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Methotrexate

Metotreksat

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Abstract

Methotrexate is a drug used in the treatment of psoriasis and psoriatic arthritis. It shows its effect by binding to dihydrofolate reductase, reducing purine synthesis and cell proliferation. When used as a monotherapy, methotrexate shows its effect late and achieves a 50-75% recovery in skin lesions. Patients using methotrexate should periodically be monitored for toxicity with relevant laboratory parameters. Its use in combination with folic acid reduces the risk of toxicity. Using it in combination with cyclosporine in low doses may lower the toxicity risk of both. Its use in combination with phototherapy and acitretin has been found considerably effective.
Keywords: Psoriasis, methotrexate, treatment

Öz

Metotreksat psoriasis ve psoriatik artrit tedavisinde kullanılan etkisini dihidrofolat redüktaza bağlanarak purin sentezini ve hücre proliferasyonu azaltarak gösteren bir ilaçtır. Metotreksat tedavide monoterapi olarak kullanıldığında etkisi geç başlar. Monoterapi olarak kullanıldığında deri lezyonlarında %50-75 oranında iyileşme sağlar. Metotreksat kullanan hastalar toksisite açısından belirli periyotlarda ilgili laboratuvar parametreleri ile izlenmelidir. Folik asitle birlikte kullanılması toksisite riskini azaltır. Siklosporin ile birlikte düşük dozlarda kullanılması her iki ilacın da toksisite riskini azaltabilir. İlacın fototerapi ve asitretin ile birlikte kullanımının oldukça etkili olduğu bulunmuştur.
Anahtar Kelimeler: Psoriasis, metotreksat, tedavi

General information

Methotrexate (MTX) is used for the treatment of serious and refractory, moderate plaque psoriasis, pustular, erythrodermic forms, and arthritis[1,2].

Mechanism of action

The anti-inflammatory effects of MTX emerge as a result of a series of cellular mechanisms. By binding to dihydrofolate reductase, MTX reduces purine synthesis and cell proliferation[3]. It shows its anti-inflammatory action by inhibiting enzyme 5-aminoimidazole-4-carboxamide ribonucleotide transformilase. As a result of this, adenosine accumulation, lymphocyte proliferation, secretion of inflammatory cytokines such as interleukin (IL)-1, interferon-γ and TNF-α, free radical formation from polymorphonuclear cells, adhesion of these cells, and neutrophil chemotaxis are suppressed[4]. It also suppresses keratinocyte proliferation and dermal inflammatory infiltration by reducing IL-22 levels[5]. Inhibition of tissue damaging polyamines (spermines and spermidines) is another mechanism responsible for the anti-inflammatory action[4].

Dosage/treatment scheme

A MTX administration scheme for patients with psoriasis is shown in Table 1. Addition of folic acid to the treatment in

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patients using MTX reduces toxicity without changing the efficacy[6]. Folate deficiency caused by MTX plays a major role in developing hepatotoxicity; for this reason, folate supplementation is needed to reduce hepatotoxicity[7]. Although there is no consensus about the optimal dose for folic acid supplementation, a single dose (5 mg) at least 24 hours after the day of taking MTX is recommended[8].

Table 1. Methotrexate administration scheme

- Single dose weekly through oral (in 3 divided doses within 24 hours in 12-hour intervals to decrease side effects), intramuscular or subcutaneous routes
- Initial dose to be 5-10 mg/week (testing dose)
- Dose to be adjusted to be between 10-25 mg/week depending on the clinical response
- Waiting 4-8 weeks is required for the efficacy to manifest
- After achieving remission, long-term treatment is continued with the lowest effective dose

Efficacy

MTX is slow-acting, its effect emerges late when used as a monotherapy; maximum response to treatment generally occurs between weeks 16-24[9]. It is moderately effective when used as a monotherapy with a recovery rate of 50-75% in skin lesions[10,11]. It is less effective than cyclosporine, but is more suitable for long-term use[12]. When used >15 mg a week, 25% of patients achieve a PASI75 response in 3.2 weeks and when used <15 mg, they reach the same response level in 9.9 weeks[13].

Combining MTX with cyclosporine enables use of both agents in lower doses, thereby reducing hepatotoxicity associated with MTX and nephrotoxicity associated with cyclosporine[14,15]. Combinations of MTX with NB UVB, wide-band UVB and PUVA have also been found quite effective[16,17]. Low-dose acitretin may be combined with MTX[18]. MTX may also be combined with all biological agents that have been approved for the treatment of psoriasis and psoriatic arthritis[19]. Concurrent use of MTX in patients taking infliximab diminishes the risk of developing antibodies[20].

Follow-up

Patients for whom a MTX therapy is planned should be assessed prior to the treatment in terms of disease severity, presence of arthritis, response to previous treatments, contraindication-involving conditions, renal and hepatic functions, and presence of infections or psoriatic comorbidities[1,2]. Tests to be conducted before and after the treatment are shown in Table 2.

Table 2. Pre-treatment and follow-up tests to be performed in patients using methotrexate

	Pre-treatment	Follow-up
Whole blood count	+	- Every 2-4 weeks during the first months - Every 3 months thereafter - If there is an abnormality in the blood count, the tests should be repeated more frequently. - Follow-up tests should be carried out immediately before the second dose
Liver enzymes	+	- Every 2-4 weeks during the first months - Every 3 months thereafter
Kidney functions	+	- Every 2-3 months
Beta HCG	+	- At baseline and whenever necessary
Hepatitis B serology	+	
HIV and Hepatitis C serology	+	- Anamnesis, clinical findings and if other laboratory tests indicate
PA lung x-ray	+	- In those with pulmonary disease
Type III procollagen amino-terminal propeptide (PIIINP)	+	- Should be measured every 6 months and if the values are high compared to baseline, the test should be repeated within a few weeks.
Liver USG/ fibroscan/transient elastography	+	- To be repeated every 3 years if kPa <7.5 - To be repeated every year if kPa is between 7.5 and 9.5 and the patient should be referred to gastroenterology - Liver biopsy or other specific investigations are to be carried out if kPa >9.5
Liver biopsy	- If PIIINP and TE values are high	

MTX-related liver damage is not solely associated with the drug but also with the presence of comorbidities such as obesity, diabetes and metabolic syndrome[21]. Although liver biopsy is the gold standard for the assessment of liver damage, today non-invasive methods are being preferred to monitor liver damage due to the risks of a biopsy[22].

Serum procollagen III amino-terminal peptide (PIIINP) levels show parallelism with hepatic fibrogenic activity and reduce the need for a biopsy[22,23]. If the liver enzymes and PIIINP values measured prior to a MTX therapy are high, a transient elastography may be performed or a different treatment may be chosen. If the ALT and PIIINP values measured after starting the treatment are high compared to the baseline (ALT increasing 1.5 times or PIIINP 3 times), further tests such as TE and/or liver biopsy should be carried out[24].

In patients on a MTX therapy, the initial TE should be performed within the first 6 months and if kPa <7.5, the test should be repeated every 3 years and if kPa is between 7.5 and 9.5, every year; and if kPa >9.5, then a liver biopsy or other specific investigations should be performed[21].

Side effects/safety

Side effects observed during a MTX therapy are shown in Table 3.

Table 3. Side effects observed during a methotrexate therapy

Common side effects
- Gastrointestinal system problems (nausea, abdominal discomfort, loose feces)
- Stomatitis or sore mouth
- Liver dysfunction, elevated transaminase
- Macular punctate rashes
- Central nervous system symptoms (headache, weakness, concentration disorders)
- Alopecia
- Fever
- Haematologic changes (macrocytosis, bone marrow suppression)
Serious side effects
- Hepatotoxicity (hepatic steatosis, fibrosis, cirrhosis)
- Pulmonary changes (interstitial pneumonitis, alveolitis)
- Infection
- Bone marrow suppression
- Lymphoproliferative diseases
- Nephrotoxicity

Contraindications

Absolute and relative conditions restricting MTX use are shown in Table 4.

Table 4. Conditions restricting methotrexate use

Absolute contraindications
- Males and females intending to have children
- Pregnancy, lactation
- Insufficient contraception
- Hypersensitivity to the drug (e.g. pulmonary toxicity)
- Severe liver disease (alcoholic or non-alcoholic)
- Renal failure
- A history of tuberculosis or other serious infections
- Immunodeficiency syndromes
- Active peptic ulcer
- Haematologic changes (leukocytopenia, thrombocytopenia, anemia)
Relative contraindications
- Kidney dysfunction
- Liver dysfunction
- A history of hepatitis
- Congestive heart failure
- Diabetes mellitus
- Patient non-compliance
- Ulcerative colitis
- Diarrhoea
- Gastritis

Drug interaction

Many drugs affect the metabolism of MTX causing it to reach toxic levels. Drug interactions with MTX are shown in Table 5. Although alcohol consumption is not contraindicated in patients using MTX, women may be allowed to have 1 and men 1-2 standard alcoholic drinks daily. Contrary to patients with type II diabetes and obesity, alcohol is not associated with increased liver fibrosis in patients with psoriasis, but excessive alcohol consumption increases the risk of hepatotoxicity[8].

Table 5. Drugs interacting with methotrexate

Those reducing renal elimination of methotrexate	- Cyclosporine - Salicylates - Sulfonamides - Probenecid - Penicillin - Colchicine - Cycloxygenase inhibitors
Those increasing bone marrow and gastrointestinal toxicity	- Ethanol - Cotrimoxazole - Pyrimethamine - Chloramphenicol - Sulphonamides - Cycloxygenase inhibitors - Cytostatic agents
Drugs that separate methotrexate from plasma proteins to which it binds	- Cycloxygenase inhibitors - Probenecid - Barbiturates - Phenytoin - Retinoids - Sulphonamides - Sulphonylureas - Tetracyclines - Co-trimaxazole - Chloramphenicol
Those enhancing intracellular accumulation of methotrexate	- Dipyridamole
Hepatotoxicity	- Retinoids - Ethanol - Leflunomide

Special cases

Paediatric use

The recommended dose of MTX to be used in children is 0.2-0.5 mg/kg/week. In non-urgent cases, it is tested with a dose of 1.25-5 mg and its early toxicity is monitored through laboratory tests a week later. After making conservative dose increases (1.25-5 mg/week) until obtaining a response to the treatment, the dose is then decreased gradually to a minimum effective dose[25].

Effects on pregnancy and male fertility

MTX is a miscarriage-inducing and teratogenic agent (pregnancy category X). Contraception should be recommended in MTX-using women and men until 3 months after the cessation of the drug[1].

Vaccination

Live vaccines are not recommended during a MTX therapy. Annual influenza vaccine may be administered, but its efficacy may be less. Hepatitis B and A vaccines may be administered before starting the therapy[24].

Overdose and acute toxicity

The risk factors for haematologic toxicity include renal dysfunction, advanced age, lack of folate intake, drug interactions and treatment errors. A rise in the average volume of erythrocytes is a sign of haematologic toxicity due to folate deficiency, which necessitates suspension of the methatrexate therapy. In case thrombocytopenia,

leukopenia or anaemia develops, the dose will be decreased, or depending on the severity, the therapy may be ended; if these side effects are clinically apparent, a rescue treatment with folinic acid needs to be initiated[8]. Folinic acid (calcium leucovorin) 20 mg (10 mg/m^2) should be given via intravenous or intramuscular route and the subsequent doses (parenteral or oral) in 6-hour intervals in a way the patient can tolerate[26].

SARS-COV-2 pandemic

Although methatrexate is immunosuppressive in low doses, it has not been shown to increase the risk of contracting the SARS-CoV-2 infection or to negatively affect the course of COVID-19. A decision to start or continue methatrexate during the pandemic should be made after telling the patient about its potential benefits and harms. If it must be used, high doses should be avoided[27].

SUGGESTIONS

- Methatrexate is agreed to be the gold standard for the systemic treatment of psoriasis.
- It is effective in many forms and in psoriatic arthritis.
- It can be used orally in divided doses or subcutaneously with a pre-filled syringe.
- The treatment may be started in normal doses, or in high-risk patients (in the presence of drug interaction, diabetes, renal dysfunction or comorbidities) a lower dose may be used first, and after evaluating the laboratory tests 7 days later, the treatment dose may be decided on.
- Its effectiveness is lower than biological agents.
- Addition of folic acid to the treatment reduces toxicity.

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