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Methotrexate: Safe and effective

ABSTRACT

Rheumatoid arthritis (RA) is the most common systemic connective tissue disease. The prevalence of RA in the general population is 0.3–1.5% (in Europe 0.8% in the adult population), with women affected 3 times more often. The first clinical description of the disease was made in 1859 by Garrod. More than 100 years later, methotrexate was used for the first time in RA therapy (in 1951). To this day, it is the primary drug in the therapy of this disease, as well as many other autoimmune and cancer diseases. The article presents the most important information on the use of methotrexate and the results of a study conducted at the local Center, confirming the safety of using the drug.

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KEY WORDS: rheumatoid arthritis; methotrexate; pharmacological therapy

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic connective tissue disease characterised by arthritis, damage to periarticular structures and extra-articular lesions, which develops as an autoimmune disease. The disease, if untreated, leads to physical impairment, reduced quality of life and premature death, mainly due to increased cardiovascular risk [1]. Disease-modifying antirheumatic drugs (DMARDs) are of primary importance, among which methotrexate (MTX) plays a special role.

MECHANISM OF ACTION

Methotrexate is an antimetabolite, an antagonist of folic acid. It inhibits the activity of dihydrofolate reductase, which catalyses the conversion of dihydrofolate to tetrahydrofolate. It is an anticancer and immunosuppressive drug and is also used as a DMARD in certain diseases. By inhibiting purine nucleotide synthesis and thymidine synthesis, it interferes with DNA synthesis and repair and interferes with cellular replication.

Its role in the treatment of RA is not fully understood. It is believed that the mechanism of inhibition of purine and pyrimidine synthesis is not crucial in the treatment of arthritis, as antiproliferative doses are much higher than those used for treating rheumatic diseases. Rather, MTX is indicated to affect the adenosine pathway and alteration of the cytokine profile: it inhibits the secretion of tumour necrosis factor, interferon-gamma, interleukin 1 (IL-1), IL-6, IL-8, IL-12, inhibits phagocytosis and increases the expression of anti-inflammatory cytokines, i.e., IL-4, IL-10 [2]. However, a detailed discussion of these processes is beyond the scope of this paper.

CONTRAINDICATIONS

There are few absolute contraindications to the use of MTX. Those include severe renal and hepatic impairment (including cirrhosis), pregnancy and breastfeeding period. Other contraindications are relative and include chronic kidney disease, liver diseases, lung disease (clinically significant interstitial lung disease and clinically significant pulmonary fibrosis) [2], leukopenia < 3000/μL, thrombocytopenia < 100 000/μL, lymphoproliferative neoplasm treated in the last 5 years, acute or chronic infections (infections requiring hospitalisation or administration of parenteral antibiotics, tuberculosis — active or latent if the patient is not taking prophylactic anti-tuberculosis treatment, active chickenpox and

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Table 1. Adverse effects of methotrexate by frequency of occurrence

Very common ≥ 1/10	Common ≥ 1/100	Uncommon ≥ 1/1000
Pharyngitis	Leukopenia, thrombocytopenia, anaemia	Pancytopenia, agranulocytosis
Stomatitis and ulcerations	Drowsiness, headache, fatigue	Hair loss
Anorexia nervosa	Blurred vision	Allergic reactions
Nausea, vomiting, abdominal pain	Bleeding (nosebleed)	Diabetes
Increase in transaminase levels	Alveolitis, dry cough	Depression
Dizziness	Diarrhoea	Joint pain, muscle pain
	Rash, erythema, pruritus	Steatosis, fibrosis, cirrhosis of the liver
		Seizures, transient cognitive impairment
		Toxic reactions: vasculitis, dermatitis (Stevens-Johnson syndrome, Lyell's syndrome)

herpes virus infection, active severe fungal infections, acute or chronic hepatitis B or C). MTX should be considered in the case of absence or inappropriate contraception and alcohol abuse [2, 3].

It is necessary to elaborate on the use of MTX in patients with concomitant respiratory disease. According to the 2021 American College of Rheumatology (ACR) recommendations, the drug is conditionally recommended in patients with diagnosed mild and stable airway or pulmonary parenchymal disease, as well as incidentally detected airway disease of moderate to high activity by imaging studies [4].

ADVERSE EFFECTS

The most common adverse effects after MTX are gastrointestinal disorders and elevated transaminase levels. Adverse effects according to their frequency are shown in Table 1 [2, 3, 5].

The adverse effects of MTX depend on the dose and frequency of administration; in most cases, they are reversible. The use of folic acid at a dose of at least 5 mg/week plays an important role in reducing their presence (folic acid in low doses reduces MTX toxicity to the mucosa, liver, and bone marrow). Higher doses, usually 15 mg/week, may be used when red blood cell volume increases and when high doses of MTX are used. Folic acid should be administered orally, once a week, 24 hours after taking MTX [6].

Discontinuation of MTX therapy is necessary when serious haematological disorders occur: leukopenia < 3000/μL, granulocytopenia < 2000/μL, thrombocytopenia < 100 000/μL (Felty's syndrome is an exception), aplastic anaemia, severe hepatic and/or renal impairment (bilirubin > 5 mg/dL, creatinine clearance < 20 mL/min), drug-induced stomatitis, drug-induced skin lesions and alopecia areata.

In case of overdose and the occurrence of acute hematopoietic adverse effects (cytopenia), it is possible to administer an antidote, i.e., calcium folinate (Calcium folinate, Leucovorin): intravenously or intramuscularly, as a bolus, in a dose equal to or higher than the MTX dose used (e.g., 15 mg) and repeated several times (at least 4×), every 3–6 hours, until the serum MTX level is below 10^{-7} mol/L [5].

GENERAL RULES FOR USE

To monitor the safety of MTX therapy, periodic laboratory tests such as complete blood count, serum creatinine levels and liver aminotransferase activity are recommended. There are no clear indications to perform lung imaging before starting therapy, however, some sources recommend doing so [3].

Mild hepatic impairment during MTX therapy is often transient and if serum aminotransferase activity does not exceed three times the upper limit of normal (ULN), MTX should not be discontinued, however, the dose should be adjusted. If, on the other hand, transaminase activity exceeds three times the ULN, MTX should be discontinued [2, 5]. A return to treatment at a lower dose than previously used is possible once enzyme activity has normalised.

In the case of renal impairment, the initiation of MTX therapy or restart of the therapy is not recommended if creatinine clearance is ≤ 30 mL/min. If the patient is chronically treated with MTX and the creatinine clearance

is at least 20 mL/min, the therapy can be continued with reduced doses of the drug (for creatinine clearance 20–50 mL/min — 50–100% of the normal dose). The drug can be used in patients undergoing haemodialysis — 50% of the normal dose of the drug should be given 12 hours before the haemodialysis procedure (caution should be exercised) [7].

MTX is a teratogenic drug. Its use should be discontinued at least 3 months before planned conception (applies to both women and men) [2, 3]. According to the characteristics of medicinal products available on the Polish market, this period should be at least 6 months. The drug penetrates into breast milk and is thus contraindicated during breastfeeding.

In the perioperative period for orthopaedic surgery, MTX does not need to be discontinued [8]. This probably also applies to other types of surgery, however, there are no clear guidelines on this topic.

PHARMACOKINETICS

MTX is a pro-drug. Its active form is methotrexate polyglutamate (MTXPG). The effect of the drug on inhibiting RA activity depends on the levels of MTXPG in cells (erythrocytes) and is dose-dependent [9]. The half-life of MTX is 3–15 hours. The drug reaches maximum serum concentration approximately 1–2 hours after oral administration; it binds 35–50% to plasma albumin. Its bioavailability is higher after subcutaneous administration. MTX is metabolised mainly in the liver and excreted 48–100% by the kidneys (most in the first 12 hours). Renal impairment increases serum MTX levels.

Two studies were conducted at the Centre to assess serum MTX levels in patients using the drug (in study I, assays were performed between 8 and 24 hours after drug intake and after 36 hours, in study II — at 2 and 48 hours after drug intake). In total, assays were performed for 154 patients (Beckman AU480 analyser and Siemens reagents).

In samples taken 36 hours after drug administration (128 patients) and 48 hours after drug administration (26 patients) — regardless of route of administration and dose, MTX levels were at the limit of detection of the test, treated as a negative result (range between 0.006 and 0.001 μmol/L). Up to 24 hours after drug administration, MTX levels were adequate for the dose used (Tab. 2).

One study was also performed on a female patient who mistakenly took MTX daily per os at a dose of 20 mg for 1 week. In subsequent assays, the drug concentration was 0.89 μmol/L at baseline, 0.35 μmol/L after one week and 0.006 μmol/L after 2 weeks. No adverse effects were observed.

Aim of the study: assessment of serum MTX persistence time.

Material: patient serum.

Method: the EMIT test is a homogeneous enzyme immunoassay used for the determination of specific chemical compounds in human physiological fluids. The principle of the test is based on competition for the binding site on antibodies between the drug in the sample and the drug labelled with the enzyme glucose-6-phosphate dehydrogenase (G6PDH). The activity of the enzyme decreases upon binding to the antibody, so the concentration of the drug in the sample can be determined by measuring the enzyme activity. The active enzyme converts oxidised nicotinamide adenine dinucleotide (NAD) to NADH, resulting in a change in absorbance that can be measured spectrophotometrically. The endogenous serum enzyme G6PDH does not interfere with the study, as the NAD coenzyme only works with the bacterial enzyme (Leuconostoc mesenteroides) used in this study.

Results: they are shown in Tables 2 and 3.

Conclusions: The following conclusions were drawn from the study:

1. MTX is a drug that is rapidly metabolised in the body in most patients when doses are used according to current guidelines (the drug is eliminated from serum within 36 hours).

Table 2. Study I

Methotrexate dose	Number of assays	The concentration of the drug between 8 and 24 hours after taking methotrexate
10 mg/week	25 studies	0.007–0.011 μmol/L
15 mg/week	20 studies	0.007–0.018 μmol/L
20 mg/week	36 studies	0.05–0.16 μmol/L
25 mg/week	47 studies	0.1–0.38 μmol/L

Table 3. Study II

Methotrexate dose	Number of assays	The serum concentration of the drug 2 hours after taking methotrexate
20 mg/week	12 studies	0.7450–1.5680 μmol/L
22.5 mg/week	1 study	0.7300 μmol/L
25 mg/week	13 studies	0.2820–1.3940 μmol/L

2. MTX can become a dangerous drug when used daily (not as prescribed).
3. Assessment of serum MTX levels is useful when drug intoxication is suspected (presence of the drug in serum 36 hours after declared drug intake) and during treatment of intoxication.
4. Assessment of serum MTX levels may be useful to confirm appropriate patient cooperation.

This study has proved that MTX is a rapidly metabolised drug in the body. It can become a dangerous drug when used daily.

PHARMACOTHERAPY OF RA

DMARDs are of primary importance in the treatment of RA. These are divided into synthetic [conventional synthetic DMARDs (csDMARDs) and targeted synthetic DMARDs (tsDMARDs)] and biologic DMARDs (bDMARDs).

MTX, along with leflunomide (LEF), sulfasalazine (SSZ) and hydroxychloroquine/chloroquine (HCQ/CQ), is one of csDMARDs. Its role is consistently highlighted in European Alliance of Associations for Rheumatology (EULAR) and ACR recommendations for the treatment of RA [4, 10].

According to the 2019 EULAR recommendations (the 2022 recommendations for MTX have not changed significantly) comprising five overarching principles and twelve specific recommendations, MTX should be a component of first-line treatment; however, disease-modifying antirheumatic drug therapy should be initiated as soon as the diagnosis of RA is made. Appropriate early initiation of treatment offers a better chance of achieving disease remission (or low disease activity) and improving prognosis, especially in terms of joint destruction and patient performance. Only in the case of contraindications to MTX or the occurrence of its early intolerance is the use of other conventional synthetic DMARDs (LEF, SSZ) recommended; in the case of low disease activity, it is possible to initiate therapy with hydroxychloroquine.

The starting dose of MTX (administered orally or subcutaneously) is 10–15 mg once a week. This should be increased gradually (by 5 mg every 2–4 weeks) over 4–6 weeks to the optimal therapeutic dose, i.e., 0.3 mg/kg body weight, or approximately 20–25 mg per week for an adult. The size of the MTX dose significantly determines the efficacy of the treatment [10].

Similar recommendations were made by the ACR in 2021 — initiation of RA treatment with methotrexate (MTX before other DMARDs: HCQ, SSZ, bDMARDs, tsDMARDs; conditionally instead of LEF) was recommended, especially at moderate to high disease activity. At low disease activity, HCQ (HCQ > SSZ > MTX > LEF) was conditionally allowed as the first drug in therapy. Moreover, according to the ACR, the oral form of administration of MTX should be preferred over the subcutaneous form of administration; the subcutaneous form of administration is an option in case of intolerance of the drug in tablet form or as an intensification of treatment in case of treatment failure [4].

MTX can be used as monotherapy or in combination with other DMARDs and glucocorticosteroids (used especially as bridging therapy at the start of treatment or during treatment modification). To date, no evidence has been shown that biologics or tsDMARDs are more effective or safer than MTX as a first-line medication. In contrast, combination therapy of MTX and the above-mentioned drugs is found to be more effective than monotherapy for all bDMARDs and tsDMARDs and reduces the immunogenicity of biologics. The data indicate that an MTX dose of 10 mg/week is sufficient in this case. Therefore, according to EULAR recommendations, csDMARDs should be administered together with biologics and targeted synthetic drugs whenever possible [10].

There is also no demonstrated advantage of biologic therapy and tsDMARD therapy over csDMARD therapy with the three-drug regimen (MTX + SSZ + HCQ/CQ) — long-term treatment outcomes are similar; the cost of therapy is lower. However, due to the better persistence of biologics and the aim to maxim-

ise clinical improvement in the shortest possible time, the patient panel at the ACR conditionally recommended bDMARD/tsDMARD therapy in combination with MTX over csDMARD therapy with the three-drug regimen (as above).

If the patient achieves sustained disease remission after glucocorticosteroids withdrawal, gradual discontinuation of DMARDs may be considered. To date, EULAR has recommended reducing treatment with bDMARDs or tsDMARDs first (i.e., reducing the dose or lengthening the interval between doses), followed by csDMARDs. According to the latest 2022 recommendations, csDMARDs can also be reduced first, as can bDMARDs and tsDMARDs — the decision is up to the attending physician and the patient. It should be added that EULAR does not clearly define the durable remission of the disease.

According to the ACR recommendations, treatment reduction can be made after a minimum of 6 months of remission or low disease activity, however, the continuation of treatment with all drugs at the current dose is conditionally more advisable than dose reduction, and dose reduction alone is conditionally more advisable than gradual discontinuation of DMARDs. Discontinuation of MTX in the first place is conditionally recommended if the patient is using MTX + bDMARDs/ /tsDMARDs. The caveat, however, was that MTX prevents the formation of antibodies to biologics and many patients may require its continued use.

In 70% of cases, complete discontinuation of treatment is not possible; disease exacerbation occurs (usually within 3–6 weeks), requiring re-intensification of therapy [2].

PRACTICAL ASPECTS OF MTX THERAPY

In addition to an appropriate choice of therapy, a good collaboration between patient and physician is equally important for therapeutic success. Adequate compliance, i.e., correct adherence to therapeutic recommendations (use of the right dose of the medicine at the right time), is made up of concepts such as persistence — continuation of prescribed treatment — and adherence — the level of collaboration between patient and physician.

Compliance and adherence in inpatient wards are approaching 100%. On an outpatient basis, < 50% of patients buy prescription medicines after 6 months. Approximately 25% of patients do not take their medications despite declaring it. According to the Elderly Medication Analysis, approximately, 11% of patients do not adhere to instructions because they have difficulty swallowing tablets; 12% are unable to open the medicine package; 14% of patients are bothered by the taste of the tablet [11].

Before initiation of treatment, the physician should inform the patient about the nature of the disease, possible complications and its consequences, and outline treatment options, including the cost of treatment. The form of the medication is also an important issue for many patients, especially for those with manual limitations.

In RA therapy, we have access to different forms of MTX, i.e., MTX in an oral form (tablets, syrup) and subcutaneous form (prefilled syringes, semi-automatic injectors). This allows the treatment to be tailored to the patient's preferences and abilities and can significantly improve the quality of collaboration between patient and physician and treatment outcomes.

SUMMARY

Despite the emergence of numerous new biologics and tsDMARDs in recent years, MTX remains the "gold standard" of RA therapy. It is the drug of choice both for initiation of treatment and an essential part of combination therapy. MTX is the safest, most effective treatment for chronic arthritis, including reducing the development of structural changes in joints. It is the only DMARD that extends life span, mainly by reducing cardiovascular complications [12]. It can be taken chronically and there are no time limits to therapy. Most adverse effects after MTX administration are mild and reversible, rarely resulting in the need to discontinue the drug completely. If a drug overdose is suspected, it is useful to test MTX plasma levels after 36 hours so that appropriate treatment can be initiated.

The efficacy of the treatment is just as important as a good collaboration between physician and patient. In the absence of appropriate adherence, the most effective drugs will be ineffective. Therefore, it is important to make therapeutic decisions together with the patient, including decisions regarding the form of treatment, its convenience and cost.

CONFLICT OF INTEREST

None declared.

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