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Intralesional methotrexate in dermatology: diverse indications and practical considerations

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Abstract

Intralesional methotrexate (IL-MTX) is a long-established treatment, which is arguably underutilized 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-MTX for 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 chemotherapeutic agent, used in dermatology for many years.¹ It is particularly warranted in patients for whom surgical treatment or systemic therapies are contraindicated or undesirable. IL-MTX can be used as monotherapy or as neoadjuvant treatment with acceptable cosmetic results and a low side-effect profile.² This article reviews 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 to dermatologists.

Cutaneous oncology

IL-MTX plays an increasingly fundamental role in cutaneous oncology with 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, typically in elderly patients, often proving clinically and histologically difficult to differentiate from well-differentiated SCC. Rapid growth is a typical feature, followed by self-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 using IL-MTX in KA, most of which were confirmed on biopsy (except in three studies) (Table 2).⁷ Average treatment dose was 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 from 7-38 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 with high patient satisfaction. KA can resolve spontaneously and since treatment was not a placebo, it is possible that some well-differentiated SCCs may have responded without treatment.^{10,19-9}

One group of patients whom caution is required when using IL-MTX are organ transplant recipients (OTRs). Bender and colleagues³⁰ 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 difficulty of 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

Accepted Article

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 week for SCC.¹

Three case series and two case reports ($n=138$) detailed the use of IL-MTX in cutaneous 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 had clinical reduction of lesion size confirmed 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-effects were related to pain during injection in 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 were 0.2ml (2.5mg) given once a week, with a total dose of 70mg over 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 as solitary or grouped nodules, plaques, papules or large tumours.³⁹ IL-MTX has been used at a dose of 25-50mg/mL in such lesions.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. One randomized study, two case series and three case reports explored its use 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 were TAC (10mg/mL), IL-MTX (25mg/mL) and cyclosporine (50mg/mL in 0.05mL). A total of two intramatrix injections were given in each nail over six weeks. At 24 weeks, 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 with no 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-MTX was 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 disease⁵⁵ 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-MTX we 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 patient suffering 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 tests one 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-effective viable 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 and CCD. 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.

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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)		

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 (<i>n</i> =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 (<i>n</i> =46)	None reported
	Hurst LN, Gan BS ⁹	Patient 1 - IL-MTX 25mg/mL 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. Patient 2 – at 1 month, lesion was completely resolved and at 9 months a small scar remained (<i>n</i> =2)	None reported
	Scavizzi M, Patrizi A, Costa C, <i>et al</i> ¹⁰	Patients treated with IL-MTX weekly. 4-8 injections were required (<i>n</i> =11)	All patients had complete resolution of their tumors (<i>n</i> =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

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

Saponio R, Housewright C ¹⁸ Della Valle V, Milani M ¹⁹	3 patients with Keratoacanthoma and well-differentiated SCC given 2-3 injections of 25mg/mL of MTX 2 IL-MTX injections were given of 20mg with a week's interval between injections (Complete clinical resolution was achieved in all 3 patients 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(<i>n</i> =1)	None reported None reported
Parthar 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 (<i>n</i> =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 (<i>n</i> =1)	None reported
Doerner 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(<i>n</i> =1)	None reported
Veerula VL, Ezra N, Aouthmany M, 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 (<i>n</i> =1)	None reported
Barros B, Helm K, Zaenglein A, Seiverling 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 (<i>n</i> =1)	Injection discomfort

de Visscher JG, Wal KG, Blanken R, Willemse F ²⁵	Injection of IL-MTX given twice (25mg/mL, 1.5mL) with 2 weeks between injections (<i>n</i> =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 (<i>n</i> =1)	None reported
Remling R, Mempel M, Schnepp 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 (<i>n</i> =1)	After one week, the tumor had shrunk. After 5 weeks, the tumor had resolved completely with minimal scarring (<i>n</i> =1)	None reported
Spieth K, Gille J, Kraumann R ²⁷	IL-MTX injected once a week with 5 injections given in total of 5mg MTX in 1.0mL (<i>n</i> =1)	After 2 injections, the tumor had shrunk and 1 week after the 5 th injection, the lesion had resolved completely (<i>n</i> =1)	Moderate pain at site of injection
Rambhia SH, Rambhia KD, Gulati A ²⁸	Patient given oral acitretin and intralesional MTX 12.5mg/mL, topical tazarotene and topical 5-flourouracil (<i>n</i> =1)	After 2 injections, given the lesions had shrunk in size (<i>n</i> =1)	Pain at site of injection
Basoglu Y, Metze J, 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 (<i>n</i> =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

Salido-Vallejo R, Sureda-Asencio I, Garnacho-Suñer G, <i>et al.</i> 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 (<i>n</i> =86)	Mild pain during injection
Bergón-Sendín M, Pulido-Pérez A, Carretero López F, 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 (<i>n</i> =40)	None reported
Bergón-Sendín M, Pulido-Pérez A, Suárez-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%. (<i>n</i> =10)	None reported
Plascencia-Gomez A, Calderon-Rochet 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% (<i>n</i> =1)	None reported

<p>Moye MS, Clark Milhem MM, Van Beek MJ³⁶</p>	<p>IL-MTX, total treatment dose of 50mg MTX (<i>n</i>=1)</p>	<p>All lesions were significantly improved after 3 injections and had shrunk</p>	<p>Injection pain</p>
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LYMPHOMA

<p>Yokoi I, Ishikawa E, Koura A, <i>et al.</i>³⁵</p>	<p>2mL of MTX solution (2.5mg/mL) into nodules with a total dose of 70mg over several weeks</p>	<p>Residuals tumors disappeared after several weeks and few ulcers remained. (<i>n</i>=1)</p>	<p>Local pain at injection site</p>
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<p>Nandini A, Moore V, Sacchidanand S, Chandra S³⁷</p>	<p>Patient was started on 7.5mg/week of IL-MTX</p>	<p>Lesions resolved within 2 months of treatment and no relapse was observed at the 9-month follow-up(<i>n</i>=1)</p>	<p>None reported</p>
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<p>Blume JE, Stoll RL, Cheney RT³⁸</p>	<p>IL-MTX (25mg/cc). After this the patient received 0.4cc of MTX (25mg/cc) the following week</p>	<p>2 months after the final treatment only a minimal scar remained. No recurrence of lesions was observed after 9 months(<i>n</i>=1)</p>	<p>None reported</p>
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<p>Anvafantakis V, Dammak A, Wronicka- Hainaut E, <i>et al.</i>³⁹</p>	<p>8 lesions injected with 1.5cm³ IL- MTX (25mg/mL) with one further treatment 2 weeks later</p>	<p>Complete regression of the lesion was found at 2 months, after 12 months follow-up there was no relapse. (<i>n</i>=1)</p>	<p>None reported</p>
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Üstüner P,
Özdemir M⁴⁵

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			
Mittal J. Mahajan B 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, Dauratabad D, Singh 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 ($n=2$)

Duarte AA,
C... GP,
Murari CM,
Jesus LC⁴⁸

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

Makni 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

WALTC

Abou HM,
EM,
Elkholy MS⁵⁰

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-Khatiji BA,
Al-Khatiji HN,
Alkhafaji KA⁵²

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