when ondansetrone is administered.

Parenteral (subcutaneous or intramuscular) administration of MTX is frequently effective in reducing adverse gastrointestinal effects. There are individual reports in the literature on gastric and duodenal ulcers during MTX therapy, but nonsteroidal anti-inflammatory drugs (NSAIDs) were administered simultaneously, so the role of MTX in causing these effects is questionable. Stomatitis occurs in 6–37% patients on prolonged treatment with MTX. Onset of symptoms occurs 1–5 days after MTX administration. In most cases, erosion and painful ulceration is healed when folic acid is administered or the drug dose is reduced, but in individual cases the treatment must be withdrawn.

MTX should not be withdrawn rapidly, as unspecific gastrointestinal disorders may appear. They appear in many cases irrespective of the conducted treatment and may be caused by other agents, e.g. NSAIDs. These disorders are observed in up to 25% of patients receiving placebo (in the group treated with MTX, 42%) [6].

Cutaneous Adverse Effects

Unspecific cutaneous rash and facial flush occurred in as many as 20% of patients, but in at most 5–10% of subjects treated with low doses of MTX. There are no clinical or histological criteria for differentiating these symptoms from those caused by other drugs. In some patients, cutaneous small-vessel vasculitis occurs. The only way to differentiate this from vasculitis in the course of RA is to withdraw the drug temporarily. Hyperpigmentation, alopecia development, and porphyria cutanea tarda are very rare. MTX therapy may cause erythema induced by UV radiation. Hair loss is observed in 2–6% of patients, but one third of patients in follow-up complain of hair density diminishment. Considerable alopecia is found in less than 0.5% of patients treated with low doses of MTX [7]. An effective therapy for alopecia has not yet been found. Agents revitalizing hair texture and folic acid supplementation should be used, and lowering the MTX dose may even be considered.

Hepatological Adverse Effects

As there were reports in the literature on liver cirrhosis in 10–39% of psoriasis patients treated with MTX for more than five years, it was introduced in the treatment of rheumatic diseases very carefully. In RA patients, however, the progression of histological lesions in the liver is significantly reduced. This can be explained by a better understanding of the drug's activity, physicians' vigilance in administering the drug, better qualification of patients and, above all, improved administration of the drug. Lesions observed in histological liver specimens are unspecific and also occur in patients who never received MTX. The most frequent disorders are steatosis and mild or moderate fibrosis of the liver. Progression of previously existing lesions was proven in 23–45% of patients on prolonged MTX treatment. There are some reports of active hepatitis and few of liver cirrhosis. According to the American College of Rheumatology (ACR), one case of severe hepatic disorder or cirrhosis occurs in 1000 patients treated with MTX for five years [8].

The mechanism causing liver fibrosis in the course of MTX treatment has not yet been established. It may be associated with toxic effects rather than immunoallergic ones (it has been shown that hepatotoxicity depends on MTX level in the liver). Not all authors have confirmed this in their research. Fathi et al. [9], based on a 3.5-year follow-up of 40 patients, claimed that there was no correlation between MTX adverse effects and its level in serum or liver. MTX levels remained stable after 1 and 3.5 years of treatment. Hepatotoxic risk factors included the cumulative dose of the drug, alcohol abuse, significant obesity, diabetes mellitus, advanced age, and hepatic disorders in the medical history [8].

Although MTX leads to severe hepatic disorders (fibrosis or cirrhosis) very rarely, an increase in hepatic enzyme activity, mainly aspartate aminotransferase (AspAT) and alanine aminotransferase (AlAT), was observed in as many as 70% of patients. In the present research, increases in these enzyme levels were found in 15% of patients and they returned to normal values when the therapy was continued [1]. The significant differences found in various studies may be caused by the dose of the drug, the duration of therapy, and the rules for qualifying patients. Increases in AspAT and AlAT values rarely exceed three times the upper limit of the norm and they quickly settle to the norm after temporary therapy withdrawal. AspAT and AlAT values exceeding three times the upper limit of the norm are indications for withdrawal of the therapy. When analyzing the reasons for increases in hepatic enzymes values, one should consider hepatitis in the course of RA and the polypragmasy common in RA patients.

Nowadays, routine liver biopsy before introducing MTX therapy in not recommended, except for patients who have stated alcohol abuse, have had severe hepatic disorders (virus hepatitis), and are very obese. Rheumatologists question whether there is a necessity to perform a biopsy during MTX therapy. Owing to the risk and cost of the procedure, performing a biopsy seems inadvisable in all patients, even during long-lasting therapy or when exceeding a 2-g cumulative dose of the drug. It is estimated that liver cirrhosis may develop in 1 per 1000 patients treated with MTX for 5 years and in 14 per 1000 patients treated for 10 years. The risk of serious complications after biopsy is 1.47/1000 and of deaths 0.09/1000 performed procedures [10].

In individual cases, due to idiosyncratic reactions, severe hepatic disorders may occur even after low-dose therapy of the drug. It has been shown that folic acid supplementation limits the frequency of hepatotoxic activity [4, 11]. Recommendations for

minimizing hepatotoxic risk include: avoid taking NSAIDs on the day of taking MTX and the next day; if there are indications for combined treatment, it is advisable to administer MTX and chloroquine at the same time due to reduction in liver damage; administer folic acid (5–15 mg/week, at least 24 h after MTX administration); avoid alcohol consumption during MTX therapy; and the given dose of MTX should be received once a week.

Pulmonary Adverse Effects

One of the most serious adverse or even mortal effects of MTX therapy is interstitial pneumonia, observed in 2.5–7.5% of patients. It occurs independently of the duration of therapy and the cumulative dose of the drug (found in patients on either 12.5 mg or 6000 mg doses). The most probable cause seems to be allergy to the drug. Risk factors include pulmonary disease, mainly interstitial fibrosis, in the medical history, advanced age, and diabetes mellitus. The most common clinical symptoms are dry cough, dyspnea, and sometimes fever, fatigue, and headaches. In complementary examinations, hypoxemia, sometimes accompanied by hypercapnia, restrictive respiratory failure symptoms, decreased partial oxygen pressure, and increased blood eosinophilia are found. X-ray and histopathological examinations frequently show lesions typical for interstitial pneumonia. Lymphocyte concentration in bronchoalveolar lavage (BAL) fluid is increased. One must exclude lesions caused by opportunistic microorganisms (including *Pneumocystis carinii*, fungal infections) and RA systemic symptoms before diagnosing a toxic effect of MTX. In some cases, BAL and histopathological examination are necessary if the diagnosis is doubtful. Eosinophilia, pneumocyte proliferation, and fibrosis suggest toxic activity of the drug.

Allergic pneumonitis and granuloma interstitial reactions and the presence of giant cells and inflammatory cell clusters (mostly lymphocytes and eosinophils) in pulmonary alveoli and interstitial tissue are found in histopathological examination of pulmonary tissue. Some authors suggest performing spirometry regularly in order to detect pulmonary disorders. They have demonstrated statistically significant decreases in FEV_1, FVC, and TLC and increase in FEV_1:FVC in comparison with a control group in a two-year follow-up [12]. Other studies do not confirm the recommendation. Dawson et al. [13], based on HIRES CT scans and pulmonary function tests, did not show significant changes in a group treated with MTX and a group treated with other disease-modifying drugs. Before inducing MTX, the patient should be examined by chest X-ray. Research on finding markers for interstitial pneumonitis during MTX therapy is being carried out. Miyata et al. [14] found elevated Klebs von den Lungen (KL-6) and surfactant protein (SP-D) concentrations in interstitial pneumonitis patients and, what is more, these decreased with improvement of the inflammatory lesions. They may be useful in evaluating the efficacy of the treatment. Other authors confirmed the role of SP-D in monitoring therapeutic response only when the KL-6 concentration remained elevated [15]. The treatment of MTX pneumonitis includes MTX withdrawal, pulmonary ventilation improvement and, in severe cases, glucocorticoid therapy. Methylprednisolone and cyclophosphamide in treating pulses are sometimes necessary. Folic acid supplementation has not been proved to reduce these adverse effects considerably.

Hematological Adverse Effects

Cytopenia was observed in 5–25% of patients treated with MTX in various studies [8]. The most frequent forms are moderate leukopenia and thrombocytopenia. A very rare but the most serious complication is pancytopenia. There are two types of pancytopenia: idiosyncrasy-associated (which occurs even in the first two months of therapy) and cumulative dose-associated. Differentiation between the types is sometimes impossible. Bone marrow biopsy reveals megaloblastosis and decreases in the numbers of cells of all cell lines. Based on 70 pancytopenia cases described in Medline literature in 1980–1995, Gutierrez-Urena et al. [16] stated that it occurred in 1–2% of RA patients treated with MTX. Analyzing adverse effects, Kuitunen et al. [17] identified risk factors of pancytopenia: advanced age, impaired renal function, long-lasting RA, folic acid insufficiency, infections, concomitant medication with more than five drugs, and concomitant medication with cotrimoxazole, probenecid, and NSAIDs. Similar risk factors were confirmed by other authors, but they also underlined hypoalbuminemia and alcohol abuse [16]. Pancytopenia may occur if a patient takes a too large MTX dose by mistake or takes it every day instead of once a week. The most important risk factor is impaired renal function.

When preventing hematological side effects, one must monitor mean cell volume (MCV) and regularly assess creatinine concentration, especially in elderly people. Creatinine clearance monitoring is then more precise. Patients with elevated MCV must be carefully observed. It is advisable to

lower the MTX dose or supplement it with folic acid. If elevated MCV persists, the vitamin B_{12} and folic acid concentration should be evaluated. Usually when MTX has been withdrawn, bone marrow function is gradually restored within two weeks. The most important prognostic factor in pancytopenia patients is the leukopenia improvement rate. Kuitunen et al. [17] noted that in all patients who died on day 5 after MTX withdrawal or recombinant human G-CSF supplementation, leukocytosis had not normalized.

The role of folic acid supplementation in preventing pancytopenia has not yet been established. Scandinavian doctors observed 25 RA patients and pancytopenia occurred in 12 of them although they were supplemented with folic acid. In two of them who were not supplemented with folic acid and who were reintroduced to MTX, pancytopenia reoccurred although they were supplemented with folic acid. A frequent symptom associated with the presence or risk of pancytopenia is stomatitis.

In case of serious complications, the patient must take folinic acid (Leucovorin) as soon as possible (up to 48 h after the last dose of MTX) in doses similar to the MTX doses every 4–6 h until the drug is no longer found in serum. In severe cases, positive effects were achieved after G-CSF therapy.

Nephrotoxicity

High-dose methotrexate-induced renal dysfunction has been described mainly in cancer patients. 80–85% of MTX is eliminated by the kidneys within 24 h after administration. The drug is filtered by the renal glomerules and secreted by the proximal renal tubule in active transport. NSAIDs may lower MTX clearance as they use the same way of transport through the proximal renal tubules. Significant MTX nephrotoxicity has not yet been proven. There are case reports on interstitial renal fibrosis and vascular sclerosis, slight decrease in glomerular filtration rate, slight decrease in creatinine clearance, slight decrease in MTX clearance, and disorders in renal tubule function [19]. The present author's research showed a decrease in N-Acetyl-beta-glucosaminidase (NAG) and albumin concentrations in urine, which can be associated with the drop in the activity of the disease and lowering doses of NSAIDs [1].

One must pay attention to the more frequent incidence of MTX adverse effects in patients with renal dysfunction. Patients on low-dose MTX therapy should be periodically (every 8–12 weeks) monitored for creatinine levels and undergo urine analysis. RA patients often use other, potentially nephrotoxic drugs and the disease can contribute to renal dysfunction (e.g. amyloidosis).

Infections during MTX Therapy

There are many reports of infections in patients receiving MTX. In a retrospective analysis of 2479 patients treated with various modifying drugs in the MTX group, there were 17 infections/1000 persons/year. In the groups receiving gold compounds, D-penicillamine, azathioprine, and hydroxychlorochine there were 5 infections/1000 persons/year maximum [20]. The most common are opportunistic infections associated with the immunosuppressive activity of the drug. The most frequent are *Pneumocystis carini*, *Herpes zoster*, *Listeria monocytogenes*, *Nocardia asteroides*, and *Histoplasma capsulatum* infections. Some authors suggest discontinuing MTX therapy 1–4 weeks before surgical procedures as the perioperative infection risk is higher and wound healing is impaired. These recommendations were not proven to be adequate in a study by Perhala et al. [21], as in the group of patients who continued MTX therapy the number of infections was not higher. Patients treated with MTX should not be given live vaccines, but they should be vaccinated against influenza and pneumococcal infection.

Teratogenic Effects

MTX is strictly contraindicated in pregnancy due to its proven teratogenic effects and miscarriage risk observed in, for example, psoriasis patients. Patients in reproductive age should be informed of this and must use effective contraceptive methods. Aminopterine was used as an abortifacient and aminopterine syndrome was described: multiple skeleton deformities, hydrocephaly or acephaly, and external ear abnormalities. Women should withdraw MTX at least one month before planned conception and men at least 90 days before planned conception.

Carcinogenicity

At present, MTX is not considered carcinogenic. Although there were reports on lymphomas, skin, pulmonary, laryngeal, nasopharyngeal, esophageal, hepatic, pancreatic, prostatic, and urothelial neoplasms in patients treated with MTX, concomitant incidence of both diseases cannot be ruled out. Evaluation of lymphoprolifera-

tive disorders is very difficult as they occur frequently in the course of RA. There were individual reports on EBV virus-associated lymphoma that followed spontaneous remission after MTX withdrawal [22].

Central Nervous System Adverse Effects

The most common central nervous system (CNS) adverse effects are cephalgia, vertigo, memory deficit, fatigue, sleepiness, shivering, and depression. These may be associated with increased adenosine in the cerebrospinal fluid. This activity was described during high-dose MTX therapy, and adenosine normalization was achieved when aminiphiline, an adenosine receptor antagonist, was administered. In high-dose MTX therapy (> 1 g/m^2), neurotoxicity occurs in ca. 15% of patients and it manifests as encephalopathy that resembles cerebral stroke and hemiparesis or chronic leukoencephalopathy. In low-dose MTX therapy, CNS adverse effect occurrence was 1–30% according to different authors [23]. It is difficult to prove that MTX is responsible for the unspecific and frequent adverse effects, e.g. cephalgia, fatigue, depression, and memory deficit. These disorders occur in the healthy population and are more common in RA patients. The best way to confirm MTX's role is withdrawal and retreatment.

Adverse Effects on Bone Tissue

The influence of MTX on bones is ambiguous. In pediatric cancer patients treated with high doses of MTX, osteopathy, i.e. pain, osteoporosis, and fractures, was observed. It also occurs in RA patients treated with low doses of MTX. Osteopenia and osteporosis are identified mainly in cortical bone and fractures of tibial, fibular, and metatarsal bone. Fractures are sudden and associated with severe pain. Sometimes they remain undiagnosed as they are thought to be due to inflammatory changes in talocrural joints. The real role of MTX in RA patients is difficult to establish as it involves many osteoporosis risk factors, e.g. immobilization, inflammation, and other drugs (glucocorticosteroids).

In vitro studies showed that MTX inhibited osteoblast proliferation but not their differentiation. Rat model research showed that MTX negatively affected bone development by inhibiting osteoblast activity and stimulating osteoclasts [24]. If MTX has a positive effect on the inflammatory process and the glucocorticosteroid dose is lowered or withdrawn, these activities overcome the possible negative MTX influence on bones. In most studies a negative effect on bone density was not observed in RA patients during MTX therapy [24].

Postdosing Reactions

One to ten percent of patients suffer from postdosing reactions, i.e. reactions that are seen within 24 h of drug dosing [25]. These include arthalgia, myalgia, stiffness, fatigue, and depression. They occur longer than 24 h and arise frequently when the MTX dose is higher. Relief in these symptoms can be achieved by dose reduction, or dividing the dose into two parts taken every 12 h. Fifty percent of patients suffer from such severe symptoms that MTX must be withdrawn.

MTX-induced Nodulosis

MTX-induced nodules develop or enlarge during MTX therapy. They occur in 8–11% of patients, especially involving the hands and feet, but also the auricle and even the penis. They frequently decrease in size when MTX is withdrawn and relapse in retreatment. They are not a contraindication to the therapy. They resemble rheumatoid nodules in histopathological image. Their etiology has not yet been established. A possible explanation is an MTX-associated elevated adenosine concentration that causes multi-nucleated giant cell production. The nodules occur after a few months or years of MTX therapy, even in patients in remission. In some patients they coexist with cutaneous vasculitis. Especially predisposed are patients positive for HLA-DRB1*0401, a genetic risk factor associated with accelerated rheumatoid nodulosis. There is currently no effective therapy. Colchicine (which inhibits multinucleated giant cell production *in vitro*), hydroxychlorochine, and locally applied glucocorticosteroids are used to treat the disease. The treatment is effective in not every case [26, 27].

Folic and Folinic Acid Supplementation

MTX is a folate antagonist, and it decreases the intracellular folate concentration in hepatocytes and lymphocytes. This suggested folinic or folic acid supplementation to reduce MTX-associated adverse effects. Unless MTX intoxication is

acute, folic acid should be administered at least four hours after the MTX dose, in order to avoid the reduction of therapeutic MTX activity. Cumulative weekly folic acid should be as low as possible. It has been shown that the therapeutic effects of MTX were limited when folinic acid was administered in a 45-mg dose weekly or a 15-mg dose two hours after the MTX dose [28]. The best results were achieved in gastroenterological adverse effects and eliminating stomatitis. Folic acid supplementation is effective in hyperhomocysteinemia prevention. Some rheumatologists suggest lowering the MTX dose instead of introducing folic acid supplementation [28]. Considering the potential benefit associated with folic acid supplementation, at present it is indicated to administer a 5- to 10-mg dose of folic acid 24–48 hours after the MTX dose. If adverse effects emerge, the dose may be increased.

Risk Factors Associated with MTX Adverse Effects

Many authors have tried to find risk factors for possible adverse effects. Adverse effects are noted statistically significantly more frequently in MTX patients in active disease process and older than 50 years of age. This may be associated with the high incidence of impaired renal function in that group, which implies worse toxicity of the drug.

Research had been carried out on finding markers enabling to test whether MTX administration would be effective in a patient and with a low probability of adverse effects. An interesting direction of study is investigating the role of genetic predisposition. One of MTX's mechanisms is the inhibition of folate metabolism by blocking methylenetetrahydrofolate reductase (MTHFR). MTHFR catalyses the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is the methyl donor for the conversion of homocysteine to methionine. A few MTHFR polymorphisms have been described [29]. A known polymorphisms of MTHFR is the C677T MTHFR polymorphism that results in an alanine to valine substitution. MTHFR activity is decreased (in 677TT homozygote subjects by 70%) [30]. This may lead to hyperhomocysteinemia. If MTHFR polymorphism's role in inducing hyperhomocysteinemia would be proved, these patients should be supplemented with higher doses of folic acid and should be monitored more frequently during RA treatment. Haagsma et al. showed higher homocysteine concentrations in C677T heterozygote subjects than in 677CC patients, but other authors did not confirm this [31, 32].

The relationship between the 677TT polymorphism and the toxicity and efficacy of treatment with MTX was proved in cancer patients. The relationship in RA patients treated with MTX described in a few new papers was not unequivocal: two studies showed that it was associated with an increase in the number of adverse effects, and one that it had no influence on adverse effects. An increased incidence of neutropenia in RA patients treated with MTX who had the 677TT polymorphism was demonstrated, and Ede et al. showed intensified hepatotoxicity [33]. Another studied polymorphism is A1298C. Ten percent of patients showed homozygous mutation and revealed a 40% decrease in enzyme activity. In a study by Herrlinger et al. on inflammatory bowel disease patients treated with MTX, patients homozygous for the MTHFR 1298C allele were more likely to experience more side effects than patients with the wild-type 1298AA genotype [34]. Berkun et al. showed that the 1298CC polymorphism was associated with a reduction in MTX-related adverse effects in methotrexate-treated rheumatoid patients [32]. If the significance of the gene polymorphisms were confirmed, then patients with a certain polymorphism would need more frequent monitoring efficacy and safety of the therapy in the rheumatological practice.

Discussion

Although MTX therapy involves possible side effects, the results of trials assessing MTX influence the survival of RA patients. Many years of follow-up of a cohort of RA patients showed that mortality was lower in patients treated with MTX due to reductions in cardiovascular mortality and disease activity [35–37]. Methods for eliminating possible side effects include: using effective contraceptive methods, advising all patients against alcohol consumption, prescribing initially a limited amount of methotrexate tablets in order to prevent medication errors, administering MTX subcutaneusly, administering folic acid in a dose of 5–10 mg no sooner than 24–48 h after the MTX dose, and controlling AspAT, AlAT, blood tests, creatinine, and albumin concentration every four weeks at first, and later every four to eight weeks.

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Conflict of interest: None declared

Received: 13.04.2006
Revised: 19.09 2006
Accepted: 8.03.2007