Intralesional triamcinolone acetonide therapy for inflammatory oral ulcers

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Objectives. The aim of this study was to report on the clinical indications and treatment outcomes of intralesional steroid therapy (IST) for oral ulcerative conditions in an oral medicine practice.

Study Design. This was a retrospective single-center study of patients with oral ulcerative conditions treated with IST. Demographic data, clinical diagnosis of the oral condition, size of the ulcer, and pain were abstracted from patients' electronic medical records.

Results. Ninety-three patients (51 females [54.8%]) were treated for persistent traumatic oral ulcers (n = 38 [40.8%]), ulcers in oral chronic graft-versus-host disease (n = 23 [24.7%]), oral lichen planus (n = 19 [20.4%]), and other conditions (14%). Complete resolution was achieved in 81.7% of patients in a median of 96 days (range 10−357 days), with 80% fully healed in a median of 84 days (range 10−140 days). Overall, patients received a median of 2 injections (range 1−5 injections) and a median dose of 12 mg per injection (range 2−36 mg). Nearly half the patients were also treated with concomitant topical steroid therapy. After the first injection, the median pain score reduced from 5 (range 1−10) to 1 (range 0−10; $P < .001$) and the median size of ulcers reduced from 1 cm (range 0.1−5 cm) to 0.3 cm (range 0−2 cm; $P < .001$).

Conclusions. IST may be an effective treatment for inflammatory and immune-mediated oral ulcers. (Oral Surg Oral Med Oral Pathol Oral Radiol 2019;128:485−490)

Oral inflammatory conditions are common and often associated with painful ulcerations.[1] Although the mainstay of management for oral ulcers is topical steroids, some lesions remain refractory to treatment and require a more intensive approach.[2,3] Intralesional steroid therapy (IST) has been reported to be effective in a variety of conditions, including oral lichen planus (OLP),[4,5] recurrent aphthous stomatitis,[6,7] oral chronic graft-versus-host disease (cGVHD),[8] pemphigus vulgaris,[9] mucous membrane pemphigoid,[10] traumatic ulcers, including traumatic ulcerative granuloma with stromal eosinophilia (TUGSE),[11] and medication-induced ulcers.[12,13] This therapy delivers a high concentration of corticosteroid directly to the ulcerative site, with minimal dispersion and systemic absorption,[14] thereby effectively promoting healing with less adverse effects compared with systemic steroid therapy.[15] Despite IST being a routine therapeutic modality utilized in oral medicine practice, data describing its use and effectiveness in the management of ulcerative conditions are limited.[7,12,14] The objective of this study was to report on the use of IST for management of inflammatory and immune-mediated oral ulcers in a single center oral medicine practice.

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MATERIALS AND METHODS

Study design

This was a retrospective single-center study of patients who were diagnosed with noninfectious, inflammatory oral ulcerative conditions and were treated with IST in the Division of Oral Medicine and Dentistry at Brigham and Women's Hospital between June 2015 and October 2017. An *ulcer* was defined as an area of loss of epithelial integrity with an overlying yellow or gray fibrinous membrane. All patients received at least 1 intralesional injection of triamcinolone acetonide (TA) 40 mg/mL and returned for at least 1 follow-up visit. According to the clinic protocol, injections with triamcinolone acetonide were administered by using a disposable 1-cc syringe at the periphery of the ulcer. Only 1 injection per single lesion was performed at each visit. Resolution was defined as complete re-epithelialization of the ulcerative lesion. This study was approved by the Partners Healthcare Institutional Review Board, and it was performed in accordance with the tenets of the Declaration of Helsinki.

Statement of Clinical Relevance

This article reports that intralesional steroid therapy is an effective and safe treatment for persistent oral ulcers and promotes healing by delivering the drug at a high-concentration in the ulcerative site, with little to no side effects and minimal dispersion.

Clinical data

Demographic data, including age and gender, past medical history, and clinical diagnosis of the oral condition, were abstracted from patients' electronic medical records. Histopathology reports of ulcerative conditions for which a biopsy was obtained were reviewed.

Information regarding the location and size (largest diameter in centimeters) of oral ulcers for which patients received IST and the associated pain score (0−10 on a visual analogue scale [VAS]) was recorded at each visit. When patients had greater than 1 ulcer and multiple treatments were performed at the same visit, the injection for the largest ulcer was considered. The number of injections, dose of TA (in milligrams) per injection, and the total cumulative dose were recorded.

Additional data collected included concurrent topical and/or systemic steroid therapy, as well as any other immunomodulatory or anti-inflammatory therapy prescribed for the management of the oral ulcerative condition.

Statistical analysis

Data were analyzed by using JMP Pro 14 statistical software (SAS Institute, Marlow, Buckinghamshire, UK). Differences in lesion size and pain were evaluated by using the Wilcoxon signed-rank test. All P values were considered statistically significant at $P < .05$.

RESULTS

Patient characteristics

There were 93 patients (51 females [54.8%]) with a median age of 63 years (range 18−91 years) (Table I). Patients were both established patients of record (58 of 93 [62.4%]) and new consultations (36 of 93 [37.6%]). The most common oral ulcerative conditions were persistent traumatic ulcers/TUGSE (n = 39 [41.9%]), oral cGVHD (n = 23 [24.7%]), OLP (n = 19 [20.4%]), drug-related ulcers (n = 5 [5.4%]), and aphthous ulcers (n = 3 [3.2%]), which, together, constituted 96.8% of cases (see Table I). Oral biopsies were performed in less than half the patients (34 of 93 [36.5%]), all before initiation of IST. The most common locations of oral ulcers were the buccal mucosa (n = 35 [37.6%]), ventrolateral tongue (n = 32 [34.4%]), and lip mucosa/vermilion (n = 15 [16.1%]) (see Table I). Patients presented with both solitary (51 of 93 [54.8%]) and multiple (42 of 93 [45.2%]) oral ulcers; those with multiple ulcers presented with a median of 3 lesions (range 2−9 lesions). At the initial visit, over one-third of patients (35 of 93 [37.6%]) were already taking at least 1 systemic immunosuppressive medication for the management of systemic disease.

Table I. Patient characteristics

	Patients (N = 93)
Median age (range)	63 (18−91) years
	n (%)
Females	51 (54.8)
Males	42 (45.1)
Clinical diagnosis	
Traumatic ulcer	39 (41.9)
Chronic graft-versus-host disease	23 (24.7)
Oral lichen planus	19 (20.4)
Drug-related ulcer*	5 (5.4)
Aphthous ulcer	4 (4.3)
Crohn's disease	1 (1.1)
Discoid lupus erythematosus	1 (1.1)
Radiation-induced ulcer	1 (1.1)
Lymphomatoid papulosis	1 (1.1)
Ulcer location	
Buccal mucosa	36 (38.7)
Ventrolateral tongue	32 (34.4)
Lip mucosa	10 (10.7)
Lip vermillion	5 (5.4)
Tongue dorsum	4 (4.3)
Floor of mouth	3 (3.3)
Hard palate	3 (3.3)
Soft palate	1 (1.1)

*These were associated with mesalamine/sulfasalazine, methotrexate, mycophenolate mofetil, and sirolimus.

In addition to IST, patients were also prescribed topical and systemic steroids. At the first IST visit, of the 93 patients, 51 (54.8%) were already being managed with topical steroids, 26 (27.9%) with a combination of topical and systemic steroids, and 7 (7.5%) with systemic steroids only. Of the patients already being treated with systemic steroids (n = 29), 10 patients had been prescribed steroids specifically for the management of their oral condition. The remaining 19 patients were on long-term steroid therapy for an underlying condition (e.g., cGVHD). Of those who were not already being treated with a topical steroid, 34.4% of patients (32 of 93) were also prescribed topical therapy at the first IST visit, such that after the first IST visit, 89.2% of patients (83 of 93) were being managed with topical steroid therapy. This reduced to 61.2% at the second visit and less than half (39.8%) at the third visit and beyond. Clobetasol 0.05% gel and dexamethasone 0.1 mg/mL solution were the most frequently used topical steroids (Table II). Prednisone was prescribed for 8 patients (8.6%) at the first visit, with a median daily dose of 35 mg (range 10−60 mg). At the second visit, 3 patients (3.2%) continued to be treated with prednisone, with no additional patients initiated on systemic steroid therapy. Only 1 patient continued on systemic steroids after the third visit. Five patients were already on immunomodulators (i.e., hydroxychloroquine, thalidomide, and pentoxifylline) at the first visit, and 4 were prescribed immunomodulatory therapy at the

Table II. Topical agents used for the management of oral ulcers

Medication	*Patients (N = 93) n (%)*
Clobetasol 0.05% gel	38 (40.8)
Dexamethasone 0.1 mg/mL solution	32 (34.4)
Clobetasol 0.05% solution	10 (10.7)
Fluocinonide 0.05% gel	6 (6.4)
Desonide 0.05% ointment	2 (2.1)
Triamcinolone acetonide 0.1% ointment	1 (1.1)

Numbers do not add to 93 because some patients were on more than one topical medication.

second visit; these patients remained on immunomodulatory therapy through the study follow-up period.

Intralesional steroid injections

Indications for IST included (1) traumatic ulcers (including TUGSE), which had persisted despite topical and/or systemic steroid therapy; (2) traumatic ulcers where patients opted for first-line therapy with IST; and (3) persistent ulcers or ulcers during disease flare in inflammatory and autoimmune diseases that were refractory to topical and/or systemic therapy. Patients received a median of 2 injections (range 1−5 injections) with a median dose of 12 mg per injection (range 2−36 mg), and in a median of 15 days between injections (range 3−210 days; Figure 1). The median size of the ulcer at the initial visit was 1 cm (range 0.1−5 cm), which, after the first IST, reduced to 0.3 cm (range 0−2 cm; $P < .001$) (Figure 2). When the number of injections was considered over time, the median size of the ulcer was 0.5 cm (range 0.2−5 cm) in patients who received a single treatment, compared with 1 cm (range 0.2−4 cm) in patients who received greater than 1 injection ($P < .001$). The median pain score reduced from 4 (range 1−10) to 1 (range 0−10) after the first IST ($P < .0001$) (Figure 3). After IST, complete resolution of the ulcer occurred in greater than 80% of patients (76 of 93 [81.7%]) in a median of 96 days (range 10−357 days) corresponding to a median of 2 injections (range 1−5 injections). Patients

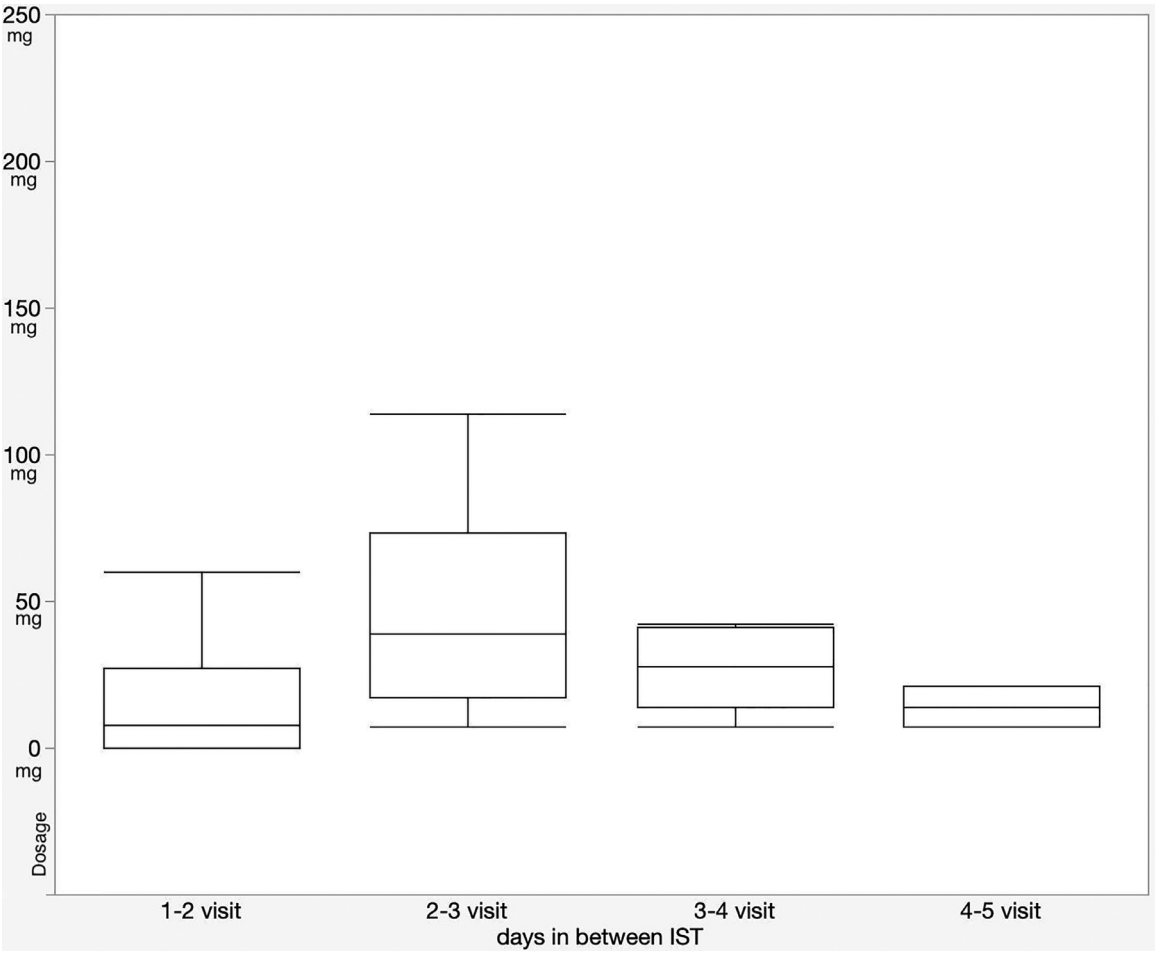

Fig. 1. Median number of days between injections. Box: 25th and 75th percentiles; bars: Range (minimum and maximum values); middle line: Median dose.

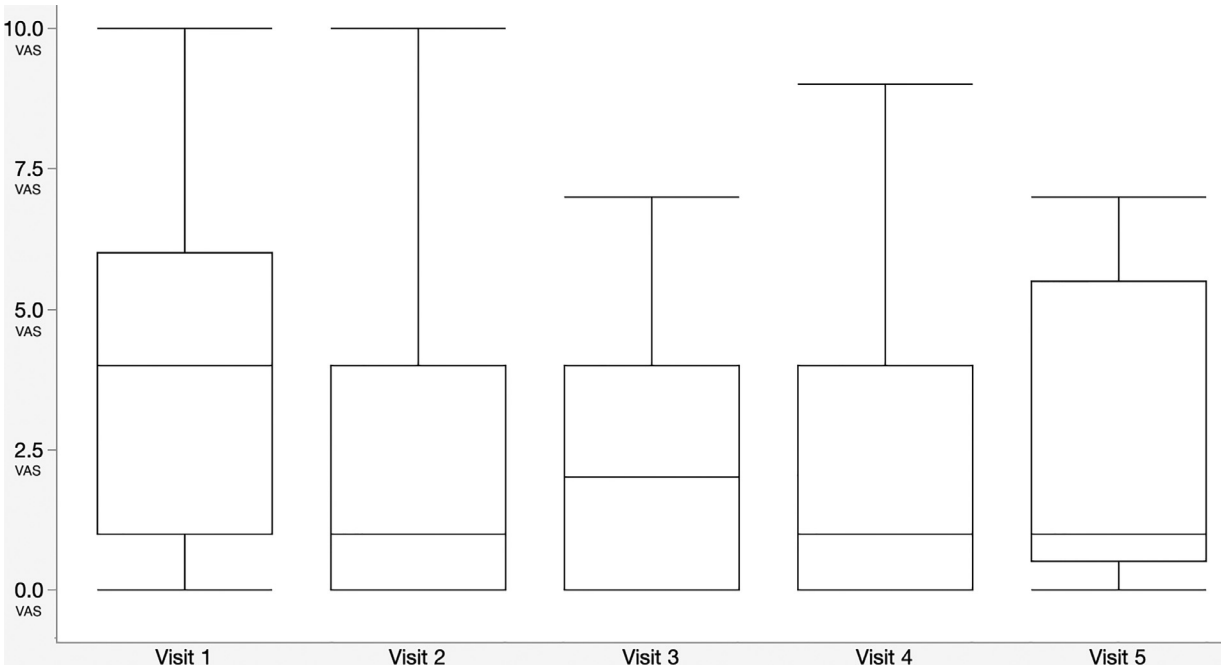

Fig. 2. Ulcer size at each visit. Box: 25th and 75th percentiles; bars: Range (minimum and maximum values); middle line: Median size.

with traumatic ulcers had a higher resolution rate (33 of 38 [86.8%]) compared with patients with OLP/cGVHD (n = 30/41 [73.2%]). Patients with traumatic ulcers required a median of 2 injections (range 1−5 injections) and the median time to resolution was 69 days (range 21−305 days), whereas patients OLP/cGVHD had an overall median resolution time of 140 days (range 21−357 days).

Ulcers persisted in 3 patients (3.2%; cGVHD, OLP, and discoid lupus erythematous) despite IST (median of 4 injections; range 2−6 injections) and required further treatment (e.g., high-dose prednisone, hydroxychloroquine, and topical steroids); 14 patients (15%) were lost to follow-up before observed healing.

Side effects of IST

Secondary candidiasis developed in 9 patients, all of whom were also being managed with topical steroids, and two-thirds (6 of 9) were also treated with systemic steroids. No other local or systemic treatment-related complications were observed.

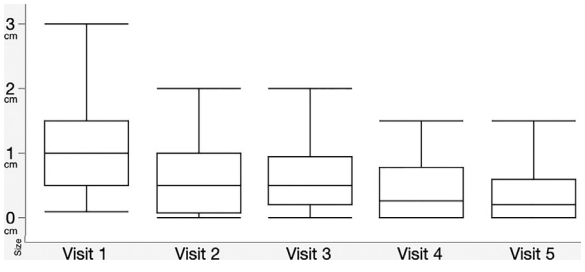

Fig. 3. Median pain score at each visit. Box: 25th and 75th percentiles; bars: Range (minimum and maximum values); middle line: Median pain. *VAS*, visual analogue scale.

DISCUSSION

We reported on clinical indications and treatment outcomes of IST with triamcinolone acetonide for inflammatory and immune-mediated oral ulcers. There was complete resolution of oral ulcers in greater than 80% of patients, and even in patients who did not experience complete healing, there were significant reductions in both lesion size and associated symptoms. The range of reported outcomes was attributed, in part, to the variable nature of the conditions being treated; some diseases, such as traumatic and aphthous ulcers, were expected to heal completely after the treatment, whereas chronic remitting−relapsing conditions, such as lichenoid inflammation and inflammatory bowel disease, would be expected to require long-term ongoing treatments, with the occurrence of periodic flares.

The effectiveness of IST for the management of oral medicine conditions has been described previously.[3,14] In addition to managing oral ulcerative conditions, IST has also been effectively used for nonulcerative orofacial conditions, such as oral submucous fibrosis,[16,17] osteoarthritis of the temporomandibular joint,[18] orofacial granulomatosis,[19] central giant cell granuloma,[20] pyogenic granuloma,[21] and oral manifestations of inflammatory bowel disease.[12,13,22-24] Lee et al. compared the efficacy and safety of intralesional TA (40

mg/mL) compared with TA 0.4% topical solution for the management of OLP.[25] Twenty patients used topical therapy 3 times a day for 6 weeks, and the other 20 patients were administered one 0.5 mL intralesional injection once a week for the first 4 weeks, and 1 additional injection after 2 weeks (5 injections in total). The results showed significantly fewer side effects (oral candidiasis and cushingoid features) in the IST group compared with the topical group, whereas the pain scores and clinical responses were similar for both groups. Xia et al. evaluated the efficacy of intralesional TA injections for the management of OLP in a controlled study in which each patient had 1 "experimental site," where 20 mg of TA was administered, and 1 "control site," which was not injected. After the first week, if the treated ulcer reduced greater than 80% in size, no additional TA injection was necessary. At the end of 2 weeks, 23 patients (51.1%) had greater than 80% of resolution of the lesion, and 22 (48.9%) received a second injection. Overall, 39 patients (75.6%) experienced complete resolution, and 6 (24.4%) had a partial resolution. In the experimental group, there was a 55% pain reduction during the first week and further reduction at the end of the second week; the control group showed minimal changes in the VAS score ($P > .05$) within the same period.[14] In our study, 13 (68.4%) of 19 patients with OLP had complete resolution of signs and symptoms in a median time frame of 91 days; some patients had complete resolution after 1 injection (n = 6 [42.8%]), and none required more than 4 injections to achieve complete resolution.

There are several limitations to this study. First, this was a retrospective analysis, which, by its nature, results in data not being collected in a uniform manner, with some patients potentially not returning for follow-up when they experienced symptomatic improvement. Second, there was no control group, patients were not managed per a single uniform protocol, and most patients received concomitant therapies; thus, it was not possible to determine the true efficacy of IST with TA. However, many of our patients were already being treated with topical steroids without improvement until IST therapy was initiated.

CONCLUSIONS

In summary, IST alone or in combination with topical and systemic immunomodulators was effective in reducing pain and ulcer size in noninfectious ulcerative oral conditions of various etiologies, with a better response seen in traumatic ulcerative conditions. The therapy was well tolerated and had no significant complications or adverse events. This therapy should be considered in patients who have symptomatic ulcerative oral inflammatory diseases and experience inadequate benefit from topical therapy alone. Accurate diagnosis of the ulcerative condition is essential and may require biopsy and histopathologic analysis, either before initiation of IST or in case of inadequate response or worsening of the condition after IST. Further prospective studies are needed to elucidate and to better define optimal treatment parameters, such as the dose and frequency of IST.

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