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

Aleksandra Dańczak-Pazdrowska

Department of Dermatology, Poznan University of Medical Sciences, Poland
Head: Prof. Wojciech Silny MD, PhD

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].

Address for correspondence: Aleksandra Dańczak-Pazdrowska MD, PhD, Department of Dermatology, Poznan University of Medical Sciences, 49 Przybyszewskiego, 60-355 Poznan, Poland, e-mail: aleksandra.pazdrowska@onet.eu
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. 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]. Irrespective 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. Re-administration 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 (folic 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
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


35. Salim A, Tan E, Ilichyshyn A, Berth-Jones J, Folic acid supplement-


