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REVIEW ARTICLE

An Insight about Role of Methotrexate in Treatment of Psoriasis: A Review Article

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Abstract

Background: Methotrexate (MTX), which is an anti-proliferative, anti-inflammatory, and immunomodulation medication, was licensed by the United States Food and Drug Administration (FDA) in 1971. Methotrexate is still used as standard systemic therapy for moderate to severe psoriasis that has not responded to topical therapy due to its low cost, great efficacy, and quick outcomes. Once the cumulative dose (1.0-1.5 gm.) is reached, a fast and dramatic reaction may be observed. We aimed to present an Insight into the Role of Methotrexate in the Treatment of psoriasis.

Conclusion: While methotrexate was initially used to treat cancer, it has now shown promise in treating a variety of non-neoplastic proliferative skin conditions, such as psoriasis. A unique perspective on the findings and new information regarding MTX over time is provided by the guidelines for its usage in psoriasis patients. Traditional systemic treatment for moderate to severe psoriasis has mostly relied on it for a long time. The drug has been licensed by the USDA for the treatment of psoriasis since 1972, and the most current recommendations state that it is still the main treatment for moderate to severe psoriasis.

Keywords: Methotrexate, Management, Psoriasis

INTRODUCTION

A systemic inflammatory disorder characterized by a proliferative skin issue, psoriasis lasts for a long time and affects many people. Environmental factors are just as important as genetic ones [1]. The sacral region, scalp, and knees are typical sites for the scaly, strongly delineated, irritating plaques that characterize this prevalent condition [2]. Psoriasis puts a heavy strain on healthcare systems and has a detrimental effect on patients' quality of life because it is a chronic condition that requires long-term treatment [3]. Two to three percent of the global population suffers from psoriasis [4]. The peak age for both men and women is between 20 and 30 years old, with a second, less severe peak between 50 and 60 years old [5].

Although the exact cause of psoriasis is unknown, immunological, environmental, and genetic variables may interact to cause the skin disorder. While autoimmune diseases may be the cause of psoriasis, no specific autoantigen has been identified as the cause until now. Both internal and external factors, including minor trauma, sunburn, infections, systemic medications, and stress, can potentially cause psoriasis [6].

Psoriasis is clinically diagnosed by taking a patient's history and analyzing the results of a physical examination. Lesions are red, raised plaques with visible borders and scales covering them. A patient may report itching, burning, sensitivity, discomfort, bleeding, or a mix of these and other symptoms [7].

To measure the severity of psoriasis, many different scoring systems have been suggested. An excellent way to measure the severity of psoriasis is with the Psoriasis region and Severity Index (PASI), which takes into account both the size of the affected region and the severity of the lesions [8].

The skin symptoms of psoriasis can be alleviated with a variety of topical and systemic treatments. Disease severity, pertinent comorbidities, patient choice (including convenience and cost), effectiveness, and assessment of individual patient response are all factors that go into treatment method selection [9]. Topical therapy such as corticosteroids, retinoids, and keratolytic drugs (such as urea or salicylic acid) that dissolve scale, tar, and emollient

moisturizers can be beneficial in treating mild diseases. Considerations such as the plaque's size, thickness, and location on the body, as well as whether the treatment is being initiated or maintained, dictate the choice of topical medication [10].

When treating the trunk or extremities, it is best to start with a mixture of betamethasone dipropionate and calcipotriol rather than just one drug. You shouldn't use this on your face or folds because it's extremely harsh. Maintenance treatment with vitamin D derivatives is suggested after disease control has been achieved. Emollients, stronger topical corticosteroids, keratolytic treatments like salicylic acid or urea, and ointment formulations are all effective against thick plaques (clinical thickness >0.75 mm) [11].

The most frequent photo-chemotherapy methods for psoriasis include targeted or excimer UVB laser (308 nm), broadband ultraviolet B (BB-UVB; 280-320 nm), and a combination of 8-methoxy psoralen and ultraviolet A (PUVA; 320-400 nm) either orally or topically prescribed. Patients who have not shown improvement after receiving topical treatments or whose BSA levels are above 10% are typically selected for the start of photochemotherapy. On the other hand, excimer lasers are reserved for secondary or treatment-resistant lesion types; first-line photo-chemotherapy is most often administered with NB-UVB due to its lower photo-damage profile [12].

Systemic Treatments

The systemic medications that are most commonly recommended are methotrexate, sulfasalazine, acitretin, and cyclosporine. Acutretin, methotrexate, and cyclosporine are systemic medicines that are used as first-line treatments. Sulfasalazine and apremilast are two options that may be considered when first-line systemic medicines fail to meet expectations, when first-line therapy is not appropriate, or when the medication leads to unwanted side effects [13].

Methotrexate and cyclosporine should be used as first-line systemic induction treatment, according to a 2018 review. Hepatic impairment (such as from heavy alcohol use or active hepatitis B or C), pregnancy, and active infections like tuberculosis are absolute contraindications to methotrexate. Methotrexate has the best safety profile of all regularly used systemic drugs and biological treatments, and it has evidence of benefit for psoriatic arthritis [14].

The US Food and Drug Administration (FDA) authorized methotrexate in 1971. It is an agent that modulates the immune system, reduces inflammation, and inhibits cell proliferation [15]. When topical treatments fail to alleviate moderate to severe psoriasis, the gold standard systemic treatment is methotrexate because of its low cost, great efficacy, and rapid results. When the whole dosage of 1.0–1.5 gm. is taken, a remarkable and quick effect may be observed [16].

Mechanism of action:

Anti-proliferative action: It blocks the enzyme dihydrofolate reductase and methylenetetrahydrofolate (MTHF) via inhibiting purine, methionine, and thymidylate synthase. As a result, it stops cells from replicating and breaks down DNA. After entering cells, MTX undergoes polyglutamation (a process that may involve a folate carrier or passive diffusion) [17]. Polyglutamates of MTX remain in cells and tissues for weeks or months, in contrast to the 5-8-hour half-life of MTX. [18].

Anti-inflammatory effects include elevated adenosine levels. Adenosine blocks the formation and synthesis of leukotrienes by neutrophils, making it a powerful endogenous anti-inflammatory mediator. In addition to its ability to limit the proliferation of antigen-stimulated T cells, adenosine also exhibits pro-apoptotic qualities by making T cells more sensitive to cell death. [17].

Immune-modulatory effect: Research has demonstrated that MTX can influence immune cell behavior and reduce tumor necrosis factor-alpha (TNFα) levels [17].

Pharmacokinetics:

Active transport in the intestines ensures complete absorption of MTX at doses below 30 mg weekly when taken orally. Saturation of transport occurs at greater doses, rendering absorption partial. The drug's bioavailability is poor because it is largely inactivated in the intestines and liver after absorption. Although it is systemic, its peak concentrations are 30 times lower in pleural and cerebral fluid compared to plasma because of the slow and difficult penetration of these fluids [19].

Filtration and active secretion remove the medication from the body almost completely (90%) in the urine. Therefore, creatinine clearance is the determining factor in MTX elimination. Oral and parenteral bioavailabilities are similar but vary greatly (25–70%). One to two hours following oral dosing and thirty to sixty minutes following intramuscular injection yield blood concentrations at their peak [20].

Pharmacological forms

Preloaded syringes containing7.5,10,15,20, or 25 mg of MTX are available for parenteral injection (subcutaneous or intramuscular). Oral dosage forms of 2.5 mg are also on the market. There are also 50-milligram vials that can be injected intramuscularly. Although they can be broken into smaller doses, it is important to be aware that MTX is hazardous and poses some disposal and handling challenges [20].

Psoriasis treatment guidelines typically call for a weekly dose of 5–15 mg, with a progressive increase to 25–30 mg as needed to control symptoms. After 8 to 12 weeks of treatment at a dose of 15 mg once weekly, you may notice a maximum effect [21].

MTX can be taken orally or injected intravenously. Due to its relative ease and inexpensive cost, the oral administration route was typically preferred. On the other hand, switching to parental injection as an administration method can improve efficacy and acceptability in cases of unacceptable adverse effects or lack of efficacy [22].

If methotrexate absorption is impaired due to gastrointestinal issues or if oral methotrexate does not work, the subcutaneous method may be the best option [23].

Patients with relative contraindications, older patients, and situations requiring clinical necessity should be given great attention while administering a low (test dose). Half the dose should be given in the first week or two of treatment in such a scenario. Here is the suggested medication: When administering the oral formulation, start with a 7.5 mg test dosage. The dosage range for the injectable medication is 5–10 mg[23].

No matter how big of an initial dose is recommended, what's more crucial is to evaluate the patient soon after therapy begins (within a week or two), regardless of the amount. It is recommended that blood testing and a clinical examination be part of this evaluation. It is reasonable to raise the dosage to a maintenance level if no anomalies are discovered in this early examination [20].

Taking folic acid supplements can lessen the risk of toxicities in the blood, mucocutaneous areas, and gastrointestinal tract, as well as the liver, but it has little effect on preventing or reducing toxicity in the lungs [21]. On days when MTX is not used, the recommended daily dosage of folic acid is 5 mg, to be given at least 24 hours after taking MTX [24].

For a long time, MTX was the go-to treatment for moderate to severe psoriasis in the following conditions: plaque psoriasis, erythrodermic psoriasis, pustular psoriasis (acute and localized), psoriatic arthritis, extensive psoriasis that didn't respond to other treatments, psoriasis that severely impacts a patient's mental or financial health, and a lack of improvement after phototherapy, PUVA, or retinoid treatments [24].

Patient assessment before treatment:

Methotrexate may not be suitable or acceptable for all patients due to risk factors such as renal impairment, substantial hemostatic abnormalities, or abnormal liver function. Before administering methotrexate to patients of either sex, it is crucial to evaluate the drug's teratogenic and mutagenic properties and provide adequate counseling [19].

1-Pre-treatment laboratory tests:

Blood tests: complete blood counts, fasting blood sugar, lipid profile, Kidney function tests: serum creatinine, serum urea. Liver function tests serum glutamine pyruvate transaminase (SGPT), serum glutamine oxalate transaminase (SGOT), alkaline phosphatase, and serum bilirubin (total and conjugated). Chest X-rays and serum electrolytes are performed at the beginning and the end of the treatment in each patient. Pregnancy test, HIV, and Hepatitis B and C [16].

2-Laboratory test during treatment:

It includes Quantitative evaluation of all blood cells and platelets every 2–4 weeks for the first several months, about once every 1–3 months thereafter, based on patient stability and leukocyte count, beginning 1–2 weeks after beginning or increasing dosage. Renal function studies: For patients with normal values: blood urea nitrogen and serum creatinine levels at 2–3-month intervals are also required. For patients at risk of decreased renal function, glomerular filtration rate should be calculated. Liver function tests: every 4 to 12 weeks. The pregnancy test is indicated in women of childbearing potential [25].

Side effects:

Nosebleeds, anorexia, stomatitis, lethargy, fever, and malaise are common mild side effects that typically occur at the same time as the medicine is taken. They are usually not severe, can be fixed, and don't usually necessitate stopping treatment. Folate supplements, intramuscular or subcutaneous injections of methotrexate, dose splitting, or taking the medication at night may reduce these side effects, according to clinical experience [25].

Blood, liver, lungs, and kidney-related adverse events constitute the bulk of MTX's negative effects. Because of its reputation as a hepatotoxic medicine, methotrexate's potential therapeutic applications may be constrained. Folate deficiency in the liver is

caused by MTX. Thus, folic acid supplementation significantly decreases hepatotoxicity.

Pathological changes in the liver following MTX: Fat infiltration with subsequent inflammation, fibrosis, and cirrhosis. A number of drugs may increase the risk of MTX-induced liver toxicity., e.g. non-steroidal anti-inflammatory drugs (NSAIDs) are also important risk factors [26].

Hematologic toxicity is most commonly associated with diminished kidney function, advancing age, insufficient folate supplementation, and medication interactions. In patients with hematologic risk factors, pancytopenia, an extremely rare side effect of low-dose weekly methotrexate, can develop at any point during treatment. Regular monitoring of total blood cell counts is essential [25].

Acute interstitial pneumonitis is the most prevalent type of pulmonary toxicity seen in patients taking MTX. Radiographs showing widespread bilateral interstitial involvement and alveolar infiltrate, along with symptoms such as non-productive cough, dyspnea at rest, fever, and overall malaise, are diagnostic of this condition. with psoriasis and psoriatic arthritis, a weekly low-dose regimen is effective, but with high-dose treatment, pulmonary fibrosis develops [27].

Although the kidneys are responsible for clearing over 90% of MTX, the toxic effects of the drug on the tubules or the precipitation of MTX and its metabolites are thought to have a role in the development of MTX-induced renal failure [28].

Methotrexate Withdrawal:

When side symptoms, intolerance, or inadequate treatment response occur, or when the cumulative dose is clinically inconsequential, methotrexate should be stopped or adjusted as needed. The recommended doses for individuals at high risk for hepatotoxicity are 1.5–2 g, and for those at low risk, it is 3.5–4 g. It is advisable to gradually lower the dose or lengthen the gap between the last doses before withdrawal or to give any alternative substitutes to prevent the rebound of symptoms when abruptly stopping MTX treatment [20].

Drug Interactions:

Multiple drugs interact with methotrexate through various mechanisms, increasing the risk of methotrexate toxicity, which in turn increases the risk of pancytopenia and death. There have been numerous published cases of fatal interactions involving methotrexate [29]. The medicine that is most commonly used that poses the greatest risk is trimethoprim-sulfamethoxazole. Both components of trimethoprim-sulfamethoxazole are involved in the mechanism by which methotrexate is potentiated. The folic acid antagonist trimethoprim and the methotrexate competitive inhibitor sulfamethoxazole are also used in this context [30].

In an imiquimod-induced animal model, MTX combined with GNPs has better anti-inflammatory effectiveness than MTX alone, showing a significant decrease in γδ T cells, CD4+ T cells, and neutrophils. In addition, both systemic and topical treatments were well-tolerated. Two weeks of topical MTX-GNPs treatment considerably reduced skin hyperplasia in an AGR129 human xenograft mouse model, outperforming topical calcipotriol-betamethasone. This treatment also caused extensive tissue remodeling, with elevated levels of extracellular matrix reorganization and decreased levels of cornification and keratinization. [31].

Treatment with MTX-GNP significantly reduced the amount of resident T cells in the grafts and the generation of interleukin-17. Although MTX and MTX-GNPs worked in different ways, they both inhibited T-cell proliferation and triggered death through the same mechanism: they both reduced cytokine production. Ultimately, MTX-GNPs effectively suppress the development of preclinical psoriasis by affecting the skin's immunological and stromal components. A new non-steroidal topical option for psoriasis treatment, MTX-GNPs outperform both standard of care and traditional MTX [32]

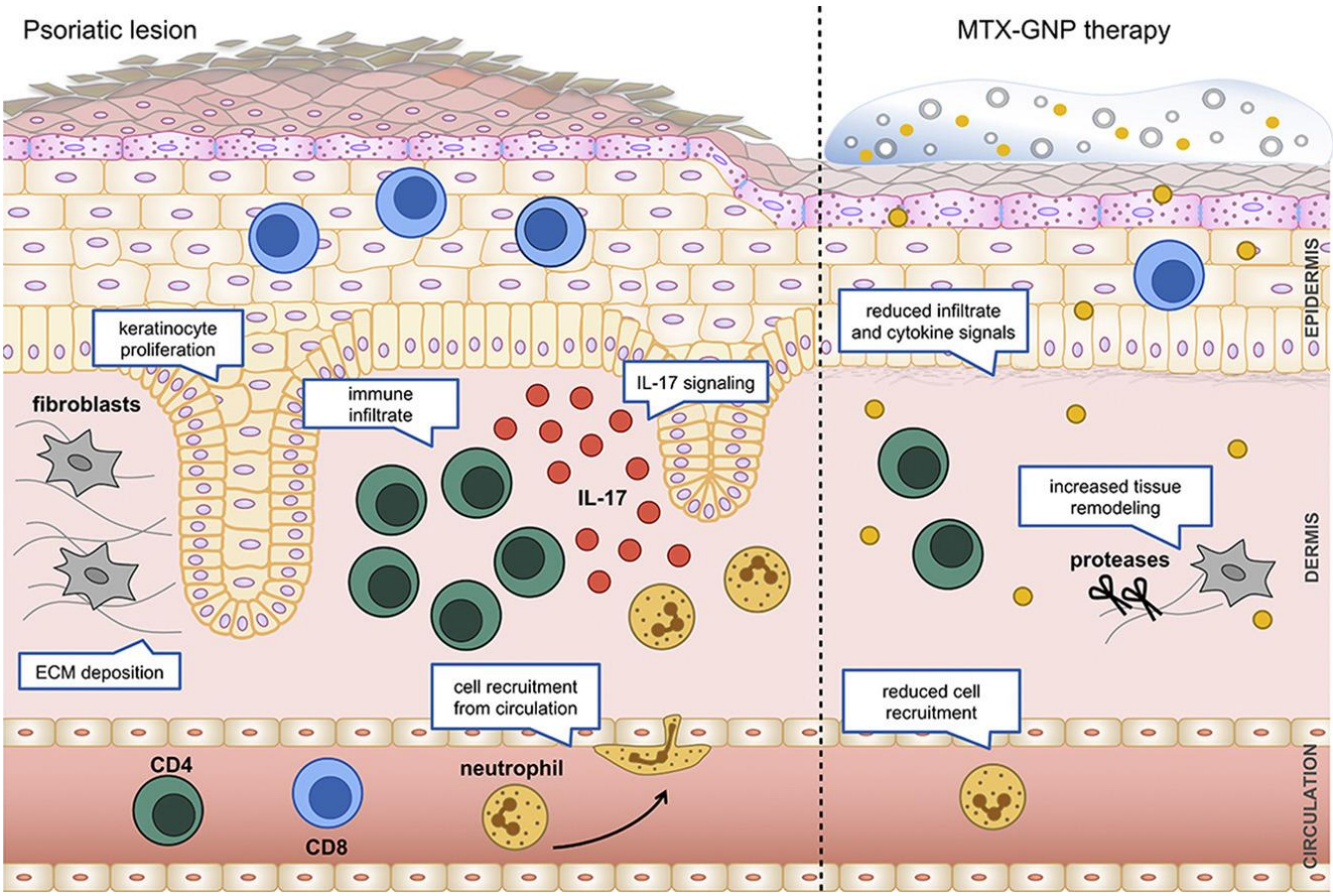

Figure 1: Nanoparticle-Coupled Topical Methotrexate Can Normalize Immune Responses and Induce Tissue Remodeling in Psoriasis [32].

CONCLUSION

Although methotrexate was first developed as an anti-cancer medication, it has recently found utility in treating a variety of non-cancer proliferative skin conditions, including psoriasis. A fresh viewpoint on the findings and new information about MTX over the years is included in the guidelines for the use of MTX in psoriasis patients. For many years, it was the standard systemic treatment for psoriasis ranging from moderate to severe cases. The most recent recommendation maintains the drug's status as the principal treatment for moderate to severe psoriasis, and the drug's approval for this purpose came from the USDA in 1972.

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