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Assessment of Role of Topical Methotrexate in the Treatment of Vitiligo: Review Article

Khaled Mohamed Gharib [1], Yasmeen Ahmed Fahmi El Sharkawi *[1], Nagia Ahmed Elmegrab[2] Al Shimaa Mohamed Ibrahim[1]

Departments of 1 Dermatology, Venereology & Andrology and 2 Pharmaceutics, Zagazig University Hospital, Egypt.

***Corresponding author:** Yasmeen Ahmed Fahmi El Sharkawi, **Mobile:** (+20) 0 109 043 6692,

E-Mail: yasmeenfahmi1992@gmail.com

ABSTRACT

Background: Long-term treatment with low to moderate dosages of the antimetabolite and antifolate medication methotrexate (MTX) has been shown to be effective, safe, and well-tolerated for a wide range of autoimmune diseases. As a result, methotrexate may be used to treat vitiligo and other autoimmune disorders. The hepatotoxic and hematologic side effects of the drug's topical formulations, which were developed for the treatment of localized lesions, were deemed to be clinically insignificant.

Objective: This review article aimed to **a**ssess the possible role of topical methotrexate in the management of vitiligo.

Methods: Methotrexate, and the vitiligo were all looked for in PubMed, Google scholar, and Science direct. References from relevant literature were also evaluated by the authors, but only the most recent or complete studies from January 2005 to May 2021 were included. Due to the lack of sources for translation, documents in languages other than English were ruled out. Papers that did not fall under the purview of major scientific investigations, such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations, were omitted.

Conclusion: Topical methotrexate use could be an effective and safe treatment modality of vitiligo.

Keywords: Methotrexate, Vitiligo, Topical.

INTRODUCTION

A kind of vitiligo, in which the body's immune system attacks and destroys melanocytes, resulting in white patches of skin and hair, was one of the earliest skin conditions to be formally identified by doctors. Skin and mucous membranes both suffer from melanin loss. Melanocyte loss can be explained by several different processes including genetic susceptibility, environmental stimuli (such friction), metabolic changes, and altered inflammatory and immunological responses [(1)].

Depigmentation of the skin, hair, and mucosal surfaces is caused by the selective loss of melanocytes in the most prevalent depigmentation disorder, vitiligo. Approximately 1% of the population is affected by this condition, with an average onset age of 24 years. It appears to be equally common in males and females, and there is no discernible variation in the incidence rate based on skin color or ethnicity [(2)].

Genetic and environmental variables interact with metabolic, oxidative stress, and cell detachment disorders to cause vitiligo, making it a complex (multifactorial) illness. The pathophysiology of vitiligo defies reduction to the sum of its parts, and the two separate mechanisms cannot do so. Instead, the convergence hypothesis has been offered as a unifying approach, combining immunological, biochemical, and environmental components in genetically predisposed patients [(3)].

Treatment of Vitiligo:

Specifically, vitiligo attacks the epidermal melanocytes that reside in the skin's outermost layer, in the spaces between hair follicles (interfollicular epidermis). However, melanocytes in the hair follicle are typically resistant to infection because of their immunological privilege. This is true not only in the brain, eye, and inner ear, but also in other highly specialised organs that include melanocytes. Found in hair follicles, melanocyte stem cells have the ability to repopulate the epidermis of vitiligo lesions with completely functional, newly differentiated melanocytes, ultimately restoring normal pigmentation. In this way, areas of vitiligo lesions that previously had no hair or white hairs repigment in a punctate, perifollicular pattern [(4)].

Vitiligo is difficult to treat, and the current options for doing so are not promising. Phototherapy, topical treatment (calcineurin inhibitors, corticosteroid), and systemic treatment are all moderately successful remedies, although they can be both time-consuming and expensive to implement [(5)].

Methotrexate in the treatment of vitiligo:

Inhibitor of cell proliferation and folic acid antagonist methotrexate (MTX) has a profound effect on the proliferation of T lymphocytes. It acts as a competitive inhibitor of dihydrofolate reductase, making it an antimetabolite. Protein, RNA, and DNA synthesis are all stymied [(6)].

Its antiproliferative and immunomodulatory actions made it a popular treatment in dermatology, sarcoidosis, atopic dermatitis, psoriasis, dermatomyositis, mycosis fungoides alopecia areata and cutaneous lupus erythematosus as well as prurigo nodularis are only some of the skin disorders that respond well to systemic MTX [(7)].

It has been claimed that vitiligo can be treated with MTX at a dose of 12.5-25 mg/week, with the latter being the optimal range. No serious side effects were noted [(8)].

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Nageswaramma *et al.* [9] revealed that seventy percent of patients showed mild repigmentation, and 90% of patients showed no disease activity after treatment. They concluded that MTX is promising as a treatment alternative to steroid and phototherapy for producing repigmentation and preserving stability.

Mechanism of action:

Allosteric inhibitors of dihydrofolate reductase (DHFR) like methotrexate impair DHFR-dependent protein expression systems. A key enzyme in the production of the nucleotide bases purines and pyrimidines is inhibited, leading to stunted growth and, ultimately, cell death (apoptosis) [7].

By inhibiting DNA synthesis, MTX helps inflammatory skin diseases like psoriasis by reducing epithelial hyperplasia, bolstering apoptosis in activated T cells, and suppressing neutrophil chemotaxis [10].

MTX suppresses T-cell activation and the expression of intracellular adhesion molecules. Methotrexate can also inhibit B-cell function by down regulating their transcription [11].

Inhibiting and reducing the amount of TNF-α-producing T cells, while increasing the number of IL-10-producing T cells, MTX has been used to treat vitiligo. As a result, it can slow the spread of disease [12].

MTX's potential anti-inflammatory, immunomodulatory, and antiproliferative actions may be due, in part, to its ability to inhibit induced nuclear factor-κB (NF-κB) activation generated by tumour necrosis factor alpha [13].

Singh *et al.* [13], found that IL-6 and IL-2 production is elevated in vitiligo patients, suggesting that they may play a significant role in melanocytic cytotoxicity. The therapeutic effects of MTX could be due, in part, to its ability to modulate IL-6 synthesis and reactive oxygen species generation [14].

Topical methotrexate:

A new modality in the treatment of vitiligo.

Some systemic absorption of 1% MXT gel used topically may occur depending on the amount and vehicle used, leading to "immune-editing" at the treatment site [15].

For both psoriasis vulgaris and palmoplantar pustulosis, topical MXT has been used, with varying degrees of success. Reports on premycotic mycosis fungoides and lymphomatoid papulosis are also included [16].

Because of the potential for systemic absorption of locally applied MXT of variable concentrations and carriers, it is advised that the same follow-up examinations as with systemic MTX administration be undertaken. Preventative use of folic acid supplements is not recommended. However, topical MTX use is not well-studied, and there is a dearth of data about its safety [16].

In addition, the possibility of MTX-induced lung fibrosis needs to be taken very seriously. As a result, less of the pill version of the drug is available. Treatment with MTX may be helpful for patients who have not responded to or who have not found relief from previous medications like topical treatments, phototherapy, and acitretin treatment [17].

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I. Pharmacokinetics:

Inhibiting cutaneous drug penetration include the stratum corneum layer and the physicochemical features of drug molecules. Cholesterol, ceramide, and free fatty acids form the intercellular lipid matrix of the stratum corneum, which is a multilayer hydrophobic structure [18].

Due to its high hydrophobicity and large molecular weight, MTX is predominantly in the ionized form at a physiologic pH, limiting its skin permeability and its penetration to the basal layer. Consequently, it appears that research into new topical formulations to address this shortcoming is warranted [7].

Traditional liposomes, ethosomes, deformable liposomes (transfersomes), and other lipid carriers have all been used for topical MTX delivery [19]. **According to Raza *et al.*** [20], the inability of typical liposomes to permeate deep skin layers and aggregate in the epidermis has led to the development of alternative drug delivery techniques such as nano-vehicle preparations, laser-assisted delivery, electroporation, and iontophoresis [7].

- **Nanoparticle drug delivery:**
  Nanostructured lipid carriers (NLC) are a type of drug delivery system that combine solid lipids with spatially incompatible lipids to generate a lipid matrix with a drug inside of it, allowing for improved drug loading, release profile, and stable drug integration during storage [21].
- **Lasers:**
  Microchannels, or microscopic ablation zones, created by ablative fractional lasers establish a channel for topically applied drugs to penetrate the skin [22].
- **Iontophoresis:**
  By applying a steady electric current across the skin, transdermal iontophoresis improves the absorption of some medicines that are ionized or unionized [23].

II. Side effects of MTX:

A number of undesirable side effects are associated with systemic MTX use. These include, one of severe adverse outcomes, which is bone marrow suppression (also known as myelosuppression) then other side effects with less severity as nephrotoxicity,

mouth sores, pneumonitis, oligospermia, menstrual disorders, infections, hepatotoxicity and depression, as well as gastrointestinal issues [24]. The hepatotoxic and hematologic adverse effects of topical formulations of MXT, which were developed for the treatment of localized lesions, were found to be statistically insignificant compared to those of systemic MXT [15].

CONCLUSION

Topical methotrexate use could be an effective and safe treatment modality of vitiligo.

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