

Methotrexate

Methotrexate (MTX) is a cornerstone therapeutic agent in the management of severe dermatologic conditions, particularly psoriasis, and has been in clinical use since the early 1960s. Initially developed as a chemotherapeutic agent for cancer treatment, MTX was serendipitously discovered to have beneficial effects in treating psoriasis, a chronic inflammatory skin disorder. While it was initially utilized at higher doses for malignancies, in dermatology, MTX is administered at significantly lower doses for the management of a variety of skin conditions, including rheumatoid arthritis and severe forms of psoriatic arthritis.

Mechanism of Action

MTX is an antimetabolite that exerts its effects by inhibiting dihydrofolate reductase, an enzyme crucial for the synthesis of purines and thymidylate, which are essential for DNA synthesis. By impeding these processes, MTX suppresses rapidly proliferating cells, such as those seen in psoriasis. This mechanism results in immunosuppression and anti-inflammatory effects, which are particularly beneficial in managing the hyperproliferative skin conditions characteristic of severe psoriasis. MTX also reduces the infiltration of inflammatory cells into the skin and prevents the activation of pro-inflammatory cytokines, further helping to control the disease.

Indications for Use

Methotrexate is most effective in the management of moderate to severe psoriasis, including difficult-to-treat forms such as erythrodermic psoriasis, acute pustular psoriasis, and psoriasis affecting the palms and soles. It is particularly valuable in older adults and those with physically disabling psoriasis that does not respond to topical therapies or phototherapy. MTX is also a key therapeutic option in the treatment of psoriatic arthritis, where it helps to control both the skin and joint manifestations of the disease.

Patients receiving MTX often experience significant or complete clearing of their psoriasis, with sustained remission lasting from several weeks to over a year after discontinuation of therapy. However, while effective for many, MTX does not provide a permanent cure for psoriasis, and relapse is common once therapy is stopped.

Dosage and Administration

Methotrexate is typically administered once weekly, as the pharmacokinetics of the drug favor a prolonged effect with this dosing schedule. The initial dose generally starts at 7.5 to 10 mg per week, which can be titrated upwards based on clinical response and tolerability, with a common

maintenance dose of 15 to 25 mg weekly. It usually takes 2 to 3 weeks for noticeable improvements to appear. MTX can be taken orally in tablet form, but in cases of gastrointestinal intolerance, subcutaneous or intramuscular injections may be used.

Contraindications and Precautions

Despite its efficacy, MTX is not suitable for all patients due to its potential for severe side effects and interactions with other medications. Contraindications include:

- **Pregnancy:** MTX is teratogenic, and exposure during pregnancy can cause birth defects. Women are advised to stop MTX at least 3 months before conception. This recommendation also applies to men, as MTX can affect sperm function.
- **Blood disorders:** Individuals with anemia, leukopenia, or thrombocytopenia are at increased risk of further hematologic toxicity.
- **Liver disease:** MTX is contraindicated in patients with cirrhosis, active hepatitis, or significant liver abnormalities due to its potential for hepatotoxicity.
- **Renal impairment:** MTX is eliminated primarily through the kidneys, so caution is needed in patients with renal dysfunction.
- **Active infections:** Because of its immunosuppressive effects, MTX should not be used in patients with ongoing infections, including HIV/AIDS.
- **Excessive alcohol consumption:** Chronic alcohol use increases the risk of liver toxicity when combined with MTX.

Side Effects

Although MTX is generally well-tolerated, it is associated with a range of adverse effects, some of which can be serious. Common side effects include:

- **Gastrointestinal symptoms:** These include nausea, vomiting, and mucosal ulcers, which are often dose-dependent and can be mitigated by dividing the weekly dose or taking MTX with food.
- **Hematologic toxicity:** MTX can suppress bone marrow function, leading to leukopenia, anemia, and thrombocytopenia. Regular blood tests are essential to monitor these potential complications.
- **Liver toxicity:** Cirrhosis or hepatic fibrosis may develop with long-term use. A liver biopsy is often recommended after cumulative doses of MTX exceed 1.5 to 2 grams to assess liver health.
- **Pulmonary toxicity:** Rarely, MTX can induce interstitial lung disease, presenting as cough, dyspnea, and fever.
- **Alopecia:** Hair loss can occur, although it is generally mild and reversible upon discontinuation of the drug.

- **Renal toxicity:** MTX can cause renal impairment, particularly when used in high doses or in patients with pre-existing kidney dysfunction.

Drug Interactions

MTX's side effects can be exacerbated by interactions with certain drugs, notably:

- **Nonsteroidal anti-inflammatory drugs (NSAIDs),** which can increase MTX toxicity by reducing its renal clearance.
- **Trimethoprim-sulfamethoxazole (Bactrim):** This combination can result in severe bone marrow suppression and is contraindicated.
- **Aspirin:** This can elevate MTX levels in the blood, increasing the risk of toxicity.

Combination Therapies

In patients with severe or refractory psoriasis, MTX is sometimes combined with other treatments to enhance efficacy. For example:

- **Cyclosporine:** A potent immunosuppressant, cyclosporine can be used in combination with MTX to manage difficult cases of psoriasis.
- **Phototherapy (UVB or PUVA):** UV light therapy, particularly narrow-band UVB, is often used alongside MTX to improve skin clearance, particularly in patients with erythrodermic psoriasis or extensive disease.

Conclusion

Methotrexate remains a potent and effective treatment for severe forms of psoriasis, particularly those that are extensive, disabling, or refractory to topical therapies. While it offers significant benefits in terms of disease clearance and long-term remission, its use is not without risks. Close monitoring of liver function, renal health, and blood counts is essential for patients on MTX, and careful consideration should be given to drug interactions and contraindications. In cases of severe psoriasis, MTX can be used in conjunction with other therapies, including phototherapy and cyclosporine, to maximize therapeutic efficacy. Despite its side effects, MTX continues to play a critical role in improving the quality of life for many patients with severe skin diseases.

References

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