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REVIEW ARTICLE

Low-dose methotrexate use in skin diseases: An old drug with new purposes

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Abstract

Methotrexate (MTX) has been one of the most used anti-inflammatory, antimetabolite, and steroid-sparing drugs in dermatology, it was originally developed as an antineoplastic drug for leukemia which was later introduced as a therapeutic option for psoriasis, rheumatoid arthritis, and, recently, for inflammatory skin diseases. MTX is the drug of choice for the systemic treatment of psoriasis, being an effective, safe, and low-cost option. The use of MTX has extended to other inflammatory diseases such as urticaria, atopic dermatitis, pemphigus vulgaris, bullous pemphigoid, and recently, intralesional therapy for cutaneous tumors. Despite the wide range of potential indications, is still continues to be scarce, and mainly derived from case series and reports and prospective, randomized double-blinded studies are lacking. Herein, we will review the main uses of MTX for skin diseases and the evidence regarding its efficacy and safety.

Keywords: *Methotrexate. Skin diseases. Therapy.*

Introduction

Methotrexate (MTX) usage in dermatology was first established in 1951 after observing the improvement of psoriatic plaques in patients with aminopterin for cancer treatment, this finding led to MTX development, a more stable and less toxic drug[1].

Due to its widespread use in severe diseases, MTX has been dichotomized in two main dose schemes: the "high dose" (HD-MTX), average dose 1 g/m^2, focused on hematologic malignancies and the "low dose" (LD-MTX), ranging from 7.5 to 30 mg weekly, and extensively used for skin diseases (Table 1); LD-MTX is effective during long-term treatments with mild toxicity. In this review, we will focus on LD-MTX use in different skin diseases, dosage, and recommendations for administration and surveillance.

Materials and Methods

A systematic search was conducted in the PubMed database of the literature available from 2000 to 2021 with the Mesh term "Methotrexate," combined with the following subheadings: "administration and dosage;" "low dose;" "mechanism of action;" "adverse effects;" "drug therapy;" and "drug effects;" and the following keywords: "guideline;" "skin diseases;" "psoriasis;" "urticaria;" "pemphigus vulgaris;" "bullous pemphigoid;" "dermatomyositis;" "scleroderma;" "pityriasis rubra pilaris;" "malignancy;" "mycosis fungoides;" "basal cell carcinoma;" and "keratoacanthoma." We obtained 417 articles. Forty-eight articles were assessed for eligibility (we include articles that mention the dose and time of treatment with MTX, in addition to the adverse events presented), and 40 were included in the review. Due to

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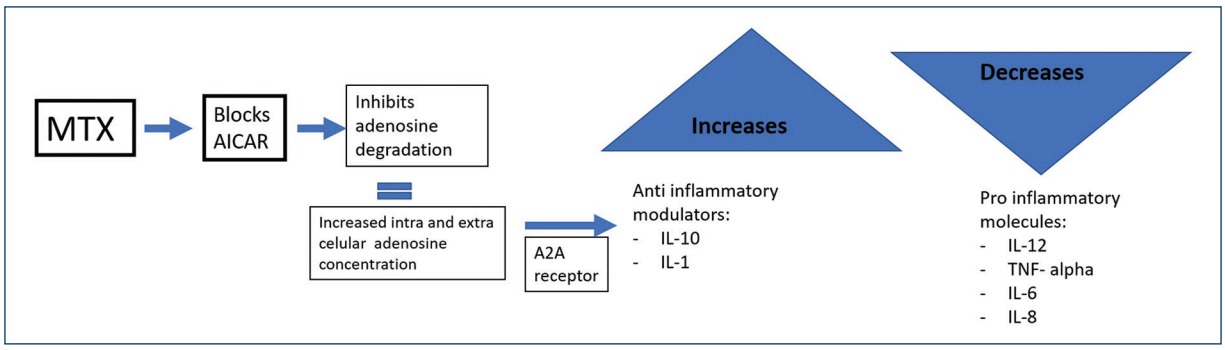

Figure 1. Proposed mechanism of action in LD-MTX: Methotrexate inhibits aminoimidazole-4-carbox- amide ribonucleotide (AICAR) upon entering the cells, which inhibits adenosine degradation, leading to an intra and extracellular increase of adenosine concentrations. Adenosine will bind to the A2A receptor on endothelial cells, leading to an increase in anti-inflammatory modulators and a decrease in proinflammatory molecules.

the broad scope of the topic, we highlighted the most important diseases and impact on the morbidity and mortality in dermatology.

Development and Discussion

Mechanism of action

The primary mechanism of action for LD-MTX is not completely understood versus the well-known mechanism of action as an antimetabolite of HD-MTX in oncology treatments[2-4]. There are several approaches to the mechanism of action of LD-MTX (Fig. 1), but we need more studies to explain its beneficial effect in dermatological conditions, where severe adverse effects are rarely seen[2,3], in contrast with the use of higher doses.

One of the main mechanisms of the action of LD-MTX includes the inhibition of dihydrofolate reductase, an essential enzyme for folate metabolism, leading to the depletion of intracellular folate with thymidine synthesis inhibition[3]; MTX is also an antagonist to folate metabolism, as well as it decreases the folate cofactors synthesis necessary for nucleic acid production[4].

At lower doses, MTX increases the intracellular and extracellular adenosine concentration, suppressing pro-inflammatory molecules such as IL 12, TNFα, IL 6, IL 8, and nitric oxide, and increases anti-inflammatory mediators such as IL 10[2-4].

Pharmacokinetics

Low-dose MTX is entirely absorbed in the gastrointestinal tract by active transport; once absorbed, it has low bioavailability (≥25%) due to intestinal tract and liver inactivation[5]. Approximately 10% of MTX is transformed to 7-OH-MTX by hepatic metabolism. It is eliminated unchanged (90%) in urine by active secretion. Peak serum levels with oral administration usually take 1-2 h and through an intramuscular injection after 30-60 min[5]. About 50% of MTX binds to serum proteins which determine the distribution in the organism. MTX is distributed in the intracellular space through the reduced folate carrier 1 receptor, and in this compartment, it is transformed into MTX polyglutamate; which

Table 1. Common dermatological indications for MTX

Highest evidence*	Lowest evidence
Psoriasis	Pityriasis rubra pilaris
Atopic dermatitis	Pityriasis lichenoides
Cutaneous scleroderma (Morphea)	Pityriasis lichenoides et varioliformis acuta
Chronic cutaneous lupus erythematosus	Chronic urticaria
Mycosis fungoides	Pemphigus
	Bullous pemphigoid
	Ocular cicatricial pemphigoid
	Dermatomyositis
	Behcet's disease
	Polyarteritis nodosa
	Cutaneous sarcoidosis
	Granuloma annulare
	Lymphomatoid papillomatosis

*Level of evidence II-III.
MTX: methotrexate.

Table 2. Adverse effects of methotrexate

Target organ/system	Side effect
Constitutional	Nausea
	Fatigue
	Malaise
	Anorexia
Gastrointestinal	Diarrhea
	Stomatitis
	Hepatotoxicity
Hematological	Cytopenia (anemia, leukopenia, and thrombocytopenia)
	Lymphoma (Epstein related)
Pulmonary	Pneumonitis
	Pulmonary fibrosis
Reproductive	Teratogenicity
	Oligospermia
Mucocutaneous	Mucositis
	Photosensitivity
	Radiation recall reaction
	Drug hypersensitivity reaction
	Diffuse non-inflammatory alopecia
	Squamous cell carcinoma
Infections	Opportunistic infections (*Pneumocystis jiroveci* pneumonia)
	Tuberculosis reactivation
	Hepatitis
Neurological	Headache
	Fatigue
	Mood alterations

Table 3. Contraindications to methotrexate

Absolute	Relative
Pregnancy	Liver disease
Lactation	Kidney disease
Severe cytopenia	Mild-to-moderate cytopenia
Women with a reproductive interest	Excessive alcohol consumption
	Concomitant use of hepatotoxic medications
	Active infections (HIV and tuberculosis)
	Immunosuppression
	Severe obesity
	Diabetes mellitus
	Recent live-attenuated vaccination
	Poor adherence to treatment

HIV: human immunodeficiency virus.

accumulates intracellularly explaining why high concentrations can be maintained from weeks to months[2].

Supplementation

Folate supplementation is controversial since there is no established information on whether folic acid or folinic acid is the best option for LD-MTX[5]. Experts recommendations include supplementing folic acid when gastrointestinal or hematologic adverse effects occur[6]. It can be administered as 1 g daily or folinic acid 5 mg three doses every 12 h once a week[6].

Other authors suggest folic acid 5 mg/day except for the day of MTX intake or folinic acid 15 mg/weekly[5]; in our experience, we have used folic acid 5 mg weekly without significant hematologic adverse events due to MTX (unpublished data).

Adverse effects

Few adverse effects have been reported with LD-MTX (Table 2), including abnormal liver function; gastrointestinal effects including nausea; hematopoietic suppression is often related to higher doses; subjective side effects such as fatigue and headaches; non-scarring hair loss; and in few cases, an increase in blood urea nitrogen retention, pneumonia, neoplasm, sensitivity to ultraviolet light, delay in wound healing, and cutaneous necrosis have been reported[7,8]. Adverse effects are more frequent in tissues with fast cellular replication such as skin and gastrointestinal system, due to MTX affinity for rapidly replicating cells. MTX is contraindicated during pregnancy and lactation (Table 3)[7].

Monitoring

Before starting MTX, the following tests are required, including complete blood count, creatinine, liver function tests, and a pregnancy test in women with childbearing

Table 4. Drugs that may interact with MTX to increase toxicity

Mechanism of interaction	Drug involved
Decreased renal elimination of MTX	Salicylates
	Nonsteroidal anti-inflammatories (naproxen, ibuprofen, and indomethacin)
Pharmacological enhancement of MTX toxic effects	Trimethoprim-sulfamethoxazole (absolute contraindication)
	Ethanol
	Phenylbutazone
Reduced tubular secretion	Salicylates
	Sulfonamides
	Probenecid
	Cephalothin
	Penicillin
	Ciprofloxacin
	Tetracycline
	Colchicine
Displacement of MTX from plasma protein binding	Salicylates
	Probenecid
	Barbiturates
	Phenytoin
Intracellular accumulation of MTX	Probenecid
	Dipyridamole
Hepatotoxicity	Retinoids

MTX: methotrexate.

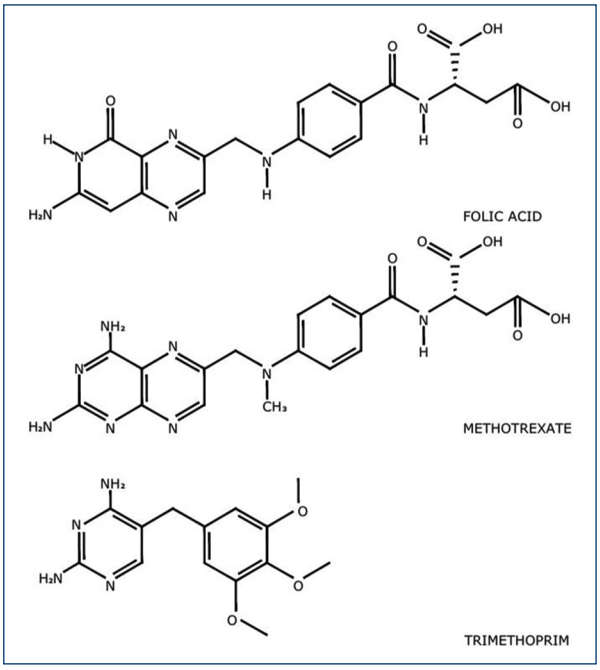

Figure 2. Comparative molecular structure of methotrexate, folic acid and trimethoprim.

potential. In certain cases, B and C hepatitis, HIV testing, as well as the identification of latent tuberculosis might be considered[4].

Follow-up includes a complete blood count every 2-4 weeks in the 1st month and every 2-3 months[4,6]. Kalb et al.[6] suggested monitoring liver function every month for 6 months and afterward every 2 months until normal.

In cases with a cumulative MTX dose of 3.5-4 g, liver biopsy or MTX withdrawal should be considered, although, in recent years, the use of the amino-terminal peptide of procollagen III levels may help to avoid or delay biopsy[4,6].

Drug interactions

Some commonly used drugs have the potential to increase MTX toxicity (Table 4), leading to pancytopenia or even death, particular care should be taken with drugs that have renal excretion which can increase adverse efects[4,6]. Trimethoprim-sulfamethoxazole is usually avoided in patients taking MTX due to folic acid antagonism (Fig. 2) and also sulfamethoxazole competitively inhibits renal secretion, increasing the risk for MTX toxicity[6].

Psoriasis

Psoriasis is an inflammatory skin disease that remains one of the main indications for MTX in dermatology, with an FDA approval for severe, recalcitrant, or non-responsive psoriasis and psoriatic arthritis[4]. It is indicated as a systemic treatment when no other treatments are available, unsuccessful results with other systemic therapies or with articular involvement. It is particularly useful in patients with moderate-to-severe plaque psoriasis including nail psoriasis, generalized pustular psoriasis, psoriatic erythroderma, and

palmoplantar psoriasis[5]. Studies have shown similar efficacy of MTX in stabilizing different types of psoriasis[7].

A recent meta-analysis described a $PASI_{75}$ response in 40% of patients after 12 weeks with LD-MTX, but less effective compared with biologic agents[9]. In addition, MTX can be used in combination with other systemic, biologic drugs (infliximab, etanercept, and adalimumab) to increase efficacy, lowering the risk of serious adverse effects[5,6].

Effective doses range between 7.5 and 25 mg weekly. Some clinicians rely on a lower "test dose" followed by laboratory tests a week or two later, but recent evidence suggests that this may not be necessary and the emphasis is made on adequate monitoring before starting and during treatment[6,10].

Psoriasis is often related with several comorbidities, including obesity and metabolic syndrome; therefore, monitoring for hepatotoxic and hematological effects in this group of patients should be continuous[6].

Chronic urticaria

Chronic urticaria is a frequent disease characterized by wheals for at least 6 weeks. First-line treatment for chronic urticaria includes antihistamines, but despite their efficacy, about 36.8% of patients will not have an adequate response to treatment and will require additional therapy[11].

LD-MTX 10-15 mg weekly has been successfully used in several case reports and case series. Sagi et al.[12] included eight patients with recalcitrant chronic urticaria using MTX with complete remission in 87% of the cases. Perez et al.[11] retrospectively evaluated 26 patients with steroid-dependent urticaria, 12/16 patients had a complete response, and seven patients reduce oral steroid doses and two patients suspended the treatment.

A recent systematic review and meta-analysis included two randomized controlled trials with recalcitrant urticaria and concluded that MTX did not provide any significant benefit over placebo, but the treatment was well tolerated[13].

Atopic dermatitis

Atopic dermatitis is a chronic inflammatory disease of the skin affecting 5-20% of the pediatric population and 2-5% of the adult population[14]; most patients with atopic dermatitis develop a mild-to-moderate disease that is usually controlled with topical therapy or phototherapy[15,16]. A small subset of patients will be unresponsive to first-line treatments, often requiring systemic treatments[15,17].

MTX is used as an off-label systemic alternative; few randomized controlled trials are available and most studies are retrospective in nature, showing that MTX is effective and safe for moderate-to-severe atopic dermatitis[17].

Several studies have shown clinical responses ranging from 53.85% to up to 93% of patients with >75% improvement and clinical response between 4 and 12 weeks of treatment with the use of MTX[18]. Adverse effects were reported in 34.62% of patients; gastrointestinal and elevated transaminase levels were the most common; bone marrow suppression was rarely reported[14].

Regarding the pediatric population, there are no guidelines for immunosuppressive drugs, leading to uncertainty of the efficacy and safety of these drugs. Anderson et al.[17] conducted a retrospective study in 55 pediatric patients with atopic dermatitis, treated with LD-MTX (median dose: 0.45 mg/kg weekly) during 15.3 months, showing 76.4% improvement; gastrointestinal symptoms, acquired skin infections, and blood count abnormalities were the most common side effects.

Pemphigus vulgaris

Pemphigus is an autoimmune blistering disease that affects skin and mucosa, mortality decreased importantly since the introduction of systemic steroids, remaining the first line of treatment[19], however, significant long-term side effects limit their extensive use, and thus, other immunomodulatory drugs are required[20].

A 2009 meta-analysis included 136 pemphigus patients treated with systemic glucocorticoids and MTX, showing clinical improvement in 82% of cases[20]. Baum et al.[21] included 30 patients with pemphigus vulgaris treated with prednisone and MTX 15 mg/weekly; prednisone tapering was possible in 76.6% of patients even in recalcitrant cases, highlighting a steroid-sparing effect.

Tran et al.[19] presented 23 patients treated with prednisone and MTX with a maximum dose of 20 mg/week; improvement of blistering was seen in 91.3% after initiation of MTX and 69.6% discontinue prednisone in a mean of 18 months.

Bullous pemphigoid

Bullous pemphigoid is an autoimmune subepidermal blistering disease, presenting as tense blisters, that

may last from months to years and usually affecting older individuals that, if left untreated, may last from several months to years to control[22]. Oral and topical corticosteroids continue to be one of the mainstay therapies despite their numerous side effects[23]. LD-MTX has been proposed for the treatment of bullous pemphigoid as monotherapy or as adjunctive management with topical corticosteroids to reduce treatment periods[22,23].

Considering patients with bullous pemphigoid tend to be older, concerns have been raised regarding the use of MTX and decreased renal function, but observations have shown no correlation with the increased risk of mortality[23]. Dosage in this subgroup of patients tends to be lower, up to 12.5 mg/week, with median doses of 5 mg that could be explained by the physiological decrease in renal function[22].

Retrospective studies have shown complete response after 1 month in 90% of patients who initially did not respond to topical clobetasol propionate[23] and its usefulness as a steroid-sparing agent with successful prednisone tapering[22].

Evidence of MTX use in bullous pemphigoid is scarce and low quality. Some authors suggest that MTX should be reserved for the unresponsive disease[22,23].

Dermatomyositis

Dermatomyositis is a multisystemic disorder, classified as a subtype of idiopathic inflammatory myopathies, and characterized by proximal muscle weakness and classic cutaneous lesions[24,25]. Glucocorticoids are considered the first-line therapy and the only Food and Drug Administration approved treatment for dermatomyositis, however, in many cases, additional immunosuppressants and immunomodulatory are required to achieve adequate control, and few studies on these medications have been conducted[24].

In dermatomyositis, patients often require higher MTX doses than the previous dermatoses (up to 25 mg weekly)[26], with a significant reduction in the severity of cutaneous signs and symptoms, and better outcomes on 5-year survival. Lung involvement in this group of patients plays a fundamental role in the treatment selection since MTX may lead to lung injury[25,26].

Ruperto et al.[27] conducted a randomized trial in patients with newly diagnosed juvenile dermatomyositis that included 139 patients and were split into prednisone, prednisone plus cyclosporine, or prednisone plus MTX. Improvement at 24 months follow-up favored the combined treatment versus prednisone alone. The safety analysis seemed to favor MTX over cyclosporine as a combination therapy. Infections were more frequent with the combined treatment and adverse effects included the increase in liver enzymes, nausea, hepatitis, and lung disorder.

Localized and systemic sclerosis

Localized sclerosis

Localized sclerosis, also known as morphea, is a disease that classically affects the dermis with excessive collagen deposition, leading to localized sclerosis, and in severe cases progressing for years developing functional, cosmetic, and psychological disabilities[28].

A recent Cochrane review concluded that out of 100 children and teenagers treated with MTX and prednisone, 67 patients improve, with little or no difference in side effects compared to the group treated with placebo and prednisone, based on low-quality evidence studies[29].

Studies have been conducted in different subtypes of localized sclerosis showing an adequate response to the recommended dose of 0.25 mg/m^2/week to a maximum dose of 25 mg/week[29]. Most studies report an 80% improvement with recurrence rates ranging from 28 to 44% in 16-20 weeks after suspending MTX[30]. Zulian et al.[31] conducted a randomized placebo-controlled trial in patients with juvenile localized scleroderma, showing that MTX is safe and effective. The authors suggest that MTX should be maintained for a minimum of 12 months before tapering the dosage.

Platsidaki et al.[28] conducted a retrospective study in patients with generalized plaque scleroderma, unresponsive to topical treatments, treated with MTX 15 mg. After 12 months of therapy, 30% presented very good response and 50% only achieved good response. Finally, a retrospective study included 7 patients with *coup de sabre* treated with MTX; 100% improved in an average of 2 months; MTX was discontinued in an average of 16 months[32]. MTX can be considered a first-line systemic treatment due to the existing evidence[33].

Systemic sclerosis

Systemic sclerosis is a chronic autoimmune disorder, targeting internal organs and skin, that leads to fibrosis[33]. Several treatments are often required and must be chosen depending on existing target organ damage. MTX is the best treatment to decrease skin fibrosis[34]

and should be considered in early diffuse systemic sclerosis, although it is important to consider that positive effects on other organs have not been shown[33]. Randomized controlled trials showed improvement in skin score at 10-15 mg/week[34], and it is recommended to maintain treatment for 6-12 months[33], studies have shown few cases with discontinuation due to adverse effects, and no significant differences in mortality were shown[34].

Alopecia areata

Alopecia areata is a cause of non-scaring hair loss with an estimated lifetime prevalence of approximately 2%[35]. Alopecia areata exerts a significant impact on morbidity and patient's quality of life[36]. In the pediatric population, it is associated with a poorer prognosis than adults[37], as the treatment frequently presents low tolerability of therapy and the need for continuing blood testing[36].

MTX has been used both as monotherapy and as an adjunct to corticosteroids, however, there is insufficient evidence regarding low-dose MTX is useful for maintaining hair growth in extensive disease[38]. The available evidence suggests that it is well-tolerated and may offer a useful treatment alternative[35], but there remains a lack of clear definitive evidence or guidelines[36].

In the pediatric population, it should be considered the use of MTX in severe and resistant cases, having the advantage that it can be maintained for several years, in contrast with other treatments with a high rate of relapse or no data in long-term effects such as methylprednisolone or diphencyprone[36,37].

Phan et al.[38] performed a systematic review and meta-analysis in patients with alopecia areata treated with corticosteroid and MTX, showing a complete response (100% regrowth of hair) in 35.8% (adults: 44.7% and pediatric: 11.6%) and good response (50-100% regrowth of hair) in 63.2% (adult: 69.3% and pediatric: 46.5%) with an average time of regrowth of 3.125 months and complete regrowth in 9.9 months.

Pityriasis rubra pilaris

Pityriasis rubra pilaris is an uncommon papulosquamous inflammatory disease of the skin, which may progress to erythroderma[39]. Some authors state that after 3 years, up to 80% of these cases may develop spontaneous remission, therefore, treatment efficacy is difficult to assess, however, non-remitting pityriasis rubra pilaris has been described[39]. The use of MTX is strongly supported and its mechanism of action is presumed as an antiproliferative and anti-inflammatory agent[39].

A literature review including 116 cases reported complete clearance in 23.3% and excellent clinical response in 17.2% of the patients[39].

Malignancy

Mycosis fungoides

Mycosis fungoides is the most prevalent subtype in the group of cutaneous T-cell lymphomas[40]. LD-MTX has been used to treat MF for many years, however, data about its effectiveness are very limited[8]. It is not clear the exact mechanism MTX in mycosis fungoides; it has been proposed that the anti-inflammatory, immunomodulatory, and cytostatic are the main involved mechanisms[41].

MTX is usually administered orally as the second-line treatment according to the European Organization for Research and Treatment of Cancer and the World Health Organization recommendations for Stages IA-IIB, with a recommended dose of 20-75 mg weekly, usually divided into three doses every 12 h and may be combined with glucocorticoids, PUVA, or interferon[41].

Zackheim et al.[8] studied 69 mycosis fungoides patients treated with LD-MTX (median dose: 25 mg/weekly, maximum dose: 75 mg), and it was observed that initially not responding patients, improved with higher doses, concluding that the effectiveness of MTX is dose dependent.

Olek-Hrab et al.[41] included 79 patients treated with MTX 25-75 mg weekly, reporting that remission was achieved in 70% of the patients in 1-3 months. Longer remission periods were associated with longer treatment duration, however, the rate of adverse effects also increased. The authors showed that remission of nodular mycosis fungoides treated with LD-MTX was achieved in six out of eight patients; on the other hand, Zackheim et al.[8] found that in a group of seven patients with nodular mycosis fungoides, only one achieved remission. MTX should be considered when all the topical methods and phototherapy have failed or cannot be used.

Keratoacanthoma

Keratoacanthoma is considered well-differentiated squamous cell carcinoma with a low malignancy potential due to their tendency to present involution. Clinically, these tumors are characterized by an initial rapid growth

rate followed by the aforementioned involution[42]. Keratoacanthoma has distinct clinical features, and histopathological confirmation is advised to rule out squamous cell carcinoma[42], before starting intralesional treatment and a repeat biopsy in case of failure to respond after two intralesional MTX treatment with low recurrence rate (1-8%)[43]. Several intralesional therapies have emerged in recent years providing advantages such as avoidance or delaying surgery in high-risk groups, better cosmetic results, or decreasing tumor size[43,44]. Due to the capacity of inhibiting growth in fast-growing tumors, MTX has shown good efficacy in managing keratoacanthomas[42].

Moss et al.[43] included 157 tumors treated with intralesional MTX, with a resolution of 88% with 1-4 doses (average total dose: 8.12 mg). In non-responding cases, 8/9 presented an average decrease in size of 3.2 × 4.4 mm, none of the tumors showed an increase in size after the intralesional MTX[43].

Basal cell carcinoma

Basal cell carcinoma accounts for almost 80% of the cases of skin cancer, occurring more frequently in the head[45], and usually had a slow growth rate with extremely rare metastasis capacity. Simple surgical excision and Mohs surgery are the gold standards[45]; but in patients who are not good candidates for surgical treatment, therapeutic alternatives are needed; intralesional MTX has been studied as an option in the treatment of basal cell carcinoma with no efficacy[45].

MTX acts by suppressing mitosis that inhibits DNA synthesis during cell replication in rapidly growing tumor, however, since basal cell carcinoma is a slow-growing tumor, MTX is not recommended. Balighi et al.[45] reported 40 nodular basal cell carcinoma in 11 patients treated with intralesional MTX in three different schemes: 2.5 mg/ml in 10 lesions, 10 mg/ml in 21 lesions, and 25 mg/ml in 9 lesions. No significant changes in the shape or the tumor size were observed, concluding in the lack of efficacy of MTX in the treatment of basal cell carcinoma.

Conclusions

MTX has been used for many years in the treatment of skin diseases; it continues to be a safe, effective, and low-cost option. In this review, we present a comprehensive discussion of the main uses of LD-MTX in cutaneous diseases. Adequate patient selection is of utmost importance for ensuring safety, also, serial laboratories are required for adverse events monitoring.

Although multiple dermatologic conditions appear to benefit from LD-MTX, high-quality evidence is still lacking, warranting further investigation for better decision-making, and improves patient outcomes.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

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Confidentiality of data. The authors declare that no patient data appear in this article.

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