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Role of Methotrexate in Psoriasis

Soheir Ghonemy, Hassan Mohamed Hassan Elgawish, Norhan Hassan

Dermatology, Venereology, and andrology Department, Faculty of Medicine, Zagazig University, Egypt

***Corresponding author:** Hassan Mohamed Hassan Elgawish

Email: Hassanmohamed536@gmail.com.

Abstract:

Psoriasis is a chronic immune-mediated inflammatory disease requiring effective systemic therapy in moderate to severe cases. Methotrexate (MTX), a folic acid antagonist, remains a cornerstone treatment due to its immunosuppressive, anti-inflammatory, and anti-proliferative effects. Despite the emergence of biologic agents, MTX continues to be widely used because of its cost-effectiveness and established clinical efficacy. This mini-review highlights the mechanism of action, pharmacokinetics, clinical indications, efficacy, safety profile, and monitoring of methotrexate in psoriasis. MTX acts by inhibiting dihydrofolate reductase and increasing adenosine levels, leading to suppression of keratinocyte proliferation and inflammatory cytokines such as TNF-α and interleukins. It demonstrates moderate efficacy, with a significant proportion of patients achieving clinical improvement. However, its use is limited by potential adverse effects, including hepatotoxicity, myelosuppression, and nephrotoxicity, necessitating careful patient selection and regular monitoring. MTX remains a reliable and cost-effective option for long-term management of psoriasis when used appropriately with adequate safety monitoring.

Keywords: Methotrexate; Psoriasis; Systemic therapy; Immunosuppression; Hepatotoxicity; PASI; Dermatology

Introduction:

Methotrexate is a well-known chemotherapeutic agent, widely used alone or in a combination with other drugs in the treatment of cancer. Methotrexate, a folic acid antagonist (4-amino-10-methyl folic acid), has antiproliferative, anti-inflammatory, and immunosuppressive actions **(1).**

Methotrexate continues to be the mainstay systemic treatment for moderate to severe psoriasis that is not responding to topical therapy because of its low cost, great efficacy, and quick results. A quick and remarkable reaction could be observed after reaching its cumulative dosage of 1.0–1.5 grams **(2).**

Mechanism of action:

Methotrexate is a folate antagonist that exerts anti-proliferative, anti- inflammatory and immuno-modulatory effects, making it effective in psoriasis therapy **(3).**

Methotrexate as an anti-proliferative agent irreversibly inhibits di-hydrofolate reductase enzyme blocking tetra-hydrofolate synthesis and preventing purine and pyrimidine de novo synthesis, thus suppressing mitosis and disrupting cell replication. This anti-proliferative effect is mostly appreciated in high-dose regimens for cancer **(4).**

Methotrexate as an anti-inflammatory and immune-modulator has a potent activity through accumulated intracellular and extracellular 5-aminoimidazole-4- carboxamide-ribonucleotide (AICAR) via inhibiting (AICAR) trans-formylase. An MTX-mediated excess of AICAR promotes the AMP and adenosine increase and subsequent release of these adenine derivatives outside the cell. To a lesser extent, MTX's anti-inflammatory activity is attributed to inhibiting rapidly dividing inflammatory cell proliferation. Moreover, MTX decreases pro-inflammatory cytokines and adhesion molecule expression, such as TNF-α, IL1ß, IL6, IL8, E- selectin, VCAM-1, and ICAM1 **(5).**

Administration:

Methotrexate is administered via oral, intramuscular (IM), or subcutaneous (SC) routes at a low-dose regimen (25–30mg/week), 0.2–0.4mg/kg/week, in a single dose for dermatological indications **(1).**

A split-dose oral regimen (three doses 12-h apart) is reserved for patients suffering gastrointestinal intolerance. SC route offers better bioavailability and gastrointestinal tolerability for high doses. Upon initiation, the full recommended dose (15mg/week) is commonly given **(6).**

A test dose (5mg/week) followed 7 days later with laboratory monitoring and dose up-titration is recommended for patients with increased risk of hematologic toxicity Every 2–4weeks, MTX dose can be increased at a rate of 2.5–5mg/week **(7).**

Patients should be maintained at the lowest effective dose. On achieving 1–2 months of full remission, MTX is gradually withdrawn with a reduction of 2.5mg/weekevery1–2 weeks **(8).**

Intralesional MTX showed effectiveness in treating many conditions. It represents a relatively non-invasive lesion directed alternative with minimal side effects including erythema and pain. Doses ranged from 2.5mg/session to 62.5mg/session, with 1- to 4-week intervals. Regular baseline and follow-up complete blood count (CBC) and renal function tests (RFTs) are recommended as pancytopenia complicated renal cases **(9).**

Pharmakokinetic data of methotrexate:

The different methods of administration affect MTX's pharmacokinetic properties. Following injection, MTX is fully and instantly absorbed, leading to increased blood serum concentrations. Many researchers consider the S.C administration route of MTX to be the optimum one. This factor is extremely important for planning the therapy of patients suffering from severe diseases. After oral administration and absorption, the drug's bioavailability is limited because it becomes partially inactivated in the liver and gastrointestinal system. About 90% of MTX is excreted in its un-altered form and the drug's half-life during the terminal elimination phase varies from 3 to 10 hours **(10).**

Dermatological indications of methotrexate :

Approved indications:

Psoriasis:

Methotrexate is European Medicines Agency (EMA) and FDA-approved for moderate/severe plaque psoriasis. Methotrexate is a suitable option for individuals with moderate-to-severe psoriasis who do not respond or are intolerant to topical treatments, oral retinoids (Acitretin), cyclosporine, narrow-band UVB, or psoralen/UVA phototherapy. Additionally, it may be used in conjunction with biological therapies when the target therapy's response is not met **(11).**

A meta-analysis found that approximately 45% of patients reach PASI75 (75% improvement in Psoriasis Area and Severity Index) after 12–16 weeks of MTX therapy, compared to only ~4% of patients on placebo. Clinical response tends to improve with continued therapy beyond 3 months: for many patients, PASI scores continue to decline at 6 months and beyond, especially with dose escalation as needed **(12).**

Methotrexate not only clears skin lesions but can also alleviate psoriatic nail involvement and has a beneficial effect on arthritis symptoms in patients with psoriatic arthritis **(13).**

Methotrexate often leads to improvement in pruritus and discomfort, and patients report better quality of life once their psoriasis is under control. In fact, recent studies show MTX treatment significantly lowers patients' Dermatology Life Quality Index (DLQI) scores in parallel with PASI improvements, indicating restoration of daily function and self-esteem as the skin lesions resolve (**14).**

In terms of comparative outcomes, MTX is often the benchmark to which newer therapies are compared. It generally produces partial disease control in a majority of patients, but complete remission is less common. Thus, for patients with inadequate response, MTX outcomes can be enhanced by combination with other therapies (e.g.

MTX plus phototherapy, or MTX to boost biologic therapy efficacy) **(15).**

Methotrexate's efficacy is generally lower than that of newer biologic therapies. Biologics often achieve PASI75 in 70–90% of patients, whereas MTX achieves this in roughly 40–50%. It is often used continuously or intermittently for long-term disease management, and many patients can maintain satisfactory control of psoriasis on MTX monotherapy for years if monitoring is carefully managed **(6).**

Off-Label indications:

1) Atopic dermatitis:

Methotrexate has been used off-label for the treatment of moderate-to-severe atopic dermatitis, particularly in adults who are refractory to topical therapy or who cannot tolerate other systemic agents **(16).**

2) Chronic urticaria:

Methotrexate is a therapeutic alternative option for chronic recalcitrant urticaria because of its anti-inflammatory properties. Also, methotrexate has a role as useful steroid-sparing agent in recalcitrant chronic urticaria **(17).**

3) Systemic lupus erythematosus:

According to European guidelines, individuals with cutaneous lupus erythematosus who are not responding to anti-malarial medications should be treated with MTX as a second-line treatment ***(18).***

4) Bullous dermatoses:

For patients with serious long-term side effects or comorbidities that make oral corticosteroids or other immunosuppressive medications inappropriate, MTX may be utilised as an alternate therapy for bullous dermatoses **(19).**

5) Mycosis fungoides:

Mycosis fungoides has been treated with MTX for many years. Although MTX's exact mode of action in mycosis fungoides is still unknown, it appears that its cytostatic actions play a major role, followed by its anti-inflammatory and immunomodulatory activities **(20).**

6) Pityriasis rubra pilaris:

Methotrexate as an anti-proliferative and anti-inflammatory drug provides compelling evidence for its utility in treating pityriasis rubra pilaris. **(21).**

7) Other indications of MTX in dermatology:

Alopecia areata, universal or total; vulvovaginal erosive lichen planus; pityriasis lichenoides; reticulohistiocytosis; vitiligo; Behcet's disease; and Reiter's syndrome are among the dermatoses that respond to off-label MTX therapy **(22).**

Adverse effects & toxicity of methotrexate:

The gastrointestinal adverse effects such as vomiting, nausea, diarrhea, anorexia, and abdominal distress are the most common side effects associated with MTX therapy **(23).**

The most serious possible adverse effect is severe myelosuppression, which causes the majority of the relatively infrequent fatalities caused by MTX (**24).** Other side effects include, liver fibrosis, pneumonitis, homeopathy, kidney dysfunction and baldness. Many patients stop taking MTX because of un-bearable toxicity **(25).**

Liver toxicity of methotrexate:

Research in 2010 discovered that increased liver enzymes, notably alanine aminotransferase (ALT) and aspartate aminotransferase (AST), were associated with MTX **(26).** Although the exact mechanism by which MTX causes hepatotoxicity is unknown, it is believed to be related to the drug's cellular pathways **(27).**

Among the many theories is the idea that MTX stimulates the liver's Ito cells **(28).** Another theory is that folate,

a component needed for the synthesis of deoxyribonucleic acid (DNA), is chronically lost as a result of long- term intracellular storage of MTX, especially MTX metabolites (γ-polyglutamates) **(29).**

Hepatotoxicity can be exacerbated by certain risk factors, including a family history of hereditary liver failure, a history of alcohol intake, diabetes, a lack of folate supplementation, exposure to elevated doses of hepatotoxic chemical agents, and dyslipidemia **(30).**

Kidney toxicity of methotrexate:

Renal tubules excrete more than 90% of MTX, so any kidney problem may cause MTX to be removed poorly. Prolonged or increased plasma levels of MTX are a consequence and may result in inefficient leucovorin, folinic acid, rescue and a significant increase in MTX-related toxicities**.** The precipitation of MTX and its metabolites in the renal tubules was assumed to be the cause of renal impairment, although this is challenged by the finding that MTX may have a direct toxic influence on the kidney tubules. According to 2006 research, MTX causes renal failure because of MTX-induced kidney failure and renal tubular enlargement **(31).**

To predict the development of kidney failure, regular monitoring of plasma and serum creatinine MTX levels is essential as soon as MTX treatment begins. Recent research has shown that biomarkers such as kidney injury molecule-1 (KIM-1) and cystatin C can be used to diagnose kidney damage **(32).** One symptomatic treatment to avoid MTX-related nephritis and the precipitation of MTX and its metabolites is the alkalinization of the urine **(33).**

Methotrexate-induced epidermal necrosis (MEN):

Skin affection presents as painful mucocutaneous erosions and ulcers commonly encountered in folds (inter-gluteal, inguinal, and inframammary), lower extremities, and preexisting skin lesions. Ulcers frequently have erythematous rim and may progress to skin detachment. MEN usually heralds impending life-threatening pancytopenia; nevertheless, it might occur with normal CBC **(34).**

Methotrexate antagonist:

Folate supplementation is recommended to prevent MTX-associated hematologic, gastrointestinal, and hepatotoxicity. This practice is a weekly 5mg dose 24h post-MTX **(1).**

Leucovorin, folinic acid, is the antidote for MTX. In the setting of acute toxicity, intravenous leucovorin is preferred for rapid onset of action and avoidance of vomiting-related reduced oral bioavailability. Typically, leucovorin is given based on MTX plasma concentration and the time elapsed since last MTX dose. Leucovorin is given at a dose of 10–15mg/m^2/6h with the last dose given 6h after MTX plasma concentration reaches <0.1μM **(35).**

Monitoring:

Before initiating MTX therapy, patients should undergo clinical and laboratory evaluation to identify risks and contraindications.

Clinical assessment: full history and physical examination to identify risk factors for hematologic toxicity and hepatotoxicity.

- Bone marrow function: (CBC) with platelet count.
- Liver assessment: baseline hepatitis B and C serology, liver function tests (ALT, AST, γGT, ALP, bilirubin, albumin). The risk of hepatic fibrosis with low-dose MTX is now considered overestimated, and monitoring recommendations vary between guidelines.
- Renal function: includes measurement of serum creatinine and blood urea nitrogen (BUN), along with estimation of glomerular filtration rate (eGFR)
- Infection screening should include testing for tuberculosis using a tuberculin skin test or interferon-gamma release assays (QuantiFERON-TB Gold or T- Spot). A chest X-ray and pulmonology consultation are required if TB testing is positive. Additional screening includes HIV testing and varicella-zoster virus serology in patients without a history of infection or vaccination.

- Pregnancy testing: required prior to MTX initiation **(8).**

Follow-up monitoring frequency is different across guidelines, it should be adjusted according to the dosage modifications, symptoms, and previous laboratory findings. The progressive change in CBC and LFTs, not just their absolute numbers, should prompt repeating laboratory follow-up in 2–4weeks **(36).**

Contraindications to methotrexate:

Absolute contraindications to methotrexate include pregnancy or planning pregnancy. Lactation is also considered an absolute contraindication **(1)**. Severe renal dysfunction and patients with significant bone marrow disease, should not receive methotrexate **(6)**. Other absolute contraindications include hypersensitivity to methotrexate, active peptic ulcer disease, alcoholic liver disease, non-alcoholic chronic liver disease, severe hepatic dysfunction or cirrhosis, immunodeficiency syndromes, active infections such as tuberculosis or untreated HIV and concurrent trimethoprim therapy **(1)**.

Relative contraindications include mild to moderate renal impairment or liver dysfunction. A history of hepatitis B or C is considered a relative contraindication. Excessive alcohol intake is a relative contraindication. Other relative contraindications include gastritis, recent live vaccination within four weeks prior to methotrexate initiation, impaired lung function, male partners of women planning conception**,** obesity (BMI >30), and diabetes mellitus **(1).**

Drug–drug interaction:

It is essential to monitor drugs co-administered with MTX. Drugs may increase MTX toxicity risk by increasing its plasma concentration, reducing renal elimination, and having synergistic toxicity or anti-folate activity **(6).**

Drugs commonly implicated in acute MTX toxicity are trimethoprim– sulfamethoxazole and nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs are commonly prescribed to control pain for arthritis; thus, drug history is important before prescribing MTX**.** Concomitant MTX with standard doses of NSAIDs or aspirin for inflammatory arthritis was deemed safe based one evidence from rheumatoid arthritis patients **(37).** Safer alternatives to the implicated NSAIDs include ketoprofen, furbiprofen, piroxicam, and meloxicam, which do not elevate MTX level **(6).**

Cephalosporins increase MTX renal clearance, thereby reducing its accumulation and potential toxicity making them a safer antibiotic alternative **(38).**

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