

The possibilities and principles of methotrexate treatment of psoriasis – the updated knowledge

Magdalena Czarnecka-Operacz^{1,2}, Anna Sadowska-Przytocka¹

¹Department of Dermatology, Poznan University of Medical Sciences, Poznan, Poland

Head of the Department: Prof. Zygmunt Adamski MD, PhD

²Laboratory of Allergic Skin Diseases, Poznan University of Medical Sciences, Poznan, Poland

Head of the Laboratory: Prof. Magdalena Czarnecka-Operacz

Postep Derm Alergol 2014; XXXI, 6: 392–400

DOI: 10.5114/pdia.2014.47121

Abstract

Psoriasis is a chronic multifactorial disease affecting 2–4% of the general population. Due to its nature, psoriasis has a negative impact on the quality of life of patients. Therefore, the choice of an appropriate and individually tailored treatment controlling the symptoms of the disorder is necessary and continues to be a challenge for dermatologists. Therapeutic modalities in psoriasis should on the one hand be effective and on the other hand present a good safety profile. Methotrexate (MTX) is one of treatment options for psoriasis and can be administered both as monotherapy or in combination schemes. The paper presents the current state of knowledge about the possible treatment of psoriatic patients with MTX according to contemporary guidelines.

Key words: psoriasis, methotrexate, treatment.

Introduction

Methotrexate (MTX) ($C_{20}H_{22}N_8O_5$) is a derivative of aminopterin, an analogue and antimetabolite of folic acid. The substance inhibits dihydrofolate reductase – an enzyme responsible for the reduction of dihydrofolic acid to tetrahydrofolic acid. Aminopterin was first used in the treatment of psoriasis and rheumatoid arthritis in 1951 [1]. In 1972, MTX was approved for the treatment of psoriasis by the US Food and Drug Administration (FDA). At present, the drug is indicated for the treatment of practically all forms of moderate or severe psoriasis, including psoriatic arthritis [2].

Mechanism of action

Methotrexate has antiinflammatory, antiproliferative and immunosuppressive properties. As mentioned above, the drug has a role in inhibiting dihydrofolate reductase (DHFR) and, therefore, in the activation of folic acid. This leads to the inhibition of the activity of thymidylate synthase which is a necessary component for the synthesis of purines and pyrimidines, and thus for the synthesis of DNA. The interference in that pathway is known to take

place during the S-phase of the cell cycle, which causes the inhibition of growth and cell death (apoptosis) [3]. By inhibiting DNA synthesis, MTX limits epithelial hyperplasia, reinforces the apoptosis of activated T cells, and inhibits the chemotaxis of neutrophils [4]. In addition, the drug is responsible for decreasing the synthesis of a range of proinflammatory cytokines such as tumour necrosis factor α (TNF- α) and interleukin-1 (IL-1).

The exact mechanism of action of MTX in psoriasis vulgaris still remains unclear. Aside from antiproliferative and immunomodulatory actions, other possible pathways require detailed clarification.

For MTX used in the treatment of rheumatoid arthritis, the mechanism of DHFR inhibition described above does not appear to be the primary one. Instead, the mechanism is likely to comprise a number of pathways including inhibition of the activity of enzymes involved in the metabolism of purines (leading to the accumulation of adenosine), suppression of T cell activation, decrease in the expression of intercellular adhesion molecules by T cells, increase in CD95 sensitivity of stimulated T cells, and suppression of the activity of methyltransferase with all the consequences of the process [5].

Address for correspondence: Prof. Magdalena Czarnecka-Operacz MD, PhD, Department of Dermatology, Poznan University of Medical Sciences, 49 Przybyszewskiego St, 60-355 Poznan, Poland, phone: +48 61 869 12 85, e-mail: czarnecka.operacz@gmail.com

Received: 4.11.2014, **Accepted:** 25.11.2014.

Pharmacokinetics

Administered parenterally, MTX is almost completely absorbed. After intramuscular injection, peak concentrations are achieved in 30 to 60 min. At serum concentrations of MTX exceeding 100 µM, the drug undergoes passive intracellular diffusion. Methotrexate in serum is approximately 50% protein bound. Following oral administration and absorption of the drug, it becomes partially inactivated in the gastrointestinal tract and in the liver, which means that its bioavailability is low. The pleural and CSF penetration of MTX is slow, so that the peak concentration is 30 times lower than the serum level. Approx. 90% of MTX is eliminated in unchanged form, and the half-life of the drug in the terminal elimination phase in patients receiving treatment for psoriasis ranges between 3 and 10 h.

The pharmacokinetic characteristics of MTX depend on the route of administration (oral, subcutaneous, intramuscular, intravenous). Following oral administration, the drug is absorbed immediately but not completely (the absorption is ca. 15% lower compared to intramuscular administration), and demonstrates high inter-individual variability and lower bioavailability (as detailed above). After injection, MTX is absorbed immediately and completely, achieving higher blood serum concentrations. It needs to be stressed that there are virtually no differences in the bioavailability of MTX between the subcutaneous and intramuscular routes. Therefore, taking into consideration pain at the intramuscular injection site, there are no arguments in favour of selecting this route.

Accordingly, many researchers, clinicians and patients consider the subcutaneous administration route of MTX to be the optimum one. This factor is extremely important for planning the therapy of patients suffering from severe psoriasis because it substantially determines the outcome of treatment.

Indications for methotrexate therapy

Methotrexate is indicated in the treatment of moderately severe and severe forms of plaque psoriasis, psoriatic erythroderma, palmoplantar pustulosis, generalized pustular psoriasis, nail psoriasis and psoriatic arthritis. The drug is especially indicated in patients who fail to improve after topical therapy, phototherapy or treatment with acitretin, or in cases when these therapies are contraindicated or impossible to administer. Methotrexate is also indicated as an element of combined therapy with other immunosuppressive drugs, primarily in combination with biologics. In such cases, MTX is responsible for inhibiting the formation of antibodies against biologic drugs, thereby increasing their efficacy. The combination therapy of MTX with etanercept has been used in the treatment of psoriasis in children [6].

Methotrexate is also utilized in the therapy of selected autoimmune diseases such as rheumatoid arthritis,

juvenile dermatomyositis, lupus erythematosus, sarcoidosis, Crohn's disease, some types of severe eczema and a wide range of forms of vasculitis [7, 8]. Although MTX was initially developed as a chemotherapeutic agent (and intended to be used in high doses), at low doses it has a generally safe and well-tolerated profile which is vital for the management of the above-mentioned selected autoimmune diseases. Also, thanks to its high clinical efficacy in the treatment of rheumatoid arthritis, the drug is recognized as first-line therapy in the first stage of the disease (either in monotherapy or in combination with conventional synthetic DMARDs – *disease-modifying antirheumatic drugs*). According to the recommendations issued by EULAR (*European League against Rheumatism*, 2013 revision), first-line treatment can additionally include short courses of low-dose glucocorticosteroids. If there is no clinical improvement, typically within 6 months, second-line and then third-line therapy should be introduced (the addition of a biologic drug followed by the substitution of the biologic drug for another, if required).

An assessment of MTX efficacy in the treatment of rheumatoid arthritis during a period of up to 12 months shows that pain relief, improved range of joint motion, decreased joint swelling and reduction in the general activity of the disease process are observed in the majority of cases, both in the opinion of patients and their physicians. Radiological assessment performed during therapy also typically demonstrates a slowing down or decrease in disease progression, and in 30% of cases even its complete suppression [9]. Furthermore, patients with rheumatoid arthritis receiving MTX treatment are at a reduced risk of cardiac infarction and cerebral vascular episodes (cerebral haemorrhage, embolism) [10].

Methotrexate has also found use in the therapy of multiple sclerosis, however it has not yet been approved by the FDA for this indication [11].

Contraindications

Prior to prescribing MTX treatment to a patient, all contraindications must be excluded. Relative and absolute contraindications to using the drug are listed in Table 1.

Methotrexate is a teratogenic drug, which is why it is contraindicated in pregnant and breast-feeding women. The drug is also known to cause severe foetal defects, particularly neural tube defects [12]. Congenital defects arise mainly between weeks 6 and 8 of gestation [13]. Methotrexate also influences the process of spermatogenesis, thus affecting male fertility. As yet, there are no clear guidelines concerning the recommended period of contraception after completing MTX therapy. Partners of male patients taking methotrexate should not become pregnant for at least 3 months after the discontinuation of treatment. In women, one complete ovulation cycle af-

Table 1. Relative and absolute contraindications to methotrexate therapy

Relative contraindications	Absolute contraindications
<ul style="list-style-type: none"> • Kidney failure • Elevated liver enzyme levels • Active or past history of hepatitis • Cirrhosis • Alcohol abuse • Interactions with other drugs • Active infectious disease (especially TB and HIV (human immunodeficiency virus)) • Treatment with immunosuppressive drugs (other than biologics) • Recent history of vaccination with a live vaccine • Gastric ulcers • Obesity (BMI (body mass index) > 30 kg/m²) • Diabetes • Hyperlipidaemia • Hypoalbuminaemia • Folic acid deficiency • Lack of patient compliance • Old age 	<ul style="list-style-type: none"> • Pregnancy and lactation • Marked anaemia, leukopenia, thrombocytopenia • Alcoholism • Active peptic ulcers • Severe respiratory failure • Immunodeficiency

ter the discontinuation of methotrexate is recommended before conception [13].

Adverse reactions

The incidence of adverse reactions associated with MTX treatment of psoriasis is estimated at approx. 78% [14]. Adverse symptoms occur with varying severity, with a marked tendency to subside following dose reduction or discontinuation of treatment. The most common complaints reported by patients include nausea and vomiting. As mentioned in the section describing the pharmacokinetics of MTX, the symptoms are intrinsic to the oral route of drug administration [15–17]. Detailed investigations of differences in the profile of adverse reactions associated with the route of administration of MTX have demonstrated a definite superiority of the subcutaneous form of the drug. Methotrexate treatment with weekly doses of either 7.5 mg and 15 mg has shown a significantly higher incidence of vomiting and loss of appetite ($p < 0.05$) following oral administration. In the group of patients receiving the drug subcutaneously, the symptoms were more frequently observed among patients treated with the 15 mg dose [15]. In contrast to patients taking MTX orally, no patient with long-lasting rheumatoid arthritis who received the drug subcutaneously experienced any vomiting or diarrhoea. In fact, the superiority of the subcutaneous route of MTX administration over its oral route has been demonstrated not only for the profile of adverse reactions but also for the therapeutic effects of the drug, which is discussed in greater detail in the subsequent sections of the review [16, 17].

With respect to laboratory test results, definitely the most common deviations are found in liver tests and morphotic blood elements. Naturally, the risk of developing such abnormalities increases in patients who had

relative contraindications to MTX therapy prior to the start of treatment (Table 1). The most severe complication of MTX therapy is considered to be myelosuppression [18]. Leukopenia and thrombocytopenia can occur at any stage of treatment, however usually between days 7 and 10 of treatment [19].

Regarding organ complications, special attention must be paid to the possibility of pulmonary fibrosis, however a chest radiograph should only be considered after the emergence of clinical symptoms [13]. Another organ which is susceptible to damage during MTX treatment is the liver. According to the revised guidelines, patients without signs of liver damage and without co-existing risk factors should have a biopsy after taking a cumulative dose of 3.5–4 g. Patients at an elevated risk of liver damage should undergo a biopsy at a cumulative dose of 1–1.5 g.

The above contraindications and the potential for developing adverse reactions oblige physicians to perform baseline eligibility assessment. Patients should undergo peripheral blood CBC analysis and assessments of kidney and liver function. Depending on the information obtained while collecting the patient's history, it is also necessary to rule out viral hepatitis and TB. Women of childbearing age are advised to take a pregnancy test. Within 7–14 days after starting treatment, a check-up peripheral blood CBC analysis should be performed. Assessments of kidney and liver function should be conducted every 1–3 months depending on the patients' test results [2].

Folic acid supplementation

There are no clear recommendations regarding the optimum dose of folic acid that should be co-administered with MTX. The primary purpose of supplementa-

tion is to prevent adverse reactions of the hematopoietic system and lessen hepatotoxicity. Folic acid supplementation has also been demonstrated to reduce a range of symptoms including nausea and mucosal ulcerations. The role of folic acid in lowering the risk of pulmonary fibrosis has not been proven, though [20]. The widely recommended dose of folic acid is 15 mg per week, administered a minimum of 12 h (usually 24–48 h) after the last dose of MTX. Another option is to use 5 mg of folic acid daily (except for MTX days). Reports claiming that folic acid reduces the efficacy of MTX have not been fully corroborated [21, 22].

Dosage

Guidelines for the dosing of MTX in psoriatic patients had been modified since 1972. The last modification was in 1972, and the most recent revision – in 2011. The current recommended dose of MTX is 7.5–25 mg/week. The preferred dosage regimen is once weekly in three divided doses at 12 h intervals (so-called Weinstein’s procedure). If the oral route is unavailable, the drug can be administered in a single weekly dose of 2.5–25 mg subcutaneously, intramuscularly or intravenously. Therapy can be initiated at low doses (e.g. 7.5 mg/week) and gradually increased. Alternatively, the maximum dose can be prescribed from the start of treatment. In 2011, Montaudié *et al.* conducted an analysis demonstrating that substantially better therapeutic effects are achieved when treatment begins with a dose between 5 and 10 mg/week which is then gradually escalated over a period of 4 weeks to the target dose of 15–25 mg/week [23]. A 75% reduction in symptoms (PASI 75 – *Psoriasis Area and Severity Index*) was observed for the 15 mg/week dose in a total of 60% of patients of the above study during a period of 16 weeks.

A minimum period of 4–8 weeks is recommended before drug discontinuation or dose modification is introduced. The period corresponds to the time which is typically needed to achieve a full therapeutic effect.

The above-mentioned 2011 guidelines for the treatment of psoriasis vulgaris, published by a group of German experts, are an update of principles governing the therapeutic management used in this clinical indication which had been in force since 2009 [24]. It appears that dermatologists, particularly those working only in their private practices, have many doubts concerning, above all, the systemic treatment of psoriasis. The study by Nast *et al.* conducted in Germany has estimated the proportion of such physicians to be as high as 76% of the study population. Overall 79% of the dermatologists encompassed by the study claimed that such doubts were responsible for the inadequate systemic treatment of psoriasis patients [25]. We believe that the same situation applies to Polish dermatologists who see patients exclusively in their private practices. They are often reluctant to prescribe systemic therapy to psoriasis patients and instead refer them to dermatology hospitals. This is, naturally, partially understandable, and definitely provides a solid foundation for updating and improving guidelines in order to draw up a clear document that would reduce the level of doubt in those physicians who only work in outpatient clinical settings. The study conducted in 2006 by Nast *et al.* in a group of 54 German dermatologists demonstrated that 50% of patients with moderately severe and severe psoriasis were only prescribed topical treatment, 17% additionally received phototherapy, and only 30% were given systemic treatment [25]. The data are alarming from every possible angle.

The primary goal of the German guidelines, which fulfil high quality standards (S3 level), was to provide dermatologists – both those running their private prac-

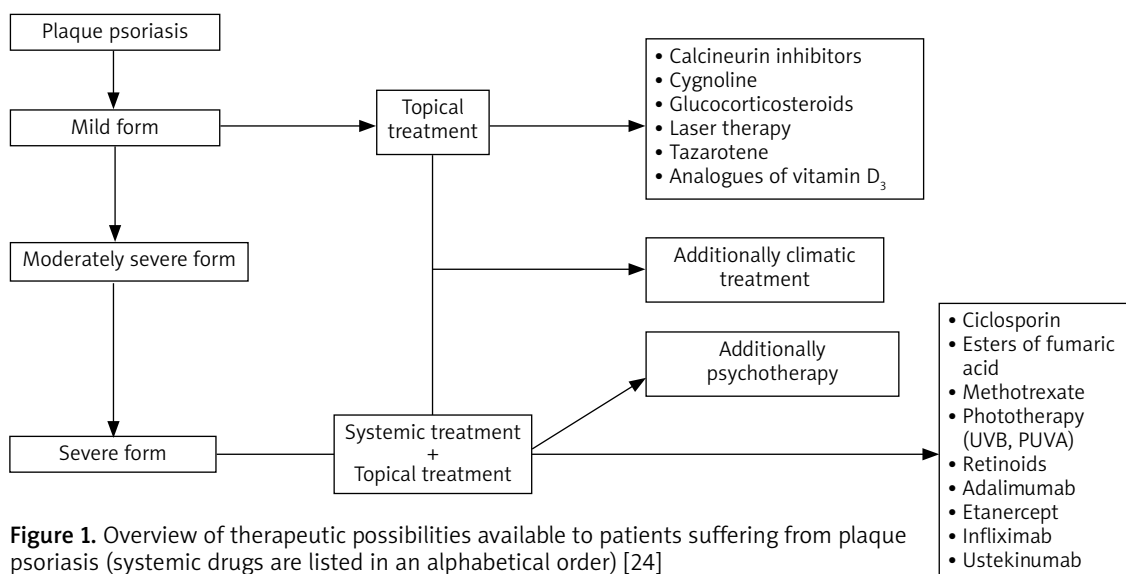


Figure 1. Overview of therapeutic possibilities available to patients suffering from plaque psoriasis (systemic drugs are listed in an alphabetical order) [24]

tices and those working in other clinical centres – with a document based on a well-established knowledge which will serve as an easily accessible and acceptable, clearly defined scheme for selecting appropriate therapeutic methods for patients suffering from psoriasis vulgaris. The document is intended to facilitate correct decision making and appropriate selection of therapeutic principles for adult female and male patients with mild to severe psoriasis vulgaris.

Going back to the status of MTX in the therapy of psoriasis, the German guidelines provide that treatment should be administered orally or parenterally, and the drug should be given once weekly. Sufficient data are now available on the differences in MTX efficacy and safety depending on the route of administration [15–17], even though the observed differences were previously thought to be insignificant [26]. Regarding the safety profile, there is no doubt that the subcutaneous route of administration is the one best tolerated by the patients, and is significantly superior to the oral and intramuscular routes. With respect to the efficacy of MTX depending on the route of administration, it seems logical, taking into account differences in the pharmacokinetics of the drug administered in different forms. The advantage of

injections over the oral route of administration in rheumatoid arthritis has been shown for the improvement in patient condition, e.g. in terms of morning joint stiffness, joint pain and swelling, self-evaluation by patients and general assessment by doctors supervising the therapy [16]. A better therapeutic effect of the subcutaneous form of MTX, combined with the lack of increased toxicity and better tolerance profile in patients with rheumatoid arthritis, clearly demonstrates the superiority of this route of administration over the oral route [17].

The starting dose of MTX is 7.5 mg/week, with a possibility to increase the dose to 22.5 mg/week depending on the clinical response to therapy. A higher starting dose, 15 mg/week or even higher, is sometimes suggested. The maximum dose of the drug has been established on the basis of general recommendations, and should not be exceeded [27, 28]. After remission is achieved, chronic maintenance treatment should be continued with the lowest possible dose of the drug. There are no literature reports on the occurrence of the rebound effect following the discontinuation of MTX therapy [29]. Also, there is unfortunately no sufficient knowledge about the appropriate procedure for discontinuing MTX therapy.

Another important aspect addressed in the guidelines is folic acid supplementation. As mentioned above, there are no unambiguous opinions on this matter, however the German guidelines recommend supplementation with 1–5 mg of folic acid on non-MTX days in order to decrease gastrointestinal adverse effects [30–32]. The uncertainty as to whether simultaneous folic acid supplementation can reduce the clinical efficacy of MTX [33, 34] clearly needs to be further explored so that more unequivocal conclusions can be drawn.

With regard to combining MTX with other methods, the guidelines suggest the combination of MTX with phototherapy, particularly UVB. Definitely, long-term studies investigating potential adverse effects of such therapy are necessary, especially in the aspect of MTX increasing the phototoxic effect of UVB radiation. This also applies to the combined treatment of MTX and PUVA. In contrast, the combination of MTX with etanercept (introduced when patients fail to improve with MTX in monotherapy) is not universally viewed as favourable [35]. A good therapeutic effect has been reported for combining MTX with 50 mg of etanercept twice a week for a period of 12 weeks, followed by 2 × 25 mg for another 12 weeks, however not all reports demonstrate the advantage of combined treatment over MTX or etanercept in monotherapy. Another valuable combination is MTX plus infliximab, which can produce a good therapeutic response, provided that all recommended precautions are followed when assessing the eligibility of patients for treatment, and patients are monitored throughout the therapy.

A crucial element associated with MTX therapy is the problem of drug interactions (Table 2). This area requires

Table 2. Interactions between MTX and other drugs, and the potential mechanism accounting for the phenomenon [24]

Mechanism	Drugs
Reduced renal elimination of MTX	<ul style="list-style-type: none"> • Ciclosporin • Salicylates • Sulphonamides • Probenecid • Penicillin • Colchicine • Cyclooxygenase inhibitors
Increased myelosuppression and digestive disorders	<ul style="list-style-type: none"> • Ethanol • Cotrimoxazole • Pyrimethamine • Chloramphenicol • Sulphonamides • Cyclooxygenase inhibitors • Cytostatics
Separation of the MTX molecule from the plasma complex of the drug-binding protein	<ul style="list-style-type: none"> • Cyclooxygenase inhibitors • Probenecid • Barbiturates • Phenytoin • Retinoids • Sulphonamides • Tetracyclines • Cotrimoxazole • Chloramphenicol • Sulphonylurea derivatives
Intracellular accumulation of MTX	<ul style="list-style-type: none"> • Dipyridamole
Increased hepatotoxicity	<ul style="list-style-type: none"> • Retinoids • Ethanol • Leflunomide

Before treatment	During treatment	After treatment
<ul style="list-style-type: none"> • Basic examinations • Exclusion of infections • Exclusion of HIV and viral hepatitis infections • Patients must be informed that they need to take the drug once weekly and about potential adverse reactions • General medical examination and exclusion of potential symptoms of jaundice • Abdominal ultrasound scan and particularly liver assessment • Radiographic chest examination • Measurement of serum procollagen type III level 	<ul style="list-style-type: none"> • Use of contraception by men and women • Check-ups every 1-3 months (CBC, liver tests, creatinine, general urine test) • More frequent laboratory tests are required if the MTX dose is increased, in patients at a risk of increase of the MTX level (dehydration, impaired kidney function, introduction of other drugs) • X-ray chest examination in patients with fever, cough, dyspnoea and cyanosis • Folic acid supplementation 	<ul style="list-style-type: none"> • Use of contraception by men and women for at least three months after completing treatment

Figure 2. Recommended examinations before and after introducing MTX therapy [24]

comprehensive knowledge and ongoing efforts to update it.

The German guidelines also specify recommended examinations before, during and after therapy, and estimated costs of patient treatment in Germany (Figure 2).

For the purpose of comparison, the UK guidelines (National Clinical Guideline Center – NCGC) issued on 2012 have a completely different character and, in our view, a decidedly lower clinical value. With respect to MTX use in the treatment of psoriasis, the guidelines contain a review and validation of available results of clinical trials, however there are no unambiguous conclusions and clear-cut recommendations [36]. Excerpts from the document and data concerning the aspects mentioned above are given below. Their final assessment is left to the reader, however it needs to be stressed that MTX-based systemic treatment is recognized as first-line drug.

Studies in which cyclosporine was superior to methotrexate:

- PASI 75 after 12 weeks (MTX dose: from 7.5 to 15 mg/week) – 1 study; 68 subjects;
- PASI 50 at 12 weeks (MTX dose: from 7.5 to 15 mg/week) – 1 study; 68 subjects;
- PASI after 12–16 weeks (MTX doses: maximum 22.5 mg/week) – 2 studies; 153 subjects;
- elevated liver enzymes in weeks 12–24 (MTX at the maximum dose of 22.5 mg/week) – 3 studies; 190 subjects;
- withdrawal due to toxicity after 16 weeks (MTX dose: from 15 to 22.5 mg/week) – 1 study; 85 subjects.

Studies in which methotrexate was superior to cyclosporine:

- reduced PASI score after 12 weeks (MTX dose: 0.5 mg/kg/week) – 1 study; 30 subjects;

- subsidence of symptoms after 10 weeks (MTX dose: 0.5 mg/kg/week) – 1 study; 30 subjects;

- elevated creatinine level in weeks 12–24 (mean MTX dose: maximum 15 mg/week) – 2 studies; 105 subjects.

Studies in which there was no statistically significant difference between cyclosporine and methotrexate:

- PASI 90 after 12 weeks (MTX dose: from 7.5 to 15 mg/week) – 1 study; 68 subjects;
- PASI 90 at 16 weeks (MTX dose: from 15 to 22.5 mg/week) – 1 study; 85 subjects;
- PASI 75 (MTX dose: from 15 to 22.5 mg/week) after a follow-up period of maximum 16 weeks – 1 study; 85 subjects;
- PASI 90 (MTX dose: from 15 to 22.5 mg/week) after a follow-up period of maximum 16 weeks – 1 study; 85 subjects;
- PASI 75 at 16 weeks (MTX dose: from 15 to 22.5 mg/week) – 1 study; 85 subjects.

Studies evaluating the maximum response time for methotrexate treatment:

- PASI improvement rate after 16 weeks – 1 study; 110 subjects;
- maximum PASI improvement between 4 and 6 months after the initiation of therapy – 1 study; 20 subjects;
- reduced PASI score after 12 weeks – 1 study; 37 subjects;
- reduced PASI score after 8 weeks – 1 study; 17 subjects.

Summing up, it can be concluded that the majority of studies have demonstrated a remission or an improvement in skin condition within 16–24 weeks after introducing methotrexate treatment. A higher starting dose (15 mg/week) in two studies has contributed to an achievement of maximum response after 8–12 weeks of treatment.

A very interesting aspect to consider is the practical application of guidelines which should be familiar to all practising dermatologists. A worldwide study investigating this problem has shown that this is not always the case [25]. The questionnaire developed by Psoriasis International Network (PIN) consisted of 41 questions addressed to clinicians. It is also worthwhile to add that the final form of the questions included in the questionnaire was agreed both by specialists in dermatology and members of patient associations from 95 countries. They concerned preliminary assessment of patient eligibility for MTX treatment (laboratory tests), monitoring of possible adverse reactions and safety of therapy, drug dosage, folic acid supplementation, evaluation of clinical efficacy of treatment and various aspects of combined therapy. The highest feedback rate was in the EU countries, which is not surprising in view of the fact that the very idea behind the studies originated in Europe. What is more, a considerable proportion of replies was – as expected – submitted by dermatologists who are keenly interested in the application of MTX for psoriasis treatment. This leads to certain shifts in percentage rates, however it was nevertheless the first project worldwide to assess the practical clinical use of MTX in the therapy of psoriasis. This aspect is evidence for its high substantive value. Some aspects of the results were thought-provoking, and verging on astonishing. Generally, MTX was used at lower doses than recommended in the guidelines [37, 38]. Approximately two thirds of dermatologists started treatment with the 10 mg dose, or even lower doses. Over 40% prescribed the same doses, 10 mg or lower, for maintenance therapy. Women turned out to be more conservative in the selection of the starting dose. For maintenance therapy, however, there were no differences associated with the sex of the dermatologists. A relatively high percentage of the study's dermatologists (38.9%) did not take into consideration the cumulative dose of MTX as a factor determining potential discontinuation of treatment. However, there were very interesting observations linked to geographical differences across the regions of the world. Regimens applied in clinical practice seem to differ quite markedly. In Africa, the starting doses are usually higher and maintenance doses – relatively low. Also, the period of treatment is shorter compared to other geographical regions. In North American countries dermatologists prescribe the highest maintenance doses, the highest weekly and cumulative doses. In contrast, MTX doses prescribed in all the above categories in Asian countries are at least 25% lower. This can result from the fact that MTX treatment in Asia is linked to a markedly higher incidence of adverse reactions: over 50% of psoriasis patients receiving MTX treatment in the Malaysia Psoriasis Centre developed disorders of enzymatic liver function, and 10% had to discontinue therapy due to drug hepatotoxicity [39]. Another important aspect is the difference in body mass index (BMI) between the

USA, Europe (France) and Asia (Japan), where BMI was, respectively, 29, 22.55 and 23.7 kg/m². Therefore, taking into account all the facts, it follows that the extrapolation of conclusions from studies conducted in a selected geographical regions to other regions is risky. Another interesting finding is the fact that in African countries MTX is routinely administered in the form of intramuscular infections (more than one third of the study's dermatologists), whereas the subcutaneous route of administration is recommended practically exclusively by dermatologists practising in Europe.

Significant differences are also observed for folic acid supplementation: both with regard to doses and dosage regimen. The weekly dose does not depend on the weekly MTX dose in maintenance treatment (higher doses are usually prescribed by African dermatologists).

Analyzing the monitoring of laboratory parameters, the greatest differences were noted for CBC and parameters of kidney function. In Europe, the methodology employed for the long-term monitoring of drug hepatotoxicity sufficiently limited the need to perform a liver biopsy (in compliance with recommendations agreed during the 2011 conference devoted to this issue) [40], whereas in North America liver biopsy is still relatively often prescribed in clinical practice.

Consequently, based on results obtained in this extremely valuable study – which represents practically the only review of recommendations developed for the treatment of psoriasis with MTX – it needs to be concluded that differences between recommendations set out in the guidelines and daily practice are noticeable in a number of significant aspects. This applies in particular to drug dosage regimens. It also depends to a certain extent on medical regulations in place in different geographical regions, discrepancies in physiological aspects (body weight, enzymatic liver function) and/or regional "traditions". Naturally, further detailed analyses are necessary in this area, followed by adjustments to the proposed recommendations, if any turn out to be required. It is beyond doubt that the use of MTX in the treatment of psoriasis absolutely requires harmonization, taking into consideration all potential geographical and ethnic differences both with respect to the drug's clinical efficacy and safety of treatment.

In conclusion, MTX is a relatively safe and effective drug. Definitely, appropriate assessment of patient eligibility must be ensured before introducing therapy, and all contraindications must be ruled out. If disorders in laboratory test results are identified, it is often sufficient to reduce the dose without having to discontinue the drug completely. The drug is indicated for the treatment of all forms of psoriasis, and also psoriatic arthritis. Methotrexate-based therapy of patients with psoriasis can be conducted on an outpatient basis, as long as all recommendations concerning dosage and safety of treatment are followed. It is worthwhile to highlight that a major factor

determining better efficacy and tolerance of MTX is the route of administration. The subcutaneous route of administering the drug seems to be the optimum solution because considering superior MTX bioavailability and markedly lower incidence of adverse reactions associated with the treatment the patient and the physician achieve a satisfying clinical outcome significantly more frequently than in the case of other administration routes.

What is more, thanks to the reimbursement scheme, MTX is a relatively inexpensive drug and thereby more easily available to Polish patients.

References

- Gubner R, August S, Ginsberg V. Therapeutic suppression of tissue reactivity. II. Effect of aminopterin in rheumatoid arthritis and psoriasis. *Am J Med Sci* 1951; 221: 176-82.
- Carretero G, Puig L, Dehesa L, et al.; Grupo de Psoriasis de la AEDV. Guidelines on the use of methotrexate in psoriasis. *Actas Dermosifiliogr* 2010; 101: 600-13.
- Cronstein BN, Naime D, Ostad E. The antiinflammatory effects of methotrexate are mediated by adenosine. *Adv Exp Med Biol* 1994; 370: 411-6.
- Elango T, Dayalan H, Gnanaraj P, et al. Impact of methotrexate on oxidative stress and apoptosis markers in psoriatic patients. *Clin Exp Med* 2014; 14: 431-7.
- Bannwarth B, Labat L, Moride Y, Schaefferbeke T. Methotrexate in rheumatoid arthritis. An update. *Drugs* 1994; 47: 25-50.
- Kress DW. Etanercept therapy improves symptoms and allows tapering of other medications in children and adolescents with moderate to severe psoriasis. *J Am Acad Dermatol* 2006; 54 (3 Suppl. 2): S126-8.
- Rossi S (ed.). Australian medicines handbook. The Australian Medicines Handbook Unit Trust. Adelaide 2013.
- Joint Formulary Committee (2013). British National Formulary (BNF) (65 ed.). Pharmaceutical Press. London, UK 2013.
- Weinblatt ME. Methotrexate in rheumatoid arthritis: a quarter century of development. *Transactions of the American Clinical and Climatological Association* 2013; 124: 16-25.
- Marks JL, Edwards CJ. Protective effect of methotrexate in patients with rheumatoid arthritis and cardiovascular comorbidity. *Ther Adv Musculoskelet Dis* 2012; 4: 149-57.
- Methotrexate. The American Society of Health-System Pharmacists. Retrieved 3 April 2011.
- Lloyd ME, Carr M, McElhatton P, et al. The effects of methotrexate on pregnancy, fertility and lactation. *QJM* 1999; 92: 551-63.
- 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.
- 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.
- Rutkowska L, Rell-Bekalarska M, Lisowska B. Oral vs. subcutaneous low-dose methotrexate treatment in reducing gastrointestinal side effects. *Reumatologia* 2009; 47: 207-11.
- Islam MS, Haq SA, Islam MN, et al. Comparative efficacy of subcutaneous versus oral methotrexate in active rheumatoid arthritis. *Mymensingh Med J* 2013; 22: 483-8.
- Cipriani P, Ruscitti P, Carubbi F, et al. Methotrexate in rheumatoid arthritis: optimizing therapy among different formulations. Current and emerging paradigms. *Clin Ther* 2014; 36: 427-35.
- Ohbayashi M, Suzuki M, Yashiro Y, et al. Induction of pulmonary fibrosis by methotrexate treatment in mice lung in vivo and in vitro. *J Toxicol Sci* 2010; 35: 653-61.
- Dańczak-Pazdrowska A. Place of methotrexate in the treatment of psoriasis in the era of biologic agents. *Postep Derm Alergol* 2012; 29: 182-8.
- Goodman TA, Polisson RP. Methotrexate: adverse reactions and major toxicities. *Rheum Dis Clin North Am* 1994; 20: 513-28.
- 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.
- Brownell I, Strober BE. Folate with methotrexate: big benefit, questionable cost. *Br J Dermatol* 2007; 157: 213.
- Montaudié H, Sbidian E, Paul C, et al. Methotrexate in psoriasis: a systematic review of treatment modalities, incidence, risk factors and monitoring of liver toxicity. *J Eur Acad Dermatol Venereol* 2011; 25 Suppl 2: 12-8.
- Nast A, Boehncke WH, Mrowietz U, et al. S3-guidelines for the treatment of psoriasis vulgaris Update 2011. *J Dtsch Dermatol Ges* 2011; 9 Suppl. 2: S1-104.
- Nast A, Reytan N, Rosumeck S, et al. Low prescription rate for systemic treatments in the management of severe psoriasis vulgaris and psoriatic arthritis in dermatological practices in Berlin and Brandenburg, Germany: results from a patient registry. *J Eur Acad Dermatol Venereol* 2008; 22: 1337-42.
- Roenigk HH Jr, Auerbach R, Maibach H, et al. Methotrexate in psoriasis: consensus conference. *J Am Acad Dermatol* 1998; 38: 478-85.
- Revicki D, Willian MK, Saurat JH, et al. Impact of adalimumab treatment on health-related quality of life and other patient-reported outcomes: results from a 16-week randomized controlled trial in patients with moderate to severe plaque psoriasis. *Br J Dermatol* 2008; 158: 549-57.
- 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.
- van Dooren-Greebe RJ, Kuijpers AL, Termorshuizen F, van de Kerkhof PC. Interruption of long-term methotrexate treatment in psoriasis. Evaluation of clinical course and laboratory parameters after discontinuation and reintroduction of weekly oral methotrexate. *Acta Derm Venereol* 1995; 75: 393-6.
- Duhra P. Treatment of gastrointestinal symptoms associated with methotrexate therapy for psoriasis. *J Am Acad Dermatol* 1993; 28: 466-9.
- Ortiz Z, Shea B, Suarez Almazor M, et al. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. *Cochrane Database Syst Rev* 2000; 2: CD000951.
- van Ede AE, Laan RF, Rood MJ, et al. Effect of folic or folinic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis: a forty-eight week, multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2001; 44: 1515-24.
- 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.

34. Chladek J, Simkova M, Vaneckova J, et al. The effect of folic acid supplementation on the pharmacokinetics and pharmacodynamics of oral methotrexate during the remission-induction period of treatment for moderate-to-severe plaque psoriasis. *Eur J Clin Pharmacol* 2008; 64: 347-55.
35. Zachariae C, Mork NJ, Reunala T, et al. The combination of etanercept and methotrexate increases the effectiveness of treatment in active psoriasis despite inadequate effect of methotrexate therapy. *Acta Derm Venereol* 2008; 88: 495-501.
36. Samarasekera E, Sawyer L, Parnham J, Smith CH; Guideline Development Group. Assessment and management of psoriasis: summary of NICE guidance. *BMJ* 2012; 345: e6712.
37. Pathirana D, Ormerod AD, Saiag P, et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris. *J Eur Acad Dermatol Venereol* 2009; 23 Suppl. 2: 1-70.
38. 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.
39. Ng LC, Lee YY, Lee CK, Wong SM. A retrospective review of methotrexate-induced hepatotoxicity among patients with psoriasis in a tertiary dermatology center in Malaysia. *Int J Dermatol* 2013; 52: 102-5.
40. Barker J, Horn EJ, Lebwohl M, et al.; International Psoriasis Council. Assessment and management of methotrexate hepatotoxicity in psoriasis patients: report from a consensus conference to evaluate current practice and identify key questions toward optimizing methotrexate use in the clinic. *J Eur Acad Dermatol Venereol* 2011; 25: 758-64.