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*Published in:*
Dermatologic Therapy

*DOI (link to publication from Publisher):*
10.1111/dth.14404



*Publication date:*
2021

*Document Version*
Accepted author manuscript, peer reviewed version

# Intralesional methotrexate in dermatology: diverse indications and practical considerations

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Keywords: Intralesional, Keratoacanthoma, Methotrexate, Squamous cell carcinoma, warts

Running title: Intralesional methotrexate in dermatology

Word count (excluding title page and references): 2030



This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/dth.14404

**Conflicts of interest**: none

**Funding:** none

Consent for publication: All authors have approved this final submitted version of the manuscript and consent to its submission for consideration of publication

Conflicts of interest: none

**Data Availability Statement:** Data sharing is not applicable to this article as no new data were created or analyzed in this study.

**Abstract**

Intralesional methotrexate (IL-MTX) is a long-established treatment, which is arguablyunderutilized by dermatologists. We describe the underlying evidence base and practical considerations for its broad range of cutaneous indications,including in cutaneous oncology (keratoacanthomas, squamous cell carcinomas, lymphomas), inflammatory dermatology (nail psoriasis, plaque psoriasis, pyoderma gangrenosum, cutaneous Crohn's disease, amyloidosis), cutaneous infections (viral warts) and for treatment of filler complications. In certain circumstances, IL-MTX can be more efficacious and less invasive than other treatments, with fewer adverse effects. Dermatologists should consider using IL-MTXfor a range of recalcitrant cutaneous conditions, particularly for those patients not amenable to surgery or systemic therapy.

## Background

Intralesional methotrexate (IL-MTX) is a cytotoxic chemotherapeuticagent, used in dermatology for many years.[1] Its particularly warranted in patients for whom surgical treatment or systemic therapies are contraindicated or undesirable. IL-MTX can be used asmonotherapy or as neoadjuvant treatment with acceptable cosmetic resultsanda low side-effect profile.[2] This articlereviews the literature and explores the uses of IL-MTX in cutaneous oncology, including keratoacanthomas (KA), squamous cell carcinomas (SCC) and lymphomas (Table 1). In addition, we elaborate on the use of IL-MTX in inflammatory, infectious and cosmetic dermatological indications. Whilst IL-MTX may not be licensed in certain indications, this review is highly applicable todermatologists.

## Cutaneous oncology

IL-MTXplays an increasingly fundamental role in cutaneous oncologywith several benefits over other chemotherapeutic agents, requiring fewer injections with longer treatment intervals and is more cost-effective.[1]Whilst surgical excision is the mainstay of treatment in cutaneous oncology, IL-MTX has a role in some cases of KA, SCC, and cutaneous lymphoma.[2]

## Mechanism of action

Rapidly growing tumors respond to MTX due to its ability to inhibit DNA synthesis in rapidly dividing cells.[3] MTX blocks tetrahydrofolate synthesis, preventing downstream production of the nucleotides thymidine and purine and is rapidly absorbed by cells with high mitotic rates.[3,4] Side-effects tend to be minor and relate mostly to injection pain.[5] Direct intralesional therapy has the advantage of higher drug concentration locally with reduced systemic effects compared with oral MTX, rendering it a good choice for localized disease where systemic therapy is less desirable or surgical intervention is not feasible.

**Keratoacanthoma**

KA is a cutaneous tumor occurring on sun-exposed areas,typicallyin elderly patients, often proving clinically and histologically difficult to differentiate from well-differentiated SCC. Rapid growthis a typical feature, followed byself-involution. Given the diagnostic challenge in differentiating KA from a well-differentiated SCC,which carries a metastatic risk, treatment is often recommended.[6]

Systematic literature review revealed 11 case series and 12 case reports usingIL-MTXinKA, most of which were confirmed on biopsy(except in three studies) (Table 2).[7] Average treatment dosewas typically 25mg per session,with lesions larger than 10mm requiring higher doses.[7,8,9]Pain associated with IL-MTX was controlled in one series by the addition of lidocaine.[8] Across the studies, 74-100% of lesions resolved. Serious systemic adverse-effects were not reported. The commonest side-effect

observed was injection-site pain.[10-13]Treatment intervals ranged from7-38 days with patients requiring one to eight sessions. Korean patients required more treatment sessions albeit with shorter intervals compared to Caucasian patients.[11,12]It was postulated that ethnicity might affect the concentration of MTX required, possibly secondary to pharmacogenomics.[14]None of the patients reported in the studies had a recurrence with follow-up periods varying from six weeks to four years.[6-13, 15-18]All treated cases achieved resolution withhigh patient satisfaction. KA can resolve spontaneously and since treatment was not a placebo, it is possible that some well-differentiated SCCsmay have responded withouttreatment.[10,19-9]

One group of patients whom caution is required when using IL-MTX are organ transplant recipients (OTRs). Bender and colleagues[30]found increased genetic expression of *MMP14*associated with the invasive capability of tumors following IL-MTX, implying that more aggressive tumor behavior could be observed following treatment with IL-MTX. The authors therefore advise caution with IL chemotherapy for KAs in OTRs.[30]

In one study, all KAs treated with IL-MTX were found on the extremities and not on the face where they are typically located, suggestive of potential selection bias.[31]Lack of confirmatory histological diagnosis added to the difficultyof distinguishing the clinical diagnosis of KA.[31] Further challenges are posed by the fact that 100% of clinically diagnosed KAs on the extremities resolved with only 79% of

facial KAs responding to IL-MTX.[15,31]Another caveat when considering KA treatment is that KAs are thought to resolve spontaneously; single reports of KA resolution following any treatment may simply be a function of their natural history. Where diagnosis is clinical rather than histological, presumed-KA lesions may represent well-differentiated SCCs that have responded to treatment. Currently, whilst there is some evidence to suggest the use of IL-MTX in KA, this is based on case series with issues of bias and lack of consistent histological analysis. Large randomized trials are required to evaluate the exact role of IL-MTX in KA management.

**Squamous cell carcinoma**

Given the successful reports of IL-MTX in KA, researchers have attempted to explore the efficacy of IL-MTX in SCC.[32]IL-MTX is typically given in doses not exceeding 50mg,twice per weekfor SCC.[1]

Three case series and two case reports (*n*=138) detailed the use of IL-MTXincutaneous SCC (subtype not specified) (Table 3). Neoadjuvant IL-MTX and excision surgery was compared with excision surgery alone in two studies (*n*=126).[32,33]Neoadjuvant IL-MTX was found to produce better resolution of lesions than surgery alone. In one study, 92% of patients hadclinical reduction of lesionssizeconfirmed on ultrasound prior to surgical intervention.[33]

In a prospective study,involving 10 patients with cutaneous SCC (histological differentiation not specified),two doses of IL-MTX 20mg (50mg/mL) with weekly intervals was administered.[34] All patients responded to treatment with average decreases in mean lesion diameter of 68% with a third achieving complete resolution of their tumors. No recurrence was observed following a mean follow-up of 18.4 months.[34]Two case reports discussed the successful treatment of IL-MTX for SCC (25mg/mL). Three to four injections were required with weekly intervals over three to four weeks.[35,36]All lesions resolved and decreased in size, with no recurrence during follow-up at eight months.[35,36]Side-effectswere related to pain during injectionin one patient.[36]

**Lymphoma**

Primary cutaneous CD30+ anaplastic large cell lymphoma (PCALCL), a type of cutaneous T-cell lymphoma in which IL-MTX has been used successfully. Its action is related to DNA synthesis inhibition and possible anti-inflammatory properties.[5] Three case reports present patients successfully treated with IL-MTX (Table 3).[5,37,38]Injections used were0.2ml (2.5mg) given once a week,with a total dose of 70mgover several weeks, 7.5mg/week over two months and 25mg/mL over two treatments respectively. The number of sessions required ranged from two to eight injections with intervals from one-two weeks. All lesions resolved and no relapses were reported at follow-up (which ranged from 9-20 months). In one case report, post-treatment biopsy supported the therapeutic efficacy of IL-MTX, showing chronic

inflammation and fibroplasia, associated with scar formation, with no residual tumor.[38]

Specific cutaneous expression of B-cell chronic lymphocytic leukemia (B-CLL) is a rare phenomenon and may present assolitary or grouped nodules, plaques, papules or large tumours.[39]IL-MTX has been used at a dose of 25-50mg/mLin suchlesions.[1]Eight tumors, injected with 25mg/mL IL-MTX over two sessions, showed complete regression at two months with no relapse at 12-months.[40]Biopsy showed chronic inflammation and fibroplasia, as found in PCALCL post-treatment with IL-MTX, with no residual tumor.[40]

Whilst there is no strong evidence to support the routine use of IL-MTX in cutaneous tumors, this treatment modality may offer a cost-effective alternative to newer and more costly therapies in cutaneous oncology and may be suitable in selected cases where systemic or surgical therapy is not possible.[41,42]

**Inflammatory disorders**

**Nail psoriasis**

MTX has long been used in psoriasis, most frequently in its oral form. Its mode of action is on epidermal hyperplasia through its anti-proliferative effects and in an anti-inflammatory and immunomodulatory capacity.[43] Some direct cytotoxic effects on

keratinocytes could occur due to the effect on DNA synthesis and subsequent mitotic activity.[44]

Localized injections of IL-MTX may avoid the need for systemic medications in recalcitrant cases of nail psoriasis not responding to topical agents.Onerandomized study, two case series and three case reports explored itsuse in nail psoriasis (Table 4).[45-49]In the randomized study (*n*=32), diluted triamcinolone acetonide (TAC)in 0.1mg/mL, MTX in 0.1mg/mL and serum physiological solution were randomly injected into psoriatic fingernails.[45] A total of four injections given at four different nail points at three weekly intervals. These were injected into the nail folds or nail matrices or both in three different nails in each patient. 62% of patients in the MTX group and 47% in the TAC group showed clinical improvement although there was little difference in the Nail Psoriasis Severity Index (NAPSI) scores between IL-MTX and TAC. Onycholysis improved significantly in the TAC group (*p*=0.039). Pitting (*p*=0.001) and leukonychia (*p*=0.002*)* improved significantly in the MTX group.[45]
In a separate comparative study,[46](*n*=20) each patient was injected with three different drugs in different nails. Drugs injected wereTAC (10mg/mL), IL-MTX (25mg/mL) and cyclosporine (50mg/mL in 0.05mL). A total of two intramatricial injections were given in each nail oversixweeks. At 24weeks, the MTX group showed greater than 75% improvement in over half of the nails with slightly lower results in the TAC group and only a third of nails improved in the cyclosporine group.The IL-MTX group did however report the lowest incidence of side-effects, mainly injection-

related pain and numbness.[46]These findings were replicated by a case series,[47] (*n*=4) (which found a significant decrease in the NAPSI from 4.87 to 2.17 following five treatments with IL-MTX (2.5mg). The two other case reports,[48-49] found progressive improvement in nail dystrophy withno relapse after one year (0.1mL, 2.5mg per nail and 0.1mL of a 5mg/2mL solution respectively, both given monthly for three months).[48-49]IL-MTX for nail psoriasis (and potentially other inflammatory nail conditions) could be considered in patients recalcitrant to topical treatments whose disease is localized to the nails.

**Infection**

**Viral warts**

Viral warts are benign lesions of the skin caused by human papillomavirus and can prove resistant to treatment.[50] MTX was found to have an anti-viral effect in cells infected with Zikavirus possibly through inhibition of dihydrofolate reductase.[51]It is plausible that MTX could act on viral warts in a similar manner (Table 4).[50]

In a randomized controlled trial (*n*=60), patients were split into IL-MTX (2mg/mL) versus saline injections as placebo.[50]Injections were given every week for a maximum of six treatments. There was no statistically significant difference in response.

In a separate open-label randomized trial,42 patients with common warts were treated.[52]IL-MTXwas administered on one side of their body whilst the other side was treated with electrocautery. Patients were given 2mg/mL, 1mg/mL or 0.5mg/mL with a maximum of three injections with a 15-day interval between treatments. Only 5% of cases were resolved by MTX compared with 71% cleared by electrocautery ($p$<0.01).[52]

The current evidence for the use of IL-MTX in warts is weak, and as such, is not recommended when alternative treatments are available.

**Miscellaneous**

IL-MTX has been used in several other conditions successfully (Table 2). IL-MTX has been used successfully in cutaneous plaque psoriasis,[53] for treating ulcers associated with pyoderma gangrenosum,[54]for cutaneous Crohn's disease[55] and cutaneous amyloidosis.[55] IL-MTX has also been used to treat granulomatous foreign body reactions associated with fillers.[57-58]

**Side-Effects**

Minor side-effects have been reported in the studies relating to IL-MTXwe have reviewed, namely transient post-injection pain.[46]These minor side-effects appear

unrelated to the treated pathology or dose used. Whilst most of the side-effects reported were minor, serious effects which included pancytopenia, mucositis and hepatitis were reported in a patient treated for SCC.[59]It is likely that a background of pre-existing renal failure contributed to serum accumulation levels and subsequent toxicity.[60]

Pancytopenia was also reported in two case reports following a single injection of IL-MTX 25mg for KA treatment,[61]with one patientsuffering from renal failure.[62]It is recommended that baseline blood cell-counts, liver-function tests and renal function are checked prior to treatment, with follow-up laboratory testsone week after the first treatment.[6] Dermatologists must exert caution in prescribing this drug when patients have known risk-factors such as renal dysfunction.[62]Notwithstanding these sporadic reports, IL-MTX appears safe, efficacious and cost-effectiveviable alternative in treating various dermatological conditions.[61]

**Conclusion**

In cutaneous oncology, most studies have demonstrated the utility of IL-MTX in KA and its potential uses in SCC with few case reports in lymphoma. In inflammatory dermatology,IL-MTX has proved effective particularly in nail psoriasis with a comparable efficacy to corticosteroids and could also be considered in localized cutaneous plaque psoriasis andCCD. A more recent interesting use of IL-MTX has been for treatment of GFBR. IL-MTX is rarely associated with severe side-effects, is

cost-effective and could be a safer and better tolerated treatment for patients suffering from a broad range of dermatological conditions.



**References**

(1) Good LM, Miller MD, High WA. Intralesional agents in the management of cutaneous malignancy: a review. *J Am Acad Dermatol*. 2011;64(2):413-22.

(2) Bonerandi JJ, Beauvillain C, Caquant L, *et al*. Guidelines for the diagnosis and treatment of cutaneous squamous cell carcinoma and precursor lesions. *J Eur Acad Dermatol.* 2011;25:1-51.

(3) Olsen EA. The pharmacology of methotrexate. *J Am Acad Dermatol*. 1991;25:306–318.

(4) Bleyer WA. The clinical pharmacology of methotrexate: new applications of an old drug. *Cance*r 1978;41 :36-51.

(5) Yokoi I, Ishikawa E, Koura A, *et al*. Successful treatment of primary cutaneous anaplastic large cell lymphoma with intralesional methotrexate therapy. *Acta Derm-Venereol*. 2014 May 1;94(3):319-20.

(6) Annest NM, VanBeek MJ, Arpey CJ, Whitaker DC. Intralesional methotrexate treatment for keratoacanthoma tumors: a retrospective study and review of the literature. *J Am Acad Dermatol*. 2007;56(6):989-993.

(7) Smith C, Srivastava D, Nijhawan RI. Intralesional methotrexate for keratoacanthomas: a retrospective cohort study. *J Am Acad Dermatol.*2020;doi: https://doi.org/10.1016/j.jaad.2020.03.096.

(8) Aubut N, Alain J, Claveau J. Intralesional Methotrexate Treatment for Keratoacanthoma Tumors: A Retrospective Case Series. *J Cutan Med Surg*. 2012;16(3), 212–217.

(9) Hurst LN, Gan BS. Intralesional methotrexate in keratoacanthoma of the nose. *Br J Plast Surg* 1995;48(4):243-6.

(10) Scalvenzi M, Patrì A, Costa C, *et al*. Intralesional Methotrexate for the Treatment of Keratoacanthoma: The Neapolitan Experience. *Dermatol Ther (Heidelb)*. 2019;9(2):369-372.

(11) Melton JL, Nelson BR, Stough DB, *et al*. Treatment of keratoacanthomas with intralesional methotrexate. *J Am Acad Dermatol*. 1991;25(6):1017-23.

(12) Yoo MG, Kim IH. Intralesional methotrexate for the treatment of keratoacanthoma: retrospective study and review of the korean literature. *Ann Dermatol*. 2014;26(2):172-6.

(13) Patel NP, Cervino AL. Treatment of keratoacanthoma: Is intralesional methotrexate an option? *Can J Plast Surg*. 2011;19(2):e15-8.

(14) Kremer JM. Methotrexate pharmacogenomics. *Ann Rheum Dis*. 2006;65(9):1121-3.

(15) Moss M, Weber E, Hoverson K, Montemarano AD. Management of Keratoacanthoma: 157 Tumors Treated With Surgery or Intralesional Methotrexate. *Dermatol Surg*. 2019;45(7):877-883.

(16) Rossi AM, Park B, Qi B, *et al*. Solitary Large Keratoacanthomas of the Head and Neck: An Observational Study. *Dermatol Surg*. 2017;43(6):810-816.

(17) Cuesta-Romero C, de Grado-Peña J. Intralesional Methotrexate in Solitary Keratoacanthoma. *Arch Dermatol.* 1998;134(4):513–514.

(18) Saporito R, Harris M, Housewright C. Intralesional methotrexate for treatment of keratoacanthoma and well-differentiated squamous cell carcinoma: 8598. *J Am Acad Dermatol.*. 2019;81(4).

(19) Della Valle V, Milani M. Efficacy and Safety of Intralesional Methotrexate in the Treatment of a Large Keratoacanthoma of the Dorsal Hand in a 99-Year-Old Woman. *Case Rep Dermato*l. 2018;10(3):247-250.

(20) Panther D, Nino T, Macknet KD Jr, Macknet C. Eruptive keratoacanthomas as a complication of fractionated CO2 laser resurfacing and combination therapy with imiquimod and intralesional methotrexate. *Dermatol Surg*. 2015;41(1):172-175.

(21) Cohen PR, Schulze KE, Teller CF, Nelson BR. Intralesional methotrexate for keratoacanthoma of the nose. *Skinmed*. 2005;4(6):393-395.

(22) Doerfler L, Hanke CW. Treatment of Solitary Keratoacanthoma of the Nose With Intralesional Methotrexate and Review of the Literature. *J Drugs Dermatol*. 2019;18(7):693-6.

(23) Veerula VL, Ezra N, Aouthmany M, *et al*. Multiple keratoacanthomas occurring in surgical margins and de novo treated with intralesional methotrexate. *Cutis*. 2016;98(6):E12-5.

(24) Barros B, Helm K, Zaenglein A, Seiverling E. Keratoacanthoma-Like Growths of Incontinentia Pigmenti Successfully Treated with Intralesional Methotrexate. *Pediatr Dermatol.* 2017 Jul;34(4):e203-4.

(25) de Visscher JG, van der Wal KG, Blanken R, Willemse F. Treatment of giant keratoacanthoma of the skin of the lower lip with intralesional methotrexate: a case report. *J Oral Maxillofac Surg*. 2002;60(1):93-95.

(26) Remling R, Mempel M, Schnopp N, Abeck D, Ring J. Intraläsionale Methotrexat-Injektion. Eine wirkungsvolle, zeit- und kostensparende Therapiealternative bei operativ schwierig zu behandelnden Keratoakanthomen [Intralesional methotrexate injection: an effective time and cost saving therapy alternative in keratoacanthomas that are difficult to treat surgically]. *Hautarzt*. 2000;51(8):612-614.

(27) Spieth K, Gille J, Kaufmann R. Intralesional methotrexate as effective treatment in solitary giant keratoacanthoma of the lower lip. Dermatol. 2000;200(4):317-9.

(28) Rambhia SH, Rambhia KD, Gulati A. A rare case of multiple keratoacanthomas treated with oral acitretin and intralesional methotrexate. *Indian Dermatol Online J*. 2016;7(4):321-3.

(29) Basoglu Y, Metze D, Nashan D, Ständer S. Keratoacanthoma with perineural invasion: an indicator for aggressive behavior?. *J Dtsch Dermatol Ges*. 2008;6(11):952-955.

(30) Bender N, Duncan NE, Schmid R, Kasprzak J, Olasz-Harken E. 129 Genetic transformation of keratoacanthoma-type cutaneous squamous cell carcinoma following intralesional chemotherapy. *J Invest Dermatol.* 2018;138(5):S22.

(31) Salido-Vallejo R, Cuevas-Asencio I, Garnacho-Sucedo G, *et al*. Neoadjuvant intralesional methotrexate in cutaneous squamous cell carcinoma: a comparative cohort study. *J Eur Acad Dermatol Venereol*. 2016;30(7):1120-1124.

(32) Wessman L, Miller DD. Neoadjuvant, intralesional methotrexate treatment of cutaneous squamous cell carcinoma. J Am Acad Dermatol. 2017;76(6):AB177.

(33) Bergón-Sendín M, Pulido-Pérez A, Carretero López F, Díez-Sebastián J, Suárez-Fernández R. Cutaneous Ultrasound for Tumor Thickness Measurement in Squamous Cell Carcinoma: The Effect of Neoadjuvant Intralesional Methotrexate in 40 Patients. *Dermatol Surg*. 2020;46(4):530-536.

(34) Bergón-Sendín M, Pulido-Pérez A, Suárez-Fernández R. Neoadjuvant intralesional methotrexate in squamous cell carcinoma of the lip. *Australas J Dermatol*. 2019;60(2):158-160.

(35) Plascencia-Gomez A, Calderón-Rocher C, Proy-Trujillo H, Moreno-Coutiño G. Neoadjuvant intralesional methotrexate before surgery in squamous cell carcinoma. *Dermatol Surg*. 2014;40(5):584-586.

(36) Moye MS, Clark AH, Legler AA, Milhem MM, Van Beek MJ. Intralesional Methotrexate for Treatment of Invasive Squamous Cell Carcinomas in a Patient Taking Vemurafenib for Treatment of Metastatic Melanoma. *J Clin Oncol*. 2016;34(14):e134-e136.

(37) Nandini A, Mysore V, Sacchidanand S, Chandra S. Primary cutaneous anaplastic large cell lymphoma arising from lymphomatoid papulosis, responding to low dose methotrexate. *J Cutan Aesthet Surg.* 2009;2(2):97-100.

(38) Blume JE, Stoll HL, Cheney RT. Treatment of primary cutaneous CD30+ anaplastic large cell lymphoma with intralesional methotrexate. *J Am Acad Dermatol*. 2006;54(5 Suppl):S229-S230.

(39) Robak E, Robak T. Skin lesions in chronic lymphocytic leukemia. Leuk Lymphoma 2007; 48: 855–865.

(40) Anyfantakis V, Dammak A, Wierzbicka-Hainaut E, *et al*. Efficacy of intralesional methotrexate in specific cutaneous involvement of B-cell chronic lymphocytic leukaemia. *J Eur Acad Dermatol.* 2010;24(7):856.

(41) Chitwood K, Etzkorn J, Cohen G. Topical and intralesional treatment of nonmelanoma skin cancer: efficacy and cost comparisons. *Dermatol Surg*. 2013;39(9):1306-1316.

(42) Kirby JS, Miller CJ. Intralesional chemotherapy for nonmelanoma skin cancer: a practical review. *J Am Acad Dermatol*. 2010;63(4):689-702.

(43) Warren RB, Chalmers RJ, Griffiths CE, Menter A. Methotrexate for psoriasis in the era of biological therapy. *Clin Exp Dermatol*. 2008;33(5):551-554.

(44) Kamel R, Al-Hakiem M, et al. Pharmacokinetics of small doses of methotrexate in patients with psoriasis. *Acta Derm Venerol (Stockh)* 1988;68:267-70.

(45) Üstüner P, Balevi A, Özdemir M. The Comparison of the Efficacy and Safety of Intralesional Triamcinolone Acetonide and Methotrexate Injections for the Treatment of Fingernail Psoriasis. *J Ank Med Sch.* 2018;71(2):145-51.

(46) Mittal J, Mahajan BB. Intramatricial injections for nail psoriasis: An open-label comparative study of triamcinolone, methotrexate, and cyclosporine. *Indian J Dermatol Venereol Leprol* 2018;84:419-23.

(47) Grover C, Daulatabad D, Singal A. Role of nail bed methotrexate injections in isolated nail psoriasis: conventional drug via an unconventional route. *Clin Exp Dermatol.* 2017;42(4):420-3.

(48) Duarte AA, Carneiro GP, Murari CM, Jesus LC. Nail psoriasis treated with intralesional methotrexate infiltration. *An Bras Dermatol.* 2019;94(4):491-2.

(49) Mokni S, Ameur K, Ghariani N, *et al*. A case of nail psoriasis successfully treated with intralesional methotrexate. *Dermatol Ther*. 2018;8(4):647-51.

(50) Abdo HM, Elrewiny EM, Elkholy MS, Ibrahim SM. Efficacy of Intralesional Methotrexate in the Treatment of Plantar Warts. *Egypt J Hosp Med.* 2019;76(6):4390-5.

(51) Beck S, Zhu Z, Oliveira MF, *et al*. Mechanism of action of methotrexate against Zika virus. *Viruses*. 2019;11(4):388.

(52) Al-Khafaji BA, Al-Kelaby HN, Alkhafaji KA. Evaluation of Intralesional Methotrexate in Comparison with Electrocutary in Treatment of Common Warts. *Med J Babylon*. 2010;7(3-4):379-82.

(53) Attia HO, Kawy FA, Hafiz HS. Intralesional methotrexate vs intralesional 5-fluorouracil in the treatment of localized plaque psoriasis: a comparative clinical and dermoscopic study. *Sci J Al-Azhar Med Fac Girls*; 2019;3(3):643.

(54) del Puerto C, Navarrete-Dechent CP, Carrasco-Zuber JE, Vera-Kellet C. Intralesional methotrexate as an adjuvant treatment for pyoderma gangrenosum: A case report. *Indian J Dermatol Venereol Leprol* 2017;83:277.

(55) Miles A, Sayed C. Using intralesional methotrexate to treat recalcitrant cutaneous Crohn's disease: 7919. *J Am Acad Dermatol*. 2018;79(3).

(56) Raymond J, Choi J. Nodular cutaneous amyloidosis effectively treated with intralesional methotrexate. *JAAD Case Rep*. 2016 Sep;2(5):373.

(57) Chiang YZ, Pierone G, Al-Niaimi F. Dermal fillers: pathophysiology, prevention and treatment of complications. *J Eur Acad Dermatol*. 2017;31(3):405-13.

(58) Broly M, Marie J, Picard C, *et al*. Management of granulomatous foreign body reaction to fillers with methotrexate. *J Eur Acad Dermatol*. 2019;34(4):817-820.

(59) Flynn KN, Johnson MS, Brink WC, Smith DL. Pancytopenia, mucositis, and hepatotoxicity after intralesional methotrexate injection in a patient treated with peritoneal dialysis. *React Wkly.* 2012;1404:29.

(60) Strang A, Pullar T. Methotrexate toxicity induced by acute renal failure. *J R Soc Med*. 2004;97(11):536-7.

(61) Goebeler M, Lurz C, Kolve-Goebeler M, Bröcker E. Pancytopenia After Treatment of Keratoacanthoma by Single Lesional Methotrexate Infiltration. *Arch Dermatol.* 2001;137(8):1104–1105.

(62) Cohen PR, Schulze KE, Nelson BR. Pancytopenia after a single intradermal infiltration of methotrexate. *J Drugs Dermatol*. 2005;4(5):648-651.

**Table 1.** Summary of IL-MTX's Uses in Dermatology

| Cutaneous Oncology | Inflammatory Dermatoses | Cutaneous Infections | Treatment of cosmetic complications |
|---|---|---|---|
| Keratoacanthoma (References 6-31) | Nail psoriasis (References 43-49) | Viral warts (References 50-52) | Granulomatous foreign body reactions (References 57-58) |
| Squamous cell carcinoma (References 32-36) | Plaque psoriasis (Reference 53) | | |
| Lymphoma (References 5,37-40) | Pyoderma gangrenosum (References 54) | | |
| | Cutaneous Crohn's disease (Reference 55) | | |

| | | |
|---|---|---|
| Cutaneous amyloidosis (References 56) | | |

**Table 2.** Uses of IL-MTXfor Keratoacanthoma

| Study Authors | Intervention | Outcomes | Side-effects |
|---|---|---|---|
| KERATOACANTHOMA | | | |
| Smith C, Srivastava D, Nijhawan RI[7] | IL-MTX (concentration 25mg/mL) | 95.7% of lesions were treated successfully.2.90% of lesions partially responded and one lesion showed no response (*n*=29) | None reported |
| Aubut N, Alain J, Claveau J[8] | IL-MTX injections 25mg/mL diluted with lidocaine and 1% adrenaline or saline. | Patients had a mean of 1.8 injection sessions and a complete resolution was observed in 74% of the tumors. 26% did not respond to treatment (*n*=46) | None reported |
| Hurst LN, Gan BS[9] | Patient 1 - IL-MTX 25mg/mL<br>Patient 2 – IL-MTX 25mg/mL, 1.0mL for 3 injections | Patient 1 - Lesion was markedly reduced after 10 days and was completely resolved after 20 days. At 18 months, a slight scar remained.<br>Patient 2 – at 1 month, lesion was completely resolved and at 9 months a small scar remained (*n*=2) | None reported |
| Scalvenzi M, Patrì A, Costa C, *et al* [10] | Patients treated with IL-MTX weekly. 4-8 injections were required (*n*=11) | All patients had complete resolution of their tumors (*n*=11) | Minimal atrophy |
| Melton JL, Nelson BR, | 9 Caucasian patients were injected with 0.4-1.5ml of 12.5 or | 100% of lesions had complete resolution of their lesions after 1-4 weeks. No recurrences were reported after follow-up. Minimal or no scarring | injection discomfort |

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| Stough DB, *et al.*[11] | 25mg/mL MTX | reported (*n*=9) | |
| Yoo MG, Kim IH[12] | 0.1-1.8ml of IL-MTX at a concentration of 12.5 -25mg/mL (*n*=11) | The mean number of treatment sessions required was 4.3. 91% of patients achieved complete resolution of their keratoacanthoma (*n*=11) | Scarring rarely |
| Patel NP, Cervino AL[13] | Patients were treated with 2-4 IL injections MTX (12.5-25mg per injection) (*n*=9) | 88.9% of patients had complete resolution of their lesions and one patient had treatment failure(*n*=9) | transient injection pain (*n*=1) |
| Mohs M, Weber E, Hoverson K, Montemarano AD[15] | 73 tumors (54 patients) were treated with IL-MTX (*n*=136) | 88% of tumors were cured. 11 patients had multiple tumors (29 tumors) all of which were successfully treated with IL-MTX (*n*=136) | None reported |
| Arnett NM, VanBeek MJ, Arpey CJ, Whitaker DC[6] | 0.3-2mL of IL-MTX injected at a concentration of 12.5 - 25mg/mL. (*n*=18) | A complete response was found in 83% of patients (*n*=18) | None reported |
| Rossi AM, Park B, Qi B, *et al.*[16] | Patients treated with IL-MTX and then Mohs (*n*=14) | 71.4% lesions responded to treatment with necrosis and decrease in size, pain and histological clearance after MMS. (*n*=14) | None reported |
| Cuesta Romero C, de Credo-Peña J[17] | Patients were given IL-MTX at doses ranging from 12.5-62.5mg/mL | All patients had complete resolution of their lesions (*n*=6) | None reported |

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| Saporito R, [illegible], Housewright C[18] | 3 patients with Keratoacanthoma and well-differentiated SCC given 2-3 injections of 25mg/mL of MTX | Complete clinical resolution was achieved in all 3 patients | None reported |
| Della Valle V, Milani M[19] | 2 IL-MTX injections were given of 20mg with a week's interval between injections ( | Full resolution of the skin lesion and almost complete resolution of the central ulceration after the two treatments. After two months, there was complete resolution of the lesion which healed completely(*n*=1) | None reported |
| Panther D, Nino T, Macknet KD Jr, Macknet C[20] | Patient treated with IL-MTX (1 injection, 0.2-0.3mL of 12.5mg/mL) and topical imiquimod (19 days) | At day 50 she had crusting and erythema. By day 80 only a slight scale remained with no residual erythema or papules (*n*=1) | None reported |
| Cohen PR, Schulze KE, Teller CF, Nelson BR[21] | 10mg (0.8mL of 12.5mg/mL) of MTX was injected into a nodule on the patient's nasal ala | . After 6 weeks, the tumor showed complete clinical resolution which was confirmed histologically (*n*=1) | None reported |
| Doenier L, Hanke CW[22] | Lesion injected with 1cc MTX (25mg/mL) once a week for 3 weeks | After 4 weeks, complete resolution was found. At 6 months follow-up, no reoccurrence was identified(*n*=1) | None reported |
| Veerula VL, Ezra N, Aouthmany M, [illegible][23] | IL-MTX 1mL of 12.5mg/mL injection was given every 2 weeks | At 3 months follow-up, there were no new lesions or a recurrence of previous lesions (*n*=1) | None reported |
| Barros B, Helm K, Zaenglein A, Selverling E[24] | IL-MTX 25mg/mL solution injected. Nodules were treated 3 times over 4 months with dose ranging from 22.5-43.75mg | 2 months after the last injection, no signs of recurrence were observed (*n*=1) | Injection discomfort |

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| de Visscher JG, [illegible] Wal KG, Blanken R, Willemze F[25] | Injection of IL-MTX given twice (25mg/mL, 1.5mL) with 2 weeks between injections (*n*=1) | 4 weeks after the final treatment the lesion had completely resolved and after 4 years, no recurrence of the lesion was observed and a small scar remained (*n*=1) | None reported |
| Remling R, Memper M, Schnopp N, Abeck D, Ring J[26] | IL-MTX injection was given (25mg/mL, 0.5mL). A second injection was given at a concentration of 12.5mg/mL 0.7mL (*n*=1) | After one week, the tumor had shrunk. After 5 weeks, the tumor had resolved completely with minimal scarring (*n*=1) | None reported |
| Spieth K, Gille J, Kaufmann R[27] | IL-MTX injected once a week with 5 injections given in total of 5mg MTX in 1.0mL (*n*=1) | After 2 injections, the tumor had shrunk and 1 week after the 5th injection, the lesion had resolved completely (*n*=1) | Moderate pain at site of injection |
| Rambhia SH, Rambhia KD, Ghiati A[28] | Patient given oral acitretin and intralesional MTX 12.5mg/mL, topical tazarotene and topical 5-flourouracil (*n*=1) | After 2 injections, given the lesions had shrunk in size (*n*=1) | Pain at site of injection |
| Basoglu Y, Metze D, Nashan D, Stander S[29] | IL-MTX given in 10 doses of 5 or 10mg over 10 months, with a total amount of MTX equal to 85mg (*n*=1) | At 3 months, Biopsy revealed perineural invasion and radiotherapy was used. After 3 years there has been no recurrence | None reported |

**Table 3.** Uses of IL-MTX in Squamous cell carcinoma and lymphoma

| SQUAMOUS CELL CARCINOMA |
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| Salido-Vallejo R, Cubas-Asencio I, Garnacho-Sucedo G, *et al*.[3] | Group A received neoadjuvant IL-MTX and patients in group B had surgery only | Patients in group A had an average tumor reduction of 0.52cm$^2$. Patients in group B tumor increased by 0.49cm$^2$(*n*=86) | Mild pain during injection |
| Bergon-Sendín M, Pulido-Pérez A, Carretero López E, Díez-Sebastián J, Suárez-Fernández R[33] | Neoadjuvant IL-MTX before surgery | 92.5% of patients responded clinically and on ultrasound to treatment with IL-MTX (*n*=40) | None reported |
| Bergón-Sendín M, Pulido-Pérez A, Suarez-Fernández R[34] | Patients given 2 doses IL-MTX 20mg (50mg/mL) | All patients responded to treatment with an average decrease in mean lesion diameter by 68.2%. (*n*=10) | None reported |
| Plasencia-Gomez A, Calderon-Rochar C, Proy-Trujillo H, Moreno-Coutiño G[35] | ILMTX injection once a week (25mg/mL) for 3 weeks | By week 3, the lesion had decreased by 80% (*n*=1) | None reported |

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| Moyé MS, Clark [illegible]gler AA, Milhem MM, Van Beek MJ[36] | IL-MTX, total treatment dose of 50mg MTX (*n*=1) | All lesions were significantly improved after 3 injections and had shrunk | Injection pain |
| LYMPHOMA | | | |
| Yokoi I, Ishikawa E, Koura A, *et al*.[5] | 2mL of MTX solution (2.5mg/mL) into nodules with a total dose of 70mg over several weeks | Residuals tumors disappeared after several weeks and few ulcers remained. (*n*=1) | Local pain at injection site |
| Nandini A, M[illegible]re V, Sacchidanand S, Chandra S[37] | Patient was started on 7.5mg/week of IL-MTX | Lesions resolved within 2 months of treatment and no relapse was observed at the 9-month follow-up( *n*=1) | None reported |
| Blume JE, Stoll HL, Cheney RT[38] | IL-MTX (25mg/cc). After this the patient received 0.4cc of MTX (25mg/cc) the following week | 2 months after the final treatment only a minimal scar remained. No recurrence of lesions was observed after 9 months( *n*=1) | None reported |
| Anyfantakis V, Dammak A, W[illegible]zbicka-Hainaut E, *et al*.[6] | 8 lesions injected with 1.5cm$^3$ IL-MTX (25mg/mL) with one further treatment 2 weeks later | Complete regression of the lesion was found at 2 months, after 12 months follow-up there was no relapse. (*n*=1) | None reported |

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| Üstüner P, [illegible], Özdemir M[45] | Diluted TAC in 10mg/dL, MTX in 10mg/dL and serum physiological solution (0.9% sodium chloride and water) were randomly injected into patient's fingernails. | 62.5% of MTX group and 46.8% of TAC group showed clinical improvement Onycholysis only improved significantly in those treated with TAC ($p$=0.039). Pitting ($p$=0.001) and leukonychia ($p$=0.002) were improved significantly only in the MTX group ($n$=32) | TAC - temporary atrophy of proximal nail fold. MTX - erythema and crusting |

**Table 4**. Uses of IL-MTX in Nail Psoriasis and Common Warts

| NAIL PSORIASIS | | | |
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| Mittal J, Mahajan BB[46] | Nails were injected with TAC 10mg/mL, IL-MTX (25mg/mL) and cyclosporine (50mg/mL) | In the MTX group, 56.7% of nails had greater than 75% improvement at 24 weeks. ($n$=20) | Post-injection numbness |
| Grover C, Daulatabad D, Singal A[47] | Patients treated with injection of IL-MTX (0.1mL of a 25mg/mL solution) | A significant decrease in the NAPSI from 4.87 to 2.17 was observed ($p$<0.001) ($n$=4) | Nail bed haemorrhage($n$=2) |

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| Duarte AA, Gamarra GP, Murari CM, Jesus LC[48] | Patient 1 was given IL-MTX 25mg/mL, patient 2 was given topical occlusive therapy with calcipotriol and betamethasone with IL-MTX 25mg/mL | Both patients had marked improvement at 5 months follow-up (*n*=2) | None reported |
| Mokni S, Ameur K, Ghariani N, *et al*.[49] | Patient treated with IL-MTX 0.1mL of a 5mg/2mL solution into proximal nail fold once a month for 3 months | Progressive improvement in nail dystrophy observed after the first treatment and this was significant after the third session and lesions resolved after 3 months and no relapse was reported after one year (*n*=1) | None reported |

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| Abdo HM, Elkholy EM, Elkholy MS[50] | Group A patients were injected with IL-MTX (2mg/mL) whilst group B patients were injected with IL saline (*n*=60) | There was no statistically significant difference between the treatment response between groups. (*n*=60) | Swelling, pain and infection in both groups |
| Al-Khafaji BA, Al-Kalaby HN, Alkhafaji KA[52] | Patients were treated with IL-MTX on one side of their body whilst the other side was treated with electrocautery. | 4.765 of cases were resolved by MTX compared with 71.43% cleared by electrocautery ($p<0.01$) (*n*=42) | None reported |