Review paper

Place of methotrexate in the treatment of psoriasis in the era of biologic agents

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Abstract

Methotrexate (MTX) belongs to a group of drugs known as antimetabolites and is a structural analog of folic acid. It was used for the first time for the treatment of psoriasis over 50 years ago. Nowadays it is used in every type of moderate-to-severe psoriasis, including psoriatic arthritis, and is considered as the most effective disease modifying drug (DMARD). In this paper we review the current state of knowledge as regards mechanisms of action, effectiveness and toxicity of MTX in psoriatic patients as well as we present ways of its administration.

Key words: psoriasis, methotrexate, cyclosporine, biologic therapy.

Introduction

Methotrexate (MTX), from the chemical point of view, is a 4-deoxy amino N-methylpteroyl glutamate or 4 amino-N10-methylfolic acid and is an aminopterin derivate and belongs to an antimetabolite group of drugs. It is a structural analog of folic acid (Figure 1) [1, 2]. Methotrexate was introduced in the treatment of psoriasis in 1958 [2, 3]. The Official Food and Drug Administration (FDA) approval as an anti-psoriatic drug was acquired in 1972. It is interesting to note that this approval was not preceded by any double-blind, randomized, placebo controlled trials [4]. Nowadays MTX is widely used in the treatment of all clinical types of moderate-to-severe psoriasis, including psoriatic arthritis [4-7]. In this paper we present the current state of knowledge considering mechanisms of action, effectiveness and toxicity of MTX in psoriatic patients as well as ways of its administration.

Mechanism of action

Folic acid and its derivatives play a role of the coenzyme in the pyrimidine and purine bases synthesis process. The reduction of dihydrofolate into tetrahydrofolate is a necessary step of this synthesis and is catalyzed by dihydrofolate reductase [1, 8]. The latter binds MTX 10 000 times stronger than dihydrofolate [1]. This leads to the blockade of pyrimidine synthesis and additionally, the accumulation of dihydrofolate inhibits thymidylate synthase which is involved in pyrimidine as well as purine synthesis [1, 2, 9]. Polyglutamate derivative of MTX also blocks the action of other enzymes taking part in the synthesis of purines and pyrimidines, e.g. ribonucleotide 5-aminoimidazole carboxamide transformylase [1, 9]. This leads to the blockade of nucleotide synthesis and cell growth inhibition. Finally, this process results in cell death, which occurs in the S phase of a cell cycle [1].

The MTX mechanism of action in psoriasis includes several different aspects. Firstly, direct inhibition of DNA synthesis decreases epidermal hyperplasia. Moreover, the apoptosis of activated T cells and inhibition of neutrophil chemotaxis occurs [1, 10]. Animal models of various diseases showed that MTX restores balance in the cytokine network. It is supposed to decrease the synthesis of the following cytokines: tumor necrosis factor α (TNF-α) and interleukin 1 (IL)-1, as well as to stimulate the production of IL-1 receptor antagonist (IL-1Ra) and soluble TNF-α receptor [1, 11–13]. The importance of TNF-α in psoriasis is well proven by multiple studies, which indicate a good treatment response to selective TNF-α inhibitors [5, 7, 8, 14, 15]. Rheumatoid arthritis patients treated with MTX in combination with prednisone therapy revealed nearly 2-fold decrease in serum IL-1 and IL-6 levels [16]. A rat model of allogeneic heart transplant showed that MTX lowers the expression of adhesion molecules, e.g. ICAM-1, whose importance in the pathogenesis of psoriasis is also well known [17, 18].

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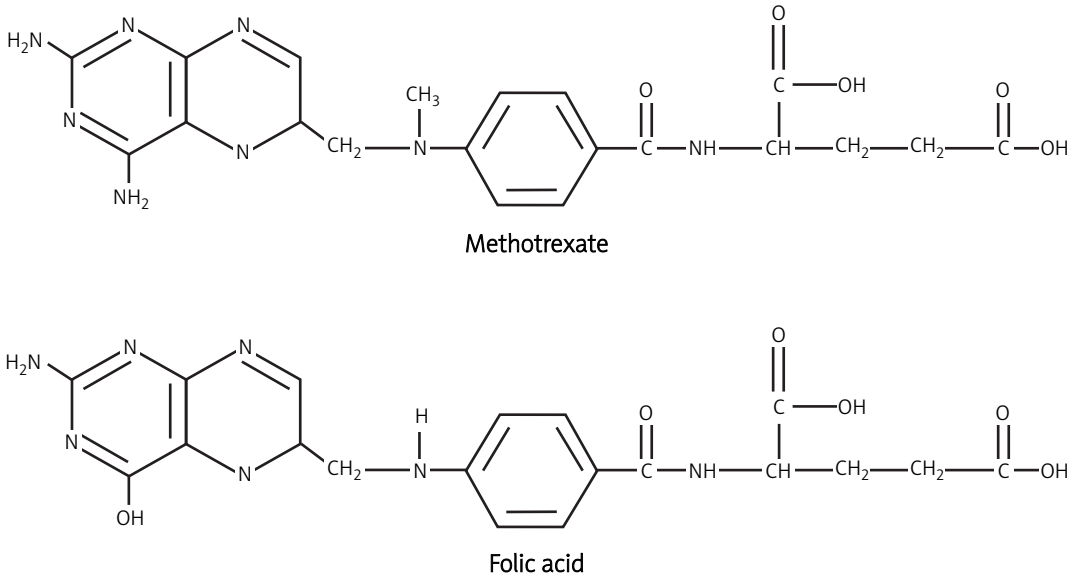

Figure 1. Methotrexate and folic acid

Efficacy

Placebo-controlled trials with MTX in psoriasis are sparse. The only one which includes placebo arm is a study performed by Saurat *et al.* [19]. In this double-blind study the researchers compared the efficacy of adalimumab and MTX in psoriatic patients. After 16-week therapy, the Psoriasis Area and Severity Index (PASI) 75 (indicating the 75% reduction in PASI score compared to starting values) was achieved by 19%, 36% and 80% of the patients treated with placebo, MTX and adalimumab, respectively. However, the dosing scheme of MTX in this trial can be questioned. During the first 2 weeks patients in the MTX group received 7.5 mg per week, during next 2 weeks – 10 mg per week, then 15 mg MTX per week for the next 4 weeks. The doses were further modified during next 8 weeks (slowly increasing the dose) if PASI 50 was not achieved. After 16 weeks of trial, all patients switched to adalimumab, irrespectively of continuously increasing MTX efficacy [19]. The construction of this study along with relatively low doses of MTX, favored underestimation of MTX efficacy. This may be a reason why Leon *et al*., contrary to the above-mentioned results, suggested that patients treated with MTX more frequently achieved PASI 75 than those treated with adalimumab [7]. In the literature there are also three studies comparing MTX to cyclosporine in the treatment of psoriasis vulgaris. In those studies, the placebo arm was not included. Heydendael *et al.* observed nearly complete remission (PASI 90) in 40% of patients after 12 weeks of MTX administration, and in 33% of patients treated with cyclosporine. PASI 75 was achieved in 60% and 71% of patients treated with MTX and cyclosporine, respectively. Those differences did not reach any statistical significance. Patients received 15 mg of MTX per week and 3 mg of cyclosporine per kilogram of body weight daily. After 4 weeks, patients who achieved less than 25% PASI reduction were allowed to receive higher doses of MTX (up to 22.5 mg per week) and cyclosporine (5 mg/kg/day). This was necessary in 4 of 44 cases treated with MTX and in 6 of 44 cases treated with cyclosporine. The total number of adverse effects in the group treated with MTX was 113 events and 166 events for cyclosporine. Twelve patients treated with MTX were withdrawn from the trial due to elevated liver enzymes. However, it is worth noticing that those patients lacked folic acid supplementation, and after discontinuation of MTX, the liver fully regained its function [20]. A similarly designed study was presented by Sandhu *et al.* In this case, differences reached a statistical significance. After 12 weeks of MTX administration patients showed 98% PASI reduction compared to 86% in the cyclosporine arm. PASI 75 was achieved in 24% of patients in MTX and 58% in the cyclosporine group. Complete remission was seen in 87% and 40% of patients treated with MTX and cyclosporine, respectively. Nevertheless, a weekly dose of MTX was high (20 mg to 30 mg). Cyclosporine dose was 125 mg to 300 mg daily. It is worth emphasizing that there were only 15 participants in each group. All patients achieved PASI 75 after around 5.3 weeks of treatment, irrespectively of the treatment mode [21]. Contrary to the above-mentioned studies, cyclosporine was statistically more effective in the analysis conducted by Flytström *et al.* [22]. Mean reduction of PASI at 12 weeks was 58% and 72% for the group treated with MTX and cyclosporine,

respectively. Nearly complete (PASI 90) remission was achieved in 11% and 29% of patients, respectively, but the difference was not statistically significant. The MTX was dosed between 7.5 mg and 15 mg per week and cyclosporine from 3 mg/kg/day to 5 mg/kg/day. Adverse effects were more common in the cyclosporine arm [22]. Irrespectively of the above-listed results, diversity in the dosage of presented drugs may give rise to a controversy considering a comparative study of two substances with a different mode of action.

In a vast meta-analysis of the efficacy of drugs used in the treatment of psoriasis, MTX (15 mg to 22.5 mg daily) proved to be more effective than cyclosporine (3 mg/kg/day), efalizumab and alefacept. In turn, the highest efficacy was observed for infliximab, adalimumab and etanercept [14]. On the other hand, according to the study by Leon *et al*., patients treated with MTX more frequently achieved PASI 75 than those treated with adalimumab, etanercept, etretinate, efalizumab, alefacept, acitretin and narrow band UVB. Stronger effects were seen with PUVA, infliximab, cyclosporine [7].

The MTX is one of the most frequently chosen drugs in the combination therapy of psoriasis. The combination of cyclosporine and MTX was reported [4]. Narrow band UVB (nbUVB) in combination with MTX has proven to be very effective. PASI 90 was achieved by 10 out of 11 patients treated with nbUVB and MTX, compared to 5 out of 13 treated solely with nbUVB. Recovery was observed faster than in the monotherapy arm. This resulted also in decreasing the cumulative dose of UVB. The incidences of adverse effects did not differ between both groups [23]. Caution should be taken as regards potential carcinogenicity of that treatment [24]. The MTX may also be combined with low doses of acitretin [25, 26]. In that situation, the cumulative hepatotoxic effects should be taken into consideration [4]. The MTX is also the most often agent which is chosen to be combined with all biologic drugs. It is accepted to use MTX along with all TNF-α inhibitors and alefacept in every type of moderate-to-severe psoriasis, including psoriatic arthritis [4, 8]. Psoriasis as well as rheumatoid arthritis showed increased efficacy of the combination therapy (etanercept and MTX, infliximab and MTX) in comparison to monotherapy [8, 27, 28]. It was proven that introduction of MTX during infliximab therapy alleviates the risk of monoclonal antibody development [4, 28]. What is more, the patient with psoriasis treated with infliximab and MTX in whom discontinuation of MTX led to worsening of the dermatological state was described. Authors suggest that it could be connected with the production of antibodies against infliximab [29]. Two other psoriatic patients treated with alefacept and MTX in whom discontinuation of MTX caused relapse were reported. Readministration of MTX allowed to obtain improvement [8]. Interestingly, some of the studies verifying the efficacy of biological therapy allowed leaving the patients on MTX during the whole study period [8].

Safety and toxicity

Frequency of adverse effects in psoriatic patients treated with MTX could reach even 78% of cases, but usually they are of mild to moderate severity and tend to fade with reduction of dose or cessation of treatment [4, 6, 15, 22]. Usually, side effects occur during the first 6 months of treatment. Fast proliferating cells are most susceptible to MTX. Therefore, the most sensitive tissues are gastrointestinal mucosa and bone marrow cells [1]. Most commonly reported side effects are nausea and emesis which are present in 20-43% of patients and occur during the first 1-8 h after administration of the drug. They diminish after a few hours or days [1, 2, 20-22]. Sometimes diarrhea is also observed [1]. Ulcers leading to perforation were also reported [1, 7].

Another quite common adverse effect is an elevated level of transaminases [20, 22]. Nevertheless, liver fibrosis or cirrhosis due to MTX are supposed to occur less often and are less aggressive than initially expected. On the other hand, those side effects can be 3-4 times more frequent in a group of patients with psoriasis vulgaris and psoriatic arthritis compared to patients with rheumatoid arthritis [30]. This is probably due to the higher incidence of comorbid diabetes mellitus, obesity, hyperlipidemia or alcoholism [4, 6, 31]. Other risk factors include abnormal liver function tests before the introduction of MTX, hepatitis (even in remission), presence of liver diseases in the family, advanced age of the patient, use of other hepatotoxic drugs [4, 6]. It is suggested that MTX rather worsens than provokes liver injury [4, 6]. It should be emphasized that the course of the above-mentioned side effect is usually mild [6]. Patients may also report malaise and fatigue or hair loss [4, 7, 22, 32].

Occasionally, hematological abnormalities like leukopenia, anemia or thrombocytopenia are observed. The risk of developing such abnormalities is higher in patients with (1) renal impairment, (2) advanced age, (3) hypoalbuminemia, (4) alcohol abuse, and (5) medication errors. Leukopenia and thrombocytopenia are usually seen 7-10 days after the first dose of the drug, but they may occur at any time during the therapy, especially after the dose is increased. Anemia develops slower and may be associated with a progressive increase in mean corpuscular volume (MCV). Myelosuppression is considered as the most serious effect, but is not commonly reported [4]. Lung fibrosis due to MTX is less common in psoriatic patients than in those with rheumatoid arthritis. This effect is so rare that thorax X-ray is ordered only after the first clinical signs occur [4].

Adverse effects with large doses of MTX include also kidney failure and central nervous system abnormalities: impairment of consciousness, speech, paralysis, epilepsies. However, they are usually reversible [1]. It is also suggested that MTX increases the risk of malignancy like lymphoma, melanoma or lung cancer, but it should be

stressed that most of the data come from rheumatoid arthritis patients [4, 7].

On the other hand, MTX limits the cardiovascular disease and what is more it decreases the number of deaths due to vascular or cardiologic events amongst psoriatic and psoriatic arthritis patients. This action is supposed to be additionally enforced by folic acid supplementation [33-36].

Supplementation of folic acid should limit nausea, mucosal ulcerations, and decreases homocysteine levels [2]. Reduction of hematologic and hepatotoxic adverse events is also seen [4]. There is no one scheme for folic acid supplementation. Usually, single or multiple doses of 5-15 mg per week, minimum 12 h after the last MTX intake is recommended [2, 4]. Some authors suggest that supplementation with folic acid may reduce effectiveness of MTX, but this is not widely accepted [4, 22, 37, 38].

Overdosage of MTX should be treated with leucovorin (folinic acid) to avoid enzymatic blockade. It is the only antidote for hematologic side effects, which increases the tetrafolate level in cell. Right after diagnosing overdose, 20 mg of leucovorin orally or intravenously (repeated every 6 h) is recommended [1, 4].

Finally, the number of side effects is limited by proper prescreening of the candidates to treatment. Absolute contraindications for MTX include pregnancy, breast feeding, significant hematological abnormalities like anemia, thrombocytopenia and leukopenia [4]. Patients should be informed about mandatory contraception during therapy and shortly afterwards. Women should avoid conception minimum during one ovulatory cycle after MTX withdrawal. The MTX may, but does not have to, lead to miscarriage and many abnormalities of the skeletal system, heart, and central nervous system [4, 39]. Men should wait 3 months prior to conception, which is due to the length of spermatogenesis [4]. It should be mentioned that no higher incidences of abnormalities were observed in children of fathers treated with MTX at the time of conception [40-42]. The drug leaflet advises that contraception for minimum 6 months after the therapy both for women and men should be recommended [43].

The purposefulness of MTX therapy should be taken into consideration when (1) the renal function is impaired (as 85% of the drug is excreted through kidneys), (2) significant hepatic abnormalities or cirrhosis occur, (3) hepatitis (active or during remission), (4) liver steatosis is diagnosed. There is a controversy over alcohol consumption. Some experts allow 2 drinks a day, without specifying the dose of alcohol. Post-alcohol hepatic damage is a relative contraindication for the use of MTX. Also concomitant use of other hepatotoxic drugs e.g. statins requires more frequent monitoring of the liver function [4]. The use of MTX in patients with active chronic infection like HIV or tuberculosis should be reconsidered. Acute infections may require a temporary cessation of the drug [4, 22]. Drug tolerance can by worsened by the advanced age of the patient, comorbid conditions (diabetes mellitus, obesity), previous non-steroidal anti-inflammatory drugs (NSAIDs), treatment with cytostatics and stress [1, 4]. Administration of the drug should be avoided in patients who underwent vaccination with live vaccine [4]. The aggravation of adverse effects may occur during simultaneous trimethoprim administration, which is a folic acid antagonist and is usually formulated with sulphometoxasole which reduces kidney elimination of MTX [4]. Some NSAIDs (e.g. ibuprofen, naproxen) and antibiotics (e.g. penicillin, ciprofloxacin) also increase levels of MTX in the serum by preventing its elimination [4]. In contrast to the latter, cephalosporins increase MTX clearance [44].

Considering the above-listed contraindications, before the administration of MTX therapy, the following steps should be taken: (1) blood morphology, (2) kidney function assessment (serum creatinine and urea level, glomerular filtration rate – GFR), (3) liver function evaluation (aminotransferases, alkaline phosphatase, bilirubin and albumin levels), with exclusion of viral hepatitis, (4) optionally a pregnancy test, HIV antibodies, tuberculin test should be conducted depending on the doctor's opinion [4]. Some patients with severe hepatic damage should undergo a liver biopsy [4].

Seven-fourteen days after MTX treatment initiation, total blood cell and platelet count should be ordered and then it should be repeated every 2-4 weeks for the first few months, and eventually every 1-3 months later. A significant decrease in the number of white blood cells or platelets may suggest the necessity of dose modification or even temporary drug discontinuation [4]. Control laboratory tests evaluating the kidney and liver function should be ordered every 1-3 months. The frequency of the above-mentioned tests is of course related to their results. It is noteworthy that liver function tests should be obtained minimum 5 days after the last dose of MTX. Otherwise, elevated transaminase levels might be observed. If the elevation of transaminase levels is higher than 2 and lower than 3 times normal levels, reduction of the dose is indicated. When significant biochemical abnormalities occur, discontinuation of the drug for 1-2 weeks may be necessary. If the abnormalities sustain longer than 2-3 months or when aminotransferase levels are elevated in 5 of 9 tests during 12 months, a liver biopsy should be performed. A low albumin level in a patient with proper nutrition, in the case of a well-controlled disease, a liver biopsy is also indicated. According to the new guidelines in patients without signs of liver damage and lacking the risk factors, the first liver biopsy should be planned after 3.5 g to 4.0 g of a total cumulative dose of MTX is taken. In patients with a higher risk of liver damage, the total cumulative dose indicating liver biopsy is 1.0-1.5 g and should be repeated after every addition of 1.0 g to 1.5 g [4]. Other experts advise to perform a liver biopsy 2 years after therapy initiation and repeat it after every 2 years [8]. Liver biopsy results suggesting liver damage of

grade I or II of the Roenigk scale should not influence the treatment. If the biopsy result is grade IIIa, a repeated biopsy should be ordered after 6 months of therapy, or cessation of MTX therapy should be considered. Grade IIIb or IV disqualify the patient from further MTX therapy [4]. Although to evaluate the liver fibrosis, the serum level of the aminoterminal peptide of type III procollagen was suggested, this test gives rise to many controversies and liver biopsy remains the gold standard in the assessment of the above-mentioned side effect [6]. Women in the reproductive age should undergo regular pregnancy tests [4].

Dose schedules

Current protocols of MTX treatment include (1) single weekly oral dose, (2) oral dose in 2 or 3 portions at 12 intervals [2]. The latter scheme was proposed by Weinstein and Forst in 1971. This administration is supposed to diminish gastrointestinal tract disturbances [45]. In the treatment of rheumatoid arthritis, subcutaneous or intramuscular MTX injections have been lately introduced. This administration allows for faster achievement of the maximum serum level as compared to oral administration and increases bioavailability of the drug [2, 46-48]. A decrease of gastrointestinal tract side effects was also observed. Moreover, the change of route of drug administration resulted in better therapeutic effects in this group of patients and allowed for the reduction of glucocorticosteroid doses [2, 49, 50]. Bingham *et al.* [51] suggested that before introduction of biological drugs in rheumatoid arthritis patients, parenteral MTX should be administered. Mild injection site reactions were observed.

Many experts advise starting the therapy with low doses (test dose) of MTX – 5 mg per week to lower the risk of severe adverse effects (mainly from bone marrow and kidneys), especially in patients with a higher risk of such events. Other authors recommend 15 mg of MTX at the beginning of treatment. There are no studies which would definitely disclose this problem. The doses recommended in psoriasis therapy are usually between 7.5 mg and 22.5 mg per week [4]. The MTX is administered usually as 2.5 and 10 mg pills. Recently, pre-filled syringes containing 50 mg per ml of MTX have been introduced to the market. Pre-filled syringes contain various doses and allow to administrate the following doses 7.5, 10, 15, 20, 25 with one shot. The 30 mg syringes are under registration. Patients may perform the injection themselves. It can take 4 to 8 weeks to achieve full therapeutic effects [2, 4].

Fifty years of psoriasis treatment experience with MTX did not derogate the importance of this drug, regardless from the fact that the market is flooded with new substances like cyclosporine or biological agents. The MTX is still one of the more frequently used drugs in the treatment of psoriatic arthritis and is a significant drug in all guidelines of psoriasis treatment [52-54]. Its co-administration with biological drugs is often desired. The Polish National Health Fund requires an inadequate response or intolerance to MTX (in doses as high as 25 mg per week) before biological treatment could be recommended [55]. The more we know, the better we deal with the adverse effects of its use, i.e. by folic acid supplementation or by modifying the way of drug administration. It turns out that the first reports often overestimated the MTX role as regards serious liver damage [4, 6]. It is also worth adding that MTX significantly improves the quality of life of psoriatic patients [20, 22, 23]. To sum up, if all recommendations (prescreening, laboratory and pregnancy tests, adequate doses, optimal route of administration and folic acid supplementation) are fulfilled, MTX seems to be a safe, effective and relatively cheap treatment option in all forms of moderate-to-severe psoriasis, including psoriasis arthritis.

References

1. Zimecki M, Artym J. Działanie metotreksatu na odpowiedź immunologiczną w wybranych modelach doświadczalnych. Postępy Hig Med Dosw 2004; 58: 226-35.
2. Świerkot J. Podskórne iniekcje metotreksatu w leczeniu reumatoidalnego zapalenia stawów. Reumatologia 2007; 45: 407-14.
3. Edmundson WF, Guy WB. Treatment of psoriasis with folic acid antagonists. Arch Dermatol 1958; 78: 200-3.
4. Kalb RE, Strober B, Weinstein G, Lebwohl M. Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. J Am Acad Dermatol 2009; 60: 824-37.
5. Ritchlin CT, Kavanaugh A, Gladman DD, et al. Treatment recommendations for psoriasis arthritis. Ann Rheum Dis 2009; 68: 1387-94.
6. Lindsay K, Fraser AD, Layton A, et al. Liver fibrosis in patients with psoriasis and psoriatic arthritis on long-term, high cumulative dose methotrexate therapy. Rheumatology 2009; 48: 569-72.
7. Leon A, Nguyen A, Letsinger J, Koo J. An attempt to formulate an evidence-based strategy in the management of moderate-to-severe psoriasis: a review of the efficacy and safety of biologics and prebiologic options. Expert Opin Pharmacother 2007; 8: 617-32.
8. Cather JC, Menter A. Combining traditional agents and biologics for the treatment of psoriasis. Semin Cutan Med Surg 2005; 24: 37-45.
9. Potemski P, Płużańska A. MTA (LY 231514) – nowy antagonista kwasu foliowego. Onkol Pol 1999; 2: 163-7.
10. Strauss G, Osen W, Debatin KM. Induction of apoptosis and modulation of activation and effector function in T cells by immunosuppressive drugs. Clin Exp Immunol 2002; 128: 255-66.
11. Dayan M, Segal R, Mozes E. Cytokine manipulation by methotrexate treatment in murine experimental systemic lupus erythematosus. J Rheumatol 1997; 24: 1075-82.
12. Neurath MF, Hildner K, Becker C, et al. Methotrexate specifically modulates cytokine production by T cells and macrophages in murine collagen-induced arthritis (CIA); a mechanism for methotrexate-mediated immunosuppression. Clin Exp Immunol 1999; 115: 42-55.

13. Seitz M, Zwicker M, Loetscher P. Effects of methotrexate on differentiation of monocytes and production of cytokine inhibitors by monocytes. Arthritis Rheum 1998; 41: 2032-8.
14. Bansback N, Sizto S, Sun H, et al. Efficacy of systemic treatments for moderate to severe plaque psoriasis: systemic review and meta-analysis. Dermatology 2009; 219: 209-18.
15. Schmitt J, Zhang Z, Wozel G, et al. Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. Br J Dermatol 2008; 159: 513-26.
16. Nowak D, Lewandowicz J, Dbkowska B, Marczak J. Combination of methotrexate and prednisone decreases circulating concentrations of interleukin 1 beta and interleukin 6 in patients with rheumatoid arthritis. Poor correlation of cytokine suppression with clinical improvement. Int J Immunopathol Pharmacol 1999; 12: 13-21.
17. Ciesielski CJ, Pflug JJ, Mei J, Piccinini LA. Methotrexate regulates ICAM-1 expression in recipients of rat cardiac allograft. Transpl Immunol 1998; 6: 111-21.
18. Gangemi S, Merendino RA, Guarneni F, et al. Serum levels of interleukin-18 and s-ICAM-1 in patients affected by psoriasis: preliminary considerations. J Eur Acad Dermatol Venereol 2003; 17: 42-6.
19. Saurat JH, Stingl G, Dubertret L, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br J Dermatol 2008; 158: 558-66.
20. Heydendael VMR, Spuls PI, Opmeer BC, et al. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. N Engl J Med 2003; 349: 658-65.
21. Sandhu K, Kaur I, Kumar B, Saraswat A. Efficacy and safety of cyclosporine versus methotrexate in severe psoriasis: a study from North India. J Dermatol 2003; 30: 458-63.
22. Flytström I, Stenberg B, Svensson Å, Bergbrant IM. Methotrexate vs. ciclosporin in psoriasis: effectiveness, quality of life and safety. A randomized controlled trial. Br J Dermatol 2008; 158: 116-21.
23. Asawanonda P, Nateetongrungsak Y. Methotrexate plus narrowband UVB phototherapy versus narrowband UVB phototherapy alone in the treatment of plaque-type psoriasis: a randomized, placebo-controlled study. J Am Acad Dermatol 2006; 54: 1013-8.
24. MacKie RM, Fitzsimons MB. Risk of carcinogenicity in patients with psoriasis treated with methotrexate or PUVA singly or in combination. J Am Acad Dermatol 1983; 9: 467-9.
25. Lowenthal KE, Horn PJ, Kalb RE. Concurrent use of methotrexate and acitretin revisited. J Dermatol Treat 2008; 19: 22-6.
26. Pastuszka M, Kaszuba A. Acitretin, a systemic retinoid for the treatment of psoriasis – current state of knowledge. Postep Derm Alergol 2011; 28: 285-92.
27. Klareskog L, van der Heijde D, de Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis; double-blind randomized controlled trial. Lancet 2004; 363: 675-81.
28. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusion of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998; 41: 1552-63.
29. Strober BE. Successful treatment of psoriasis and psoriatic arthritis with etanercept and methotrexate in patient newly unresponsive to infliximab. Arch Dermatol 2004; 140: 366.
30. Whiting-O'Keefe QE, Fye KH, Sack KD. Methotrexate and histologic hepatic abnormalities: a meta-analysis. Am J Med 1991; 90: 711-6.
31. Yang CP, Kuo MC, Guh JY, Chen HC. Pancytopenia after low dose methotrexate therapy in a hemodialysis patient: case report and review of literature. Renal Failure 2006; 28: 95-7.
32. Stankiewicz-Habrat P, Brzeźińska-Wcisło L. Changes in the dynamics of hair growth in rats after application of methotrexate, metoprolol and naproxen. Postep Derm Alergol 2010; 27: 11-7.
33. van Halm VP, Nurmohamed MT, Twisk JW, et al. Disease-modyfying antirheumatic drugs are associated with a reduced risk for cardiovascular disease in patients with rheumatoid arthritis: a case control study. Arthritis Res Ther 2006; 8: R151.
34. Prodanovich S, Ma F, Taylor JR, et al. Methotrexate reduces incidence of vascular disease in veterans with psoriasis or rheumatoid arthritis. J Am Acad Dermatol 2005; 52: 262-7.
35. Choi HK, Hernán MA, Seeger JD, et al. Methotrexate and mortality in patients with rheumatoid arthritis; a prospective study. Lancet 2002; 359: 1173-7.
36. Gladman DD, Ang M, Su L, et al. Cardiovascular morbidity in psoriatic arthritis. Ann Rheum Dis 2009; 68: 1131-5.
37. Salim A, Tan E, Ilchyshyn A, Berth-Jones J. Folic acid supplementation during treatment of psoriasis with methotrexate: a randomized, double-blind, placebo-controlled trial. Br J Dermatol 2006; 154: 1169-74.
38. Brownell I, Strober BE. Folate with methotrexate: big benefit, questionable cost. Br J Dermatol 2007; 157: 213.
39. Lloyd ME, Carr M, McElhatton P, et al. The effect of methotrexate on pregnancy, fertility and lactation. QJM 1999; 92: 551-63.
40. French AE, Koren G. Effect of methotrexate on male fertility. Can Family Phys 2003; 49: 577-8.
41. El-Beheiry A, El-Mansy E, Kamel N, Salama N. Methotrexate and fertility in men. Arch Androl 1979; 3: 177-9.
42. Hirsh A. Male subfertility. BMJ 2003; 327: 669-72.
43. Metex package leaflet.
44. Iven H, Brash H. Cephalosporins increase the renal clearance of methotrexate and 7-hydroxymathotrexate in rabbits. Cancer Chemother Pharmacol 1990; 26: 139-43.
45. Weinstein G, Frost P. Mathotrexate for psoriasis. A new therapeutic schedule. Arch Dermatol 1971; 103: 33-8.
46. Jundt JW, Browne BA, Fiocco GP, et al. A comparison of low dose methotrexate bioavailibility: oral solution, ora tablet, subcutaneous and intramuscular dosing. J Rheumatol 1993; 20: 1845-9.
47. Kabisch S, Weigand T, Plischke H, Menninger H. Bioavailability of methotrexate (MTX) following different routes of application. Akt Rheumatol 2004; 29: 197-200.
48. Hoekstra M, Haagsma C, Neef C, et al. Bioavailability of higher dose mathotrexate comparing oral and subcutaneous administration in patients with rheumatoid arthritis. J Rheumatol 2004; 31: 645-8.
49. Braun J, Kästner P, Flaxenberg P, et al. Comparison of the clinical afficacy and safety of subcutaneous versus oral administration of methotrexate in patients with rheumatoid arthritis. Arthritis Rheum 2008; 58: 73-81.
50. Alsufyani K, Ortiz-Alvarez O, Carbal DA, et al. The role of subcutaneous administration of methotrexate in children with juvenile idiopatic arthritis who failed oral methotrexate. J Rheumatol 2004; 31: 179-82.
51. Bingham SJ, Buch MH, Lindsay S, et al. Parenteral methotrexate should be given before biological therapy. Rheumatology 2003; 42: 1009-10.

52. Papp K, Gulliver W, Lynde C, et al. Canadian guidelines for the management of plaque psoriasis: overview. J Cutan Med Surg 2011; 15: 210-9.
53. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. J Am Acad Dermatol 2011; 65: 137-74.
54. Mease PJ. Psoriatic arthritis – update on pathophysiology, assessment, and management. Bull NYU Hosp Jt Dis 2010; 68: 191-8.
55. Ministerial ordinance of Polish Ministry of Health Care 17th August 2011.