Methotrexate (MTX)

Preliminary note

During the final review stage, further need for updating of this chapter was identified and will be the focus of the next version of this guideline. The comments addressed in particular liver fibrosis management and the need for chest x-ray before the treatment initiation.

Instructions for use

MTX should be preferentially given subcutaneously once weekly for increased safety (oral intake has higher risk for overdosing as patients are more likely to take tablets daily instead of once weekly) and improved bioavailability (MTX is a prodrug that is polyglutaminated into its active in vivo moiety; polyglutamination is linked to efficacy) [1]. The recommended initial and maintenance dose is usually 15 mg MTX once weekly. In case of insufficient response, the dose can be increased up to 20 mg MTX once weekly. A further increase up to 25 mg MTX is only beneficial for a small subgroup of patients, no further dose-increase is recommended [2]. S.c. dosing is recommended in patients with suboptimal response to oral treatment and may be considered as the starting route of administration in high need patients.

Table 1: Instructions for use (MTX)

Pre-treatment

100 % Agreement [1]

- History and clinical examination
- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI/Skindex-29 or -17)
- Laboratory controls (see **Table 2**)
- Chest X-ray
- Reliable contraception in women of child-bearing age (starting after menstruation), and also in men
- If abnormalities in liver screening are found, refer patient to specialist for further evaluation

During treatment

- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI/Skindex-29 or -17)
- Check concomitant medication
- Clinical examination
- Laboratory controls (see **Table 2**)
- Reliable contraception in women of child-bearing age, and also in men
- 5 mg folic acid once weekly 24 hours after MTX
- Advise alcohol abstinence

Post-treatment

- For information on the need for contraception for female or male users beyond the period of MTX use, please refer to the chapter 'Wish for child/pregnancy' and the product information.

[1] due to personal-financial conflict of interest 2 abstentions

Recommendations for lab controls

Table 2: Recommended laboratory controls (MTX)

	Period in weeks/months			
Parameter*	Pre-treatment	Within two weeks	During first two months, 1x every 4 weeks	**Thereafter, every 3 months**
Blood count	x	x	x	x
Liver enzymes **	x		x	x
Serum creatinine	x		x	x
Urine status	x			
Pregnancy test (urine or blood)	x			
HBV/HCV	x			
HIV	x			
Serum albumin***	x		x	x

	Period in weeks/months			
Parameter*	Pre-treatment	Within two weeks	During first two months, 1x every 4 weeks	**Thereafter, every 3 months**
PIIINP where available	x		Every 3 months****	
Not all tests may be necessary for all patients. Patient history, risk exposure and patient characteristics have to be taken into account. Further specific testing may be required according to clinical signs, risk, and exposure.				

* If blood leucocytes < 3.0, neutrophils < 1.0, thrombocytes < 100, , decrease the dose or discontinue the medication

** liver enzymes > 2-3x baseline values, initiate further diagnostics (including repeated testing/involve hepatologist) and consider decreasing the dose or discontinuing the medication

*** In selected cases (e. g., in cases with suspected hypoalbuminaemia or in patients using other drugs with high binding affinity for serum albumin)

****In case of abnormal PIIINP during MTX treatment a hepatologist should be consulted.

The recommendations are based on clinical experience. No evidence is available.

Adverse drug reactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

The two most important ADR associated with MTX therapy are myelosuppression and hepatotoxicity. Alcohol consumption, obesity, hepatitis, and diabetes mellitus increase the risk of hepatotoxicity.

In fact, however, most causes of death due to MTX are the result of bone marrow suppression. Informing patients about the early symptoms of pancytopenia (dry cough, nausea, fever, dyspnoea, cyanosis, stomatitis/oral symptoms, and bleeding) may aid early detection.

Hypoalbuminaemia and reduced renal function increase the risk of ADR. Special care should be taken when treating geriatric patients, in whom doses should usually be lower and kidney function monitored regularly.

Overview of important side effects

Very frequent	Nausea, malaise, hair loss
Frequent	Elevated transaminases, bone marrow suppression, gastrointestinal ulcers
Occasional	Fever, chills, depression, infections
Rare	Nephrotoxicity, liver fibrosis, and cirrhosis
Very rare	Interstitial pneumonia, alveolitis

Special consideration during treatment

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

In case of gastrointestinal complaints during MTX therapy consuming coffee and/or dark chocolate may be helpful in up to 30% of patients [3].

Elderly patients

Special care should be taken when treating geriatric patients, in whom doses should usually be lower and kidney function monitored regularly.

Important contraindications

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

Absolute contraindications

- Severe infections
- Severe liver disease
- Renal failure
- Pregnancy / breastfeeding
- Alcohol abuse
- Bone marrow dysfunction/haematologic changes
- Immunodeficiency
- Acute peptic ulcer
- Significantly reduced lung function

Relative contraindications

- Kidney or liver disorders
- Old age
- Ulcerative colitis
- History of hepatitis

- Lack of compliance
- Active desire to become pregnant (see pregnancy chapter)
- Gastritis
- Obesity (BMI>30)
- Diabetes mellitus
- Previous malignancies (see also malignancy chapter)

Drug interactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

A number of drugs, including salicylates, sulphonamides, diphenylhydantoin, and some antibiotics (i. e. penicillin, tetracyclines, chloramphenicol, trimethoprime), may decrease binding of MTX to serum albumin, thus raising the risk of MTX toxicity. Tubular secretion is inhibited by probenecid. Special care should be paid to patients who use azathioprine or retinoids simultaneously. Some NSAID may increase MTX levels and, consequently, MTX toxicity, especially when MTX is administered at high doses. As a result, it is recommended that NSAID be administered at different times of day than MTX. The question of whether folic acid reduces the efficacy of MTX remains controversial. There is some evidence that the combination of MTX and folic acid may reduce adverse reactions without affecting efficacy [4-6].

Table 3: List of most important drugs with potential interactions

Drug	Type of interaction
Colchicines, CsA, NSAID, penicillin, probenecid, salicylates, sulfonamides	Decreased renal elimination of MTX
Chloramphenicol, co-trimoxazole, cytostatic agents, ethanol, NSAID, pyrimethamine, sulfonamides	Increased risk of bone marrow and gastrointestinal toxicity
Barbiturates, co-trimoxazole, phenytoin, probenecid, NSAID, sulfonamides	Interaction with plasma protein binding
Ethanol, leflunomide, retinoids, tetracyclines	Increased hepatotoxicity

Overdose/measures in case of overdose

In MTX overdose, clinical manifestations of acute toxicity include myelosuppression, mucosal ulceration (particularly of the oral mucosa), and, rarely, cutaneous necrolysis. Relative overdose is usually precipitated by factors that interfere with MTX renal excretion or by drug interactions. Folinic

acid is a fully reduced folate coenzyme that, after intracellular metabolism, can function in nucleic acid synthesis, thus bypassing the action of MTX. As the interval between MTX administration and the initiation of folinic acid increases, the efficacy of folinic acid as an antidote to haematological toxicity decreases.

Administer folinic acid (Calcium Leucovorin) immediately at 20 mg (or 10 mg/m²) intravenously or intramuscularly. Subsequent doses should be given at six-hour intervals either parenterally or orally.

References

1. van de Meeberg MM, Hebing RCF, Nurmohamed MT, et al. A meta-analysis of methotrexate polyglutamates in relation to efficacy and toxicity of methotrexate in inflammatory arthritis, colitis and dermatitis. *British journal of clinical pharmacology*. Jan 2023;89(1):61-79. doi:10.1111/bcp.15579
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3. Malaviya AN. Methotrexate intolerance in the treatment of rheumatoid arthritis (RA): effect of adding caffeine to the management regimen. *Clinical rheumatology*. Feb 2017;36(2):279-285. doi:10.1007/s10067-016-3398-3
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6. 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 and rheumatism*. Jul 2001;44(7):1515-24.