Topical Methotrexate in Dermatology: A Review of the Literature

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To cite this article: Divya Aickara, Arjun M. Bashyam, Rita O. Pichardo & Steven R. Feldman (2020): Topical Methotrexate in Dermatology: A Review of the Literature, Journal of Dermatological Treatment, DOI: 10.1080/09546634.2020.1770170

To link to this article: https://doi.org/10.1080/09546634.2020.1770170

Accepted author version posted online: 15 May 2020.

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Funding sources: None.
Conflicts of Interest: None declared.

Disclosures: Steven Feldman has received research, speaking and/or consulting support from a variety of companies including Galderma, GSK/Stiefel, Almirall, Leo Pharma, Boehringer Ingelheim, Mylan, Celgene, Pfizer, Valeant, Abbvie, Samsung, Janssen, Lilly, Menlo, Merck, Novartis, Regeneron, Sanofi, Novan, Qurient, National Biological Corporation, Caremark, Advance Medical, Sun Pharma, Suncare Research, Informa, UpToDate and National Psoriasis Foundation. He is founder and majority owner of www.DrScore.com and founder and part owner of Causa Research, a company dedicated to enhancing patients’ adherence to treatment.

Divya Aickara, Arjun Bashyam, and Rita Pichardo have no conflicts to disclose.

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Abstract

Background: Systemic methotrexate (MTX) is a useful treatment for many dermatologic conditions, however, the risk of adverse events prevents its use in patients with minimal or localized disease. Topical application of MTX may be an option to avoid the systemic adverse effects of oral MTX.

Objective: To assess what is known about the efficacy and safety of topical methotrexate.

Methods: A search on Pubmed was conducted. There were no limits on publication date.

Results: A total of 963 articles were discovered. Using our exclusion criteria, 916 articles were excluded; 47 articles were used for full text assessment. Topical MTX has been used primarily in psoriasis but also in mycosis fungoides, lymphomatoid papulosis, and oral precancerous lesions. Optimal delivery system and formulation for adequate penetration is still under investigation.

Conclusion: The quality of evidence for the utility of topical methotrexate in psoriasis is good, however, for other dermatologic diseases, the quality is poor. Topical MTX with improved delivery methods may be a viable tool against certain localized dermatologic conditions for patients who do not tolerate oral MTX. Further double-blinded randomized control studies are needed to substantiate the utility of topical methotrexate.
Introduction

Methotrexate (MTX), a widely used antifolate drug, is valued in dermatology for its anti-proliferative and immunomodulatory effects. Systemic MTX is effective for numerous dermatologic conditions including psoriasis, alopecia areata, prurigo nodularis, atopic dermatitis, dermatomyositis, mycosis fungoides, sarcoidosis, and cutaneous lupus erythematosus. The side effects of MTX include gastrointestinal disorders, hepatic dysregulations, pneumonitis, hematologic disorders, infections, and nephrotoxicity. When considering MTX for the treatment of extensive dermatologic conditions, in many cases, the potential risk is small compared to the expected clinical benefit. However, the balance of risk to benefit may not be favorable in patients with minimal or localized disease.

MTX is an allosteric inhibitor of dihydrofolate reductase (DHFR) that reduces DHFR-based protein expression systems. This causes inhibition of thymidylate synthase, which is a vital component for the synthesis of purines and pyrimidines, resulting in the inhibition of growth and inevitable cell death (apoptosis). By inhibiting DNA synthesis, MTX is beneficial in certain inflammatory cutaneous disorders, such as psoriasis by limiting epithelial hyperplasia, reinforcing the apoptosis of activated T cells, and inhibiting the chemotaxis of neutrophils.

Topically applied MTX was popular in the 1960-1980s to treat localized psoriatic plaques with many studies showing variable efficacy. Topical MTX has limited passive diffusion through the skin depending on psoriatic plaque thickness, which may be the reason for the discrepancy between the earlier studies. This poor diffusion is due to MTX’s high molecular
weight and that it is mostly in the dissociative form at a physiologic pH, resulting in insufficient penetration to the basal layer.\textsuperscript{20}

While topical treatment could avoid many of MTX’s systemic toxicities, initial human trials on topical MTX for the treatment of psoriasis were largely unsuccessful. This was attributed to poor cutaneous absorption and penetration of topical MTX.\textsuperscript{14,15} In the past few years, novel methods have been developed to enhance cutaneous penetration of MTX, reviving topical MTX as a potential therapeutic agent.\textsuperscript{21-28} The purpose of this review is to evaluate the use of topical MTX in dermatology and the recent research on improving topical delivery of MTX.

Methods

A search on Pubmed was conducted using the following search terms: topical, methotrexate, skin, cutaneous, and dermatology. There were no limits on publication date. A total of 963 studies were initially discovered. Studies using oral MTX, subcutaneous MTX, parental MTX, intralesional MTX, and non-English-language contributions were excluded. The references of the manuscripts assessing topical MTX were examined for additional studies. Using this exclusion criteria, 47 studies were used for full text assessment (Figure 1). Each article was critically assessed by two reviewers and inclusion was based on mutual decision of both reviewers as per their relevance to the topic. After data extraction, information pertaining to the different subsections were processed and reorganized in the form of this narrative review.
Use of Topical MTX in Dermatologic Diseases

Psoriasis

Topical MTX was studied in plaque psoriasis beginning in the 1950s and showed poor clinical efficacy (Table 1).\textsuperscript{14-17} Initially, it was thought that prolonged topical treatment was needed since the studies showing ineffectiveness only treated for two weeks and systemically administered MTX may require 3-4 weeks to produce clinical results. However, a study with daily topical application of 5 mg of MTX under occlusion for three weeks did not produce a clinical improvement when compared to control.\textsuperscript{18} The formulations used in these earlier studies were topical gels, ointments, and creams in various ways, including by mixing MTX and emollients, MTX in water under occlusion, or as a powder form – all with poor results.\textsuperscript{16,17}

Weinstein et al. proposed the idea that the lack of clinical efficacy of topical MTX was secondary to its inadequate delivery to the target tissue in high enough concentrations to elicit a clinical response,\textsuperscript{10} especially considering the classical hyperkeratotic psoriatic plaques. A gel formulation containing laurocapram concentrations of 3\% with MTX (0.1\%, 0.5\%, and 1.0\%) resulted in a higher penetration level of MTX in a dose dependent manner. When laurocapram is applied onto the skin, it interacts with the lipids within the stratum corneum to enhance the penetration of the hydrophilic compound.\textsuperscript{24} When the gel preparations were applied twice daily for a total of six weeks, there was marked improvement in the combined scores for erythema, scale and elevation in all three concentrations when compared to the control (p<0.001).\textsuperscript{10} To corroborate these findings, in one case, MTX 1\% in a laurocapram gel applied once daily for 8 weeks exerted a local therapeutic effect in psoriatic skin.\textsuperscript{22}
To evaluate the histological changes after using topical MTX a placebo-controlled, double-blinded study of 60 patients with mild-to-moderate chronic plaque psoriasis randomized to a placebo hydrogel or MTX 0.25% hydrogel was conducted. The gel was topically applied to psoriatic lesions twice daily for five consecutive days per week for four weeks. No occlusion dressings were used and patients were instructed to avoid sunlight exposure to lesions. The MTX gel effectively treated chronic plaques when compared to control group (p<0.001). Histologically, the lesions had decreased levels of epidermal acanthosis, parakeratosis, thinning, papillary vessel dilation and inflammatory infiltration.

The location of the psoriatic lesions may determine the efficacy of topical MTX. In a case series (n=14), topical MTX 0.25% gel was unsuccessful in controlling palmoplantar psoriasis. The gel formulation may have difficulty penetrating the palmar and plantar lesions with thick hyperkeratosis, and may need a higher concentration or a different vehicle base.

To evaluate the utility of fractional laser to augment penetration of topical MTX in psoriatic lesions, a microemulsion consisting of jojoba oil and MTX and a combination of the same microemulsion and fractional Er:YAG laser were applied to psoriatic plaques in 30 patients. Both treatments were deemed safe and clinically promising in the treatment of psoriasis and displayed a decrease in psoriatic severity score (TES: Thickness, Erythema, Scales; p<0.05). The concomitant use of the fractional laser (Er:YAG) enhanced the delivery of the MTX preparation to provide greater improvement in the psoriatic plaques in a shorter time duration.

Regarding safety, MTX 0.1%, 0.5%, and 1% in a 3% laurocapram gel formulation that was applied to psoriatic skin developed no alterations in hematologic or biochemical profiles, and
no detectable serum MTX levels by standard radio assay (limit, 5ng/mL).\textsuperscript{10,22} When liposomal MTX gel was compared with standard MTX gel, there was no alteration in complete blood count, urinalysis, liver chemistry (serum glutamic-oxaloacetic transaminase and serum glutamic-pyruvic transaminase), or serum creatine.\textsuperscript{28}

\textit{Mycosis Fungoides}

Of ten patients with early stage mycosis fungoides who were treated with topical MTX-laurocapram once every other day for 24 consecutive weeks, three attained greater than 50% improvement, four improved less than 50%, and zero had progressive disease.\textsuperscript{24} Serum methotrexate concentration was below the lowest limit of detection, which ranged between 0.01-0.03 μmol/L, in all samples regardless of the dose received.\textsuperscript{24} The patients in this study applied the gel formulation to the total body surface, excluding genital, perianal areas, nipples, face, and skin under the breasts, every other day for 24 consecutive weeks.

\textit{Other Cutaneous Lesions}

In one patient, topical MTX resolved lymphomatoid papulosis. The patient created his own formulation by moistening a 2.5 mg tablet of MTX with tap water and rubbed the tablet on gauze until the gauze turned orange. He placed the gauze with a bandage over any newly formed papules daily. He used approximately one third of a tablet (0.83 mg) per lesion per day.\textsuperscript{30}

Photodynamic therapy (PDT) is a common surgery sparing treatment for oral precancers such as oral leukoplakia, erythroleukoplakia, and verrucous hyperplasia. In an animal model
study, pretreatment with topical MTX increased the conversion of 5-aminolevulinic acid (ALA) into protoporphyrin IX, improving the outcome of the buccal pouch precancerous lesion treated with topical ALA-PDT. The pretreatment of MTX before the ALA-PDT required fewer PDT treatments to achieve complete response than the topical ALA-PDT group (p<0.001).³¹

Optimal Delivery of Topical MTX

Due to the lack of penetration of topical MTX, several drug delivery systems are being developed, including nano-vehicle preparations, laser-assisted delivery, electroporation, and iontophoresis. The mechanisms are beyond the scope of this review; however, we have summarized the studies demonstrating various delivery methods for MTX.

Nanoparticle drug delivery

Nanostructured lipid carriers (NLC), a drug delivery technology, are produced by mixing solid lipids with spatially incompatible lipids leading to a lipid matrix with a drug, which allows for improved properties of drug loading, release profile, and stable drug incorporation during storage.³²

NLCs loaded in calcipotriol and hydrophilic MTX permeated in vitro Franz diffusion cells 2.4-4.4 times greater when compared to control, and hyperproliferative skin displayed higher methotrexate permeation when compared to normal skin (p<0.05).³³ In another study, Ferreira et al. loaded MTX to NLCs by a hot ultrasonication method which showed a biphasic MTX release profile under both physiologic and inflammatory in vitro skin environments.³⁴
Fibroblasts were not injured 24-48 hours after contact with formulations, and the authors concluded it could be used as a topical therapy for cutaneous cancers and inflammatory diseases but that animal studies would be needed prior to human trials.

Nanogels are colloidal, cross-linked particles that range between 100 nm and 1 μm in size and possess the property of swelling in appropriate environments.\(^{35}\) A nanogel loaded with MTX deliver the drug across the epidermis in levels that significantly (\(p=0.0154\)) reduced the biosynthesis of prostaglandin E2, a mediator in inflammation, in a porcine ex vivo model.\(^{35}\) Protein transduction domains (PTD) can be conjugated to medications to allow for delivery through cell membranes. Topically-applied PTD-MTX has therapeutic efficacy in the mouse model of psoriasis.\(^{36}\)

An in-vitro and in-vivo mouse models have evaluated the utility of water-soluble gold nanoparticles functionalized by sodium 3-mercaptopropanesulfonate (Au-3MPS) loaded with MTX to exhibit reduction in inflammatory infiltrate.\(^{37,38}\) Clinically, niosomal MTX gel, which are non-ionic surfactant vesicles used for drug delivery, used daily for 12 weeks is better absorbed and efficacious in psoriatic plaques when compared to standard MTX gel, without producing any significant skin irritation or sensitization.\(^{39}\) However, the sample size of each treatment arm was ten patients.

**Lasers**

Ablative fractional lasers create microchannels, or microscopic ablation zones, that disrupt the skin barrier and facilitate a pathway for topically applied medications.\(^{40}\) MTX was absorbed rapidly into the mid-dermis of skin with a 2,940 nm fractional Erbium Yttrium
Aluminum Garnet (Er:YAG) laser in an in vitro study of intact porcine skin, and the concentration of MTX delivered to the tissue is dependent on the laser channel depth.\textsuperscript{41,42} However, an in vitro study using a hyperproliferative murine skin model resulted in variability in MTX penetration using the Er:YAG laser, showing permeation behavior is dependent on the dermatologic pathology.\textsuperscript{27}

A human clinical study applied MTX 0.25% gel or liposomal MTX 0.25% gel to half the psoriatic lesions while the other half received the placebo gel once daily, under occlusion for 30 minutes. An 80-J diode laser was used one hour after application of the gel three times a week for 12 weeks. No statistical analysis was done to compare the effects of the topical medication, however the use of a diode laser to target liposomes increased MTX concentrations in the lesion without systemic effects.\textsuperscript{28}

**Iontophoresis**

Transdermal iontophoresis is the application of a constant electric current across the skin that enhances the delivery of certain ionized or unionized drugs.\textsuperscript{30} Using iontophoresis (0.25-0.5 mA/cm\textsuperscript{2}) increased the effectiveness of MTX delivery in an in vitro porcine skin, however, without knowing the optimal concentrations needed to treat certain dermatologic conditions, its clinical efficacy is still unknown.\textsuperscript{23,43} The electrical potential used in this study may not be sufficient to provide adequate penetration of MTX, as transdermal permeation of MTX increased with the higher current density (0.5 mA/cm\textsuperscript{2}).\textsuperscript{23,43} However, with the higher current density of 0.5 mA/cm\textsuperscript{2}, there was an irreversible loss of basal layers seen within 48 hours.\textsuperscript{44} In a case report, using iontophoresis to deliver MTX was successful in managing a
localized recalcitrant psoriatic plaque and was beneficial when compared to coal tar ointment for the treatment for palmoplantar psoriasis. 45

Conclusion

Topical MTX avoids the systemic adverse effects of its oral counterpart and may be an option for localized inflammatory skin disease. Topical MTX has been studied primarily in psoriasis, however, there are now many efficacious biologic agents available for patients with psoriasis. For patients with diffuse and severe psoriasis, systemic immunomodulation may be required to reduce the risk of comorbid diseases, such as psoriatic arthritis and cardiovascular disease. For patients with localized plaque psoriasis who do not tolerate systemic medications, topical MTX may be an option. Further head-to-head trials and randomized controlled trials are needed to compare the efficacy of topical MTX to other standard of practice topical medications.

The majority of adverse events were local to the application site and included mild-to-moderate pruritis, burning, irritation, and eruption. 22 The cause of these adverse events could not be distinguished as from the MTX itself or the vehicle it was placed in. Since safety data is limited, the same follow-up and lab work for systemic MTX is recommended, including folic acid supplementation. 19

Oral MTX is used for many dermatologic diseases unresponsive to topical corticosteroids such as lichen sclerosus et atrophicus, extragenital lichen sclerosus, atopic dermatitis, morphea, scleroderma, lichen planus, lichen planopilaris, and many others. 46-49 Physicians may be reluctant to prescribe oral MTX due its serious adverse effect profile. While diffuse disease
requires systemic administration of immunosuppression, localized inflammatory conditions may benefit from topical MTX.

Many dermatologists turn to oral MTX in their treatment ladder for numerous eczematous and inflammatory skin conditions after failure of topical medications. For these inflammatory cutaneous conditions, while patients may benefit from topical calcineurin inhibitors, their off label use may be cost prohibitive unlike MTX. Topical MTX, with improved delivery methods, may be a useful option for localized dermatologic conditions where oral MTX is not well tolerated.
References


**Figure Legends**

Figure 1. PRISMA Diagram of Literature Review

[Diagram showing the PRISMA flowchart with steps for PubMed searches, studies reduction, and final manuscript selection.]
## Tables:

**Table 1. Summary of Studies Utilizing Topical MTX in Psoriasis**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>N</th>
<th>Type of Psoriasis</th>
<th>MTX Formulation</th>
<th>Time of Treatment</th>
<th>Outcome</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fry, 1967</td>
<td>5</td>
<td>Psoriasis vulgaris</td>
<td>MTX 0.2% in water base</td>
<td>QD, 2 weeks</td>
<td>Improvement of &gt;50% in 77.8%</td>
<td>None Reported</td>
</tr>
<tr>
<td>Stewart, 1972</td>
<td>9</td>
<td>Psoriasis vulgaris</td>
<td>MTX 0.2% cream under occlusion</td>
<td>5-7 days</td>
<td>No benefit</td>
<td>None Reported</td>
</tr>
<tr>
<td>Bjerring, 1986</td>
<td>5</td>
<td>Psoriasis vulgaris</td>
<td>MTX 0.25% in carbamide base</td>
<td>BID, 3 weeks</td>
<td>No benefit</td>
<td>None Reported</td>
</tr>
<tr>
<td>Weinstien, 1989</td>
<td>42</td>
<td>Psoriasis vulgaris</td>
<td>MTX (0.1%, 0.5%, and 1%) in 3% laurocapram gel</td>
<td>BID, 6 weeks</td>
<td>Improvement of &gt;50% with 0.1% (64% of patients), 0.5% (59%), and 1% (56%) vs control (25%)</td>
<td>Mild irritation, temporary burning sensation</td>
</tr>
<tr>
<td>Ravi, 1999</td>
<td>16</td>
<td>Palmoplantar</td>
<td>MTX 1% in hydrogel base</td>
<td>BID, 8 weeks</td>
<td>21.4% - Total clearance 42.8% - Marked Improvement 28.3% - Moderate Improvement</td>
<td>None Reported</td>
</tr>
<tr>
<td>Sutton, 2001</td>
<td>53</td>
<td>Severe plaque psoriasis</td>
<td>MTX 1% in laurocapram gel</td>
<td>QD, 8 weeks</td>
<td>Reduced lesional scaling and thickness (p &lt; 0.05 vs. placebo)</td>
<td>Pruritus, burning, irritation, eruption, plaque soreness</td>
</tr>
<tr>
<td>Syed, 2001</td>
<td>60</td>
<td>Psoriasis vulgaris</td>
<td>MTX 0.25% in hydrogel base</td>
<td>BID for 5 days, 12 weeks</td>
<td>Improvement of &gt;50% in 83.3% vs control (4.3%)</td>
<td>None Reported</td>
</tr>
<tr>
<td>Kumar, 2004</td>
<td>14</td>
<td>Palmoplantar</td>
<td>MTX 0.25% in hydrogel base</td>
<td>BID, 12 weeks</td>
<td>Improvement of &gt;50% in 42%</td>
<td>None Reported</td>
</tr>
<tr>
<td>Eskicirsk, 2004</td>
<td>40</td>
<td>chronic</td>
<td>MTX 1% in</td>
<td>BID, 8 weeks</td>
<td>Global improvement</td>
<td>None</td>
</tr>
<tr>
<td>Year</td>
<td>Condition</td>
<td>Treatment</td>
<td>Outcome</td>
<td>Reference</td>
<td></td>
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</tbody>
</table>
| 2006 | plaque-type psoriasis | hydroxymethylcellulose gel base | MTX (97%) vs. placebo (60%) ($p < 0.01$)  
Histological improvement in treatment group ($p < 0.01$) | Reported  |