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Cosmetic Medicine

Preliminary Report

Oral Methotrexate Treatment of Delayed-Onset Inflammatory Reactions to Dermal Fillers

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Abstract

Background: In aesthetic practice, delayed-onset (late) inflammatory reactions (DIRs) to dermal fillers are encountered. The treatment of DIRs can be challenging, with a response to established therapies, including oral antibiotics, intralesional and oral steroids, and hyaluronidase injection, occasionally reported as unsatisfactory.
Objectives: Evaluate the efficacy of low-dose oral methotrexate (MTX) therapy in treating recalcitrant DIRs.
Methods: We retrospectively reviewed cases of recalcitrant DIRs treated with oral MTX. Data collected included individuals' gender and age, medical history, filler type, facial area(s) injected, previous treatments attempted to dissolve the DIR, MTX treatment dosage and duration, and outcome. Adverse events were monitored throughout the treatment.
Results: Thirteen females with a mean age of 52.6 years (range, 31-67 years) who developed recalcitrant DIRs to dermal filler injection are included. Eight reactions were triggered by the injection of hyaluronic acid (HA) fillers, 4 by liquid injectable silicone (LIS), and 1 by polymethylmethacrylate (PMMA). The average starting dosage of MTX was 12.1 mg/week (range, 7.5-12.5 mg/week). Patients were treated for 2 to 3 months in most cases. The average follow-up post-MTX therapy was 11.8 months (range, 2-36 months). A complete response to MTX treatment was observed in 10 patients (6 HA and 4 LIS cases), partial response in 1 (HA case), and an unsatisfactory response in 2 (HA and PMMA cases). Treatment was well tolerated.
Conclusions: A short course of low-dose oral MTX is a possible treatment for DIRs that have not responded to established therapies. The promising results of this report require validation by powered studies.

Level of Evidence: 4

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Delayed-onset (late) inflammatory reactions (DIRs), such as nodules, granulomas, and edema, have been reported after injection of almost any dermal filler but are more common when using permanent fillers.[1] DIRs can appear months to years after the filler injection.[2] The pathogenetic mechanisms are elusive. Consecutive relapses after enzymatic degradation of the filler material, the presence of giant cells on histology and temporary relief achieved by intralesional or systemic steroids—all support the immune system's role in the pathogenesis of DIRs.[3] DIRs can cause significant discomfort and aesthetic and functional repercussions to the patients.[4] Treatment of DIRs is challenging, and repetitive courses of systemic corticosteroids are sometimes required for years.[5]

Systemic methotrexate (MTX) is an immunomodulator used to treat a variety of inflammatory skin disorders, such as psoriasis and sarcoidosis. Low-dose (ie, up to 15 mg/week), short-term oral MTX treatment is considered safe.[6] In preliminary reports, MTX treatment was beneficial in the management of chronic inflammatory reactions induced by liquid injectable silicone (LIS), polymethylmethacrylate (PMMA), hydroxyethylmethacrylate, and polycaprolactone fillers.[7-9]

We report a series of patients with dermal filler–induced DIRs, treated in different centers by oral low-dose MTX after failure of other treatments, and summarize the outcomes to provide recommendations on MTX therapy in such cases.

We aimed to evaluate the efficacy of low-dose MTX therapy in the treatment of recalcitrant DIRs with dermal fillers.

METHODS

Study Design

This retrospective study includes individuals who developed DIR to dermal filler injections performed for aesthetic reasons in outpatient dermatology or plastic surgery offices of the authors. The study was exempt from IRB approval as the investigators recorded and disclosed de-identified information. The study complies with the Declaration of Helsinki of ethical principles for medical research involving human subject. Filler injections were performed up to 14 years before the data collection. The patient data were collected from January to October 2023. Data collected included the patient's gender and age, medical history, drug intake, filler type and facial area(s) injected, and treatments attempted before MTX.

MTX Treatment and Follow-up

MTX dosage and duration, and outcome of MTX treatment were recorded. Patients were evaluated every 3 to 4 weeks while on MTX treatment. Folate supplementation was offered. Pretreatment laboratory tests included a full blood count with differential, kidney, and liver function tests, serum lipids, hepatitis B and C serologies, HIV serology, tuberculosis testing, and pregnancy testing in patients of childbearing potential. Screening for alcohol use was done before starting treatment. Monitoring laboratory tests during MTX therapy followed the national guidelines in the investigators' countries. In the United States, laboratory monitoring guidelines, while on low-dose MTX therapy, include assessing complete blood count, creatinine, and liver function tests every 2 to 4 weeks for the first 3 months, then 8 to 12 weeks for the following 3 to 6 months, and every 12 weeks after that.[10] The adverse effects of MTX were monitored throughout the treatment. The duration of treatment depended on the clinical response. MTX was discontinued in cases showing a complete response (no residual lesion) persisting for at least 2 weeks. In cases showing a partial response (improvement), an additional month of MTX therapy was provided, and if there was no further improvement, therapy was discontinued. No response was determined as minimal or no improvement after 2 months of MTX therapy.

RESULTS

Filler Types and DIR Features

This series includes 13 females with a mean age of 52.6 years (range, 31-67 years) who developed DIR to dermal filler injection performed for aesthetic reasons (Table; Figures 1-4). Eight patients had been treated with hyaluronic acid (HA; Patients 1-8), 4 with LIS (Patients 9-12), and 1 with PMMA filler (Patient 13) before the development of the DIR. Two patients (Patients 2, 3) had consecutive injections of different filler types over many years, and 1 (Patient 4) received the mRNA-1273 COVID vaccine 2 months before the filler injection.

The lag time from filler injection to DIR varied considerably, from 2 months to 10 years. Six DIRs manifested clinically as nodules (Figures 2, 4), 4 as infiltration (Figure 1), and 3 as edema (Figure 3). Seven DIRs were clinically inflammatory (erythematous, warm to touch, tender or painful) and 6 noninflammatory (not erythematous, not tender, painless). In 2 cases (Patients 2, 3), a non-HA filler was injected several years before the HA filler injection triggered the DIR; in Patient 2, fillers were not layered–injected at different neighboring sites, and the DIR occurred close to the non-HA filler injection site (nasolabial fold). Filler deposition within the site of DIR was confirmed in Patients 2, 8, and 9 with high-frequency ultrasound imaging (Figure 5).

Therapies Before Starting MTX

Medical histories were recorded. Patients had previously failed other treatments for the DIR. These included oral

Table. Clinical Data

Patient no./ gender/ age, y	Medical history	Filler/area injected	Lag time from filler injection to reaction	Clinical features of DIR	Treatments before MTX	MTX dosage	Follow-up post-MTX	Outcomes
1/F/50	Hypothyroidism, depression	HA/lips, cheeks, NLFs, chin	8 wk	Erythematous, firm, inflammatory infiltration in the marionette areas and chin	MCN 100 mg/d and prednisone 20 mg/d; NR after 2 wk	12.5 mg/wk × 1 mo, then 10 mg/wk × 1 mo along with oral FAS 5 mg/ wk	25 mo	CR
2/F/55		HA/right malar area, above NLF; h/o PMMA injection to NLFs 7 y prior	2 mo	Noninflammatory nodules in right malar area	Hyal 200 IU	12.5 mg/wk × 1 mo (complicated by nausea), then 10 mg/ wk × 1 mo	3 mo	CR
3/F/35		2 different HAs injected 7 mo apart/left malar area; h/o LIS and CaHa injections in left malar area >10 y prior	2 mo after 1st injection; 7 mo after 2nd injection	Edema (noninflammatory DIR) in left malar area	1st edema: Hyal 200 IU × 3 Rxs; oral methylprednisolone 4 mg/d × 4 d 2nd edema: Hyal 200 IU	12.5 mg/ wk ×1 mo, then 10 mg/wk × 1 mo, then TAC 10 mg/mL	NA	NR
4/F/31		HA/malar areas	2 mo; 4 mo after mRNA-1273 (Moderna) COVID vaccination	Edema (noninflammatory DIR) in malar areas	Methylprednisolone 8 mg/12 hours × 4 d; Hyal 250 IU × 2 Rxs	12.5 mg/wk × 1 mo, then 10 mg/wk × 1 mo	3.5 mo	CR
5/F/51		HA/lips	10 mo	Inflammatory nodules in the lips	Hyal 250 IU	12.5 mg/wk × 1 mo, then 10 mg/wk × 2 mo	2.5 mo	PR
6/F/64		HA/malar prominences	5 wk	Erythematous, firm, tender inflammatory nodule on the right malar prominence	Doxy, ILC	12.5 mg/wk × 1 mo, then 10 mg/wk × 1 mo	25 mo	CR
7/F/47	Breast cancer	HA/lips	4 mo	Inflammatory nodule on the right cutaneous upper lip	2 Hyal Rxs, 1500 and 500 IU	7.5 mg/wk × 1 mo, then 5 mg/wk × 1 mo along with oral FAS 5 mg/wk	6 mo	CR
8/F/46	Smoker	HA/NLFs, infraorbital areas	3 mo	Facial edema, mild erythema; nodules on right NLF on palpation	Hyal 1000 IU × 2 Rxs; im steroid; oral antihistamines	12.5 mg/wk × 6 wk along with oral FAS 5 mg/ wk	2 mo	CR
9/F/62		LIS/NLFs	8 y	Erythematous, inflammatory infiltration along left NLF	Oral cephalosporin and prednisone 20 mg/d tapered to 5 mg/d × 1 mo	12.5 mg/wk × 2 mo with oral FAS 5 mg/wk; OCS tapering	5 mo	CR; mild temporary increase in liver enzymes
10/F/64	Kaposi sarcoma	LIS/perioral areas	10 y	Multiple erythematous, inflammatory papulonodules on the lips and perioral areas	Repetitive ILC and OCS with temporary improvement	12.5 mg/wk × 1 mo, then 10 mg/wk × 1 mo along with oral FAS 5 mg/ wk	36 mo	CR
11/F/67	NIDDM, hypertension, hypothyroidism, breast cancer	LIS/perioral areas	1 y	Perioral palpable noninflammatory nodules	Oral prednisone 20 mg/d × 1 mo with improvement	12.5 mg/wk × 1 mo, then 10 mg/wk × 1 mo along with oral FAS 5 mg/ wk	18 mo	CR

Table. Continued

Patient no./ gender/ age, y	Medical history	Filler/area injected	Lag time from filler injection to reaction	Clinical features of DIR	Treatments before MTX	MTX dosage	Follow-up post-MTX	Outcomes
12/F/55	Depression	LIS/NLFs	3 mo after filler injection 12 y ago; intermittent inflammatory reactions every few mo	Palpable, noninflammatory infiltration along right NLF	Intermittent systemic antibiotics and OCS; oral prednisone 20 mg/d × 5 mos without response	12.5 mg/wk × 5 mo along with oral FAS; OCS tapered during the 1st mo of Rx	4 mo	CR; significant improvement after 2 mo Rx without OCS[a]
13/F/57		PMMA/NLFs	8 y (filler injected 14 y ago); nodules (DIR) successfully treated with ILC; 4 y later new nodules developed	Noninflammatory, minimally palpable infiltration along NLFs	ILC with no response	12.5 mg/wk × 1 mo, then 10 mg/wk × 2 mo along with oral FAS 5 mg/wk	NA	NR

CaHa, calcium hydroxylapatite; CR, complete response; d, day; DIR, delayed-onset inflammatory reaction; Doxy, doxycycline; F, female; FAS, folic acid supplementation; h/o, history of; HA, hyaluronic acid; Hyal, hyaluronidase; ILC, intralesional corticosteroid; im, intramuscular; IU, international units; LIS, liquid silicone; MCN, minocycline; mo, month/months; MTX, methotrexate; NA, non-applicable; NIDDM, non-insulin-dependent diabetes mellitus; NLF, nasolabial fold; NR, no response; OCS, oral corticosteroid; PMMA, polymethylacrylate; PR, partial response; Rx, treatment; TAC, triamcinolone acetonide; wk, week/weeks; y, year/ years. [a]Treatment was prolonged after CR occurred at the patient's request.

corticosteroids (9 patients), hyaluronidase (Hyal) injections (6 patients), oral antibiotics (4 patients), and intralesional corticosteroids (3 patients).

Methotrexate (MTX) Therapy

The average starting dosage of MTX was 12.1 mg/week (range, 7.5-12.5 mg/week). Most patients were started on 12.5 mg/week and treated for 2 to 3 months (Table). The dose was often decreased to 10 mg/week at the beginning of the second month of treatment in cases who showed excellent therapeutic response during the first month of treatment. Such tapering may increase tolerability and enhance compliance. A complete response to MTX treatment was observed in 10 patients (Patients 1, 2, 4, 6-12), partial response in 1 (Patient 5), and treatment failure in 2 (Patients 3, 13). A complete response was observed in all patients who developed DIR secondary to LIS injections. Six patients (Patients 1, 2, 4, 6-8) who developed DIR following HA filler injectionshowed complete responses, 1 partial response (Patient 5), and 1 no response (Patient 3). The average follow-up post-MTX therapy was 11.8 months (range, 2-36 months). No DIR recurrences in cases that showed a complete response were observed in the follow-up period. In the patient with a partial response (Patient 5), DIR did not worsen after discontinuation of MTX.

MTX Therapy Tolerance

Patients did not have any comorbidities or risk factors (eg, alcohol intake) associated with an increased risk of MTX toxicity.[11] In addition, they were not taking any drugs that could increase the risk of MTX toxicity. Oral folic acid supplementation (FAS) was provided in 8 of 13 patients to decrease MTX toxicity, including gastrointestinal and liver adverse effects, that relate to folate antagonism and/or deficiency.[12] FAS decreases low-dose MTX toxicity yet does not compromise the efficacy by bypassing MTX inhibition of dihydrofolate reductase, the enzyme required to reduce folate to tetrahydrofolate.[13] MTX treatment was well tolerated, with a mild temporary transaminase elevation in 1 patient (Patient 9). One patient who did not receive oral FAS developed nausea (Patient 2).

DISCUSSION

Delayed Inflammatory Reactions (DIR) Features

DIRs are categorized into immune-mediated local and systemic and/or distant reactions.[14] Lag times until onset and type of DIR vary according to filler material.[15] In a study of facial augmentation with permanent fillers, lag time until the onset of DIR ranged from 1 month to 10 years (mean, 38 months).[15] Granulomatous reactions to LIS have been shown to occur years to decades after injection.[16,17] In 28% of DIRs induced by permanent fillers, patients reported the onset of complications after dental procedures, additional injections with fillers, or other invasive treatments in the facial area.[15]

Histopathologic analysis of adverse reactions to filler injections of the face and neck area revealed a foreign body granuloma in 87.1% of the patients, 3% inflammatory granuloma, and 3% lipogranuloma.[18] The dermal filler foreign

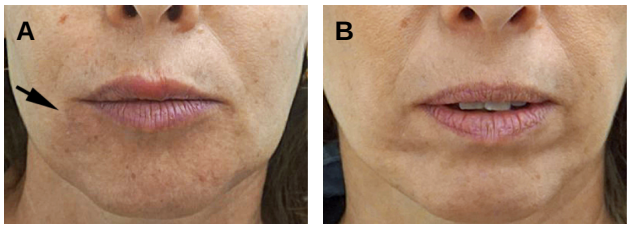

Figure 1. A 50-year-old female (Patient 1) showing (A) before MTX therapy: erythematous, inflammatory infiltration on the right marionette area (arrow), chin, and left marionette area and (B) 7 months after MTX therapy: complication resolution. MTX, methotrexate.

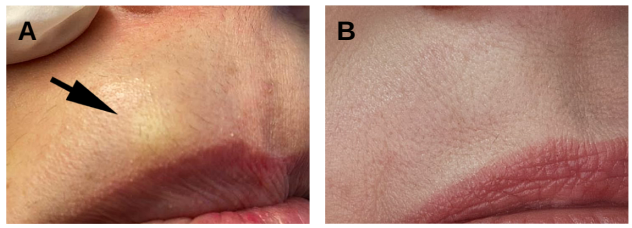

Figure 2. A 47-year-old female (Patient 7) showing (A) before MTX therapy: noninflammatory nodule on the right cutaneous upper lip (arrow) and (B) 5 months after MTX therapy: complication resolution. MTX, methotrexate.

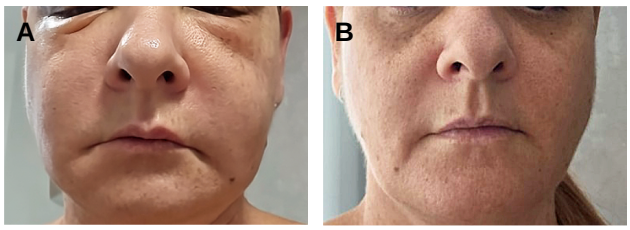

Figure 3. A 46-year-old female (Patient 8) showing (A) before MTX therapy: edema of the lower eyelids and lower face and (B) 6 months after MTX therapy: complication resolution. MTX, methotrexate.

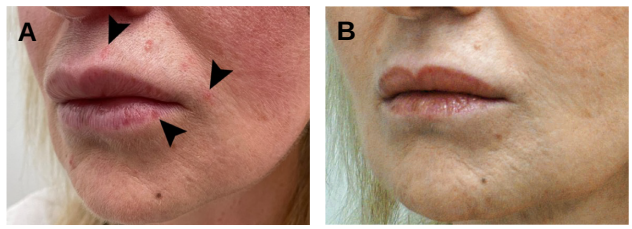

Figure 4. A 64-year-old female (Patient 10) showing (A) before MTX therapy: erythematous papulonodules on the lips and perioral areas (arrows) and (B) 6 months after MTX therapy: complication resolution. MTX, methotrexate.

body reaction shows dense lymphohistiocytic infiltration with eosinophils and granulomatous infiltration with foreign body giant cells.[19] Nonimmunologic granulomas, such as foreign body granuloma formation due to inorganic matter (eg, LIS), can be distinguished by the absence of lymphocytes in the lesion. The histology of a typical immunological granuloma is a macrophage/epithelioid core surrounded by a cuff of lymphocytes, where considerable fibrosis may also occur.[20] Multiple vacuolated cyst-like structures and "Swiss cheese" appearances may be noted.[19]

The etiopathogenesis of DIRs caused by dermal fillers is poorly understood.[2] Possible triggers include local or systemic infections, systemic medication or vaccinations, dental procedures, or other invasive treatments in the vicinity of the filler deposits.[15,21] In one of the cases we present, the COVID-19 vaccine may have played a role.[22] A foreign body reaction led by activated histocytes and giant cells, eventually resulting in chronic inflammation, may play a significant role. Epithelioid macrophages, histiocytes, lymphocytes, and giant cells were demonstrated in the histopathology of filler-induced nodules. In some cases, neutrophils, eosinophils, or plasmacytoid dendritic cells were found.

Staphylococcus epidermidis is the bacterium most found in DIRs, although its role is still debated—it could represent contamination, infection, or merely an immunological trigger. Alijotas-Reig et al suggested that an acute inflammatory process involving a quiescent granuloma years after the injection might be related to the development of bacterial biofilms or structured colonies of microorganisms encapsulated in an extracellular matrix that can surround a foreign body and can lead to a low-grade chronic infection with eventual spontaneous or injury-mediated reactivation.[14] Nevertheless, the role of biofilm formation or "low-grade" infection remains inconclusive, as cultures were not always taken or have occasionally been negative,[14] and a reported response to intralesional steroids speaks against it.

A delayed-type hypersensitivity reaction has been suggested. Silicone, HA compounds, and acrylamide can act as adjuvants and could affect the immune response.[13] Adjuvants increase innate immune responses by mimicking evolutionarily conserved molecules, for instance, bacterial wall components or unmethylated CpG-DNA residues, and binding to Toll-like receptors with further release of inflammatory cytokines from T-helper and mast cells.[22]

DIR Management

Several therapies, including oral antibiotics and oral or intralesional corticosteroids, can effectively treat DIRs.[4,14] Oral antibiotics are typically tried first when the DIR is inflammatory and/or suspected of infection (abscess formation). Intralesional steroids can be tried in such cases if

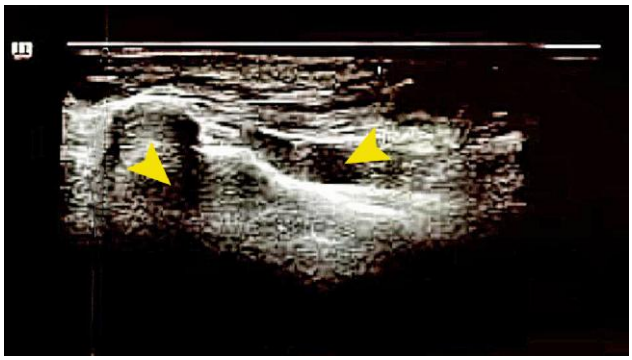

Figure 5. Ultrasound image from a DIR on the right malar area in a 55-year-old female (Patient 2). HA depots show as anechoic nodules (arrows). DIR, delayed-onset inflammatory reaction; HA, hyaluronic acid.

the DIR shows a suboptimal response to antibiotics. Hyal may be considered in the case of HA filler-triggered inflammatory DIR only after oral antibiotics have failed because there is a risk of infection spreading with Hyal injection. Management algorithms for treating delayed-onset nodules triggered by dermal fillers have been published.[23] Nevertheless, DIRs may not respond to such therapies, and alternative treatments should be explored before considering surgical removal. MTX therapy can be beneficial in this context.

MTX Therapy

We report a series of recalcitrant DIR in 13 females treated with MTX. A complete response to MTX treatment was observed in 10 patients, partial response in 1, and treatment failure in 2. Preliminary reports described MTX treatment of DIRs to LIS (3 cases),[7,8] PMMA (1 case),[7] hydroxyethylmethacrylate (1 case),[7] and polycaprolactone (1 case).[9] All patients who developed LIS-triggered DIR in this series showed a complete response to MTX therapy and experienced no recurrence of DIR after treatment completion. This finding supports the satisfactory response of LIS-triggered DIRs to MTX in the cases reported by Pérez-Ruiz et al[8] and Broly et al.[7]

However, there are insufficient data on other permanent filler types, such as PMMA. When considering the current series, more data favor MTX[7-9] than minimally studied or variably effective therapies, such as topical 5-fluorouracil, imiquimod, and calcineurin inhibitors, antimalarials, allopurinol, colchicine,[14] as a second-line treatment of DIRs. Therefore, practitioners should consider MTX when established therapies, such as oral antibiotics, intralesional and oral steroids, and Hyal, fail.

Consecutive injections with different filler types, the last being HA type, preceded 3 DIR cases in this series—in 2 of them, the HA filler was not layered over the non-HA filler. In these cases, the non-HA filler depot may function as an adjuvant in the immune response triggered by the HA filler resulting in DIR. Several authors questioned the increased risk of adverse reactions related to consecutive injections of different fillers in the same region.[24,25] Bachmann et al did not find evidence that consecutive injections increase the risk of adverse reactions, especially in the cases of biodegradable fillers.[26] In a review of 260 cases of filler-related reactions, repeated injections of different fillers in the same region or different sites did not increase the risk of adverse reactions; nevertheless, when they appeared, they were more likely to become chronic and more severe.[25,27]

Study Strengths and Limitations

To our knowledge, this is the largest series of DIRs treated with MTX. In addition, it is the first report of MTX treatment of HA filler-induced DIRs. The study also indicated a good response to MTX of LIS-triggered DIRs. Limitations of this study include a small sample size, small number of permanent fillers, lack of standardized response assessment, and lack of histopathologic study of the DIR. Most filler reactions are granulomas, and most DIRs in this series likely represent granulomas. The lack of histopathology prevents identifying histopathologic features of granulomas that may be associated with suboptimal response to MTX.

CONCLUSIONS

Low-dose oral MTX therapy can be considered as a possible second-line treatment for DIRs to fillers that have not responded to conventional therapies, such as oral antibiotics, intralesional and oral steroids, and Hyal. We suggest that MTX can be used as a second-line therapy in such cases. Its rapid efficacy and good safety profile support its use in managing challenging DIRs. Furthermore, it can be an excellent option for recalcitrant DIRs that require long-term treatment. The results of this report require validation by powered studies.

Disclosures

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