

## Treatment of mouth and jaw diseases with intralesional steroid injection

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joints. This technique is used also for a number of mouth and jaw lesions. Localized langerhans cell histiocytosis, central giant cell granuloma, oral submucous fibrosis, oral lichen planus, lichen sclerosus of the oral mucosa, lymphatic malformations and orofacial granulomatosis can be considered among these diseases. The purpose of this review is to investigate the effects of intralesional steroid injections in the treatment of oral diseases.

**Key words:** Intralesional injections; Steroids; Langerhans Cell histiocytosis; Giant cell granuloma; Oral submucous fibrosis; Oral lichen planus; Orofacial granulomatosis

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**Core tip:** Intralesional steroid injections are often used in the lesion occurred in oral and maxillofacial region in recent years. Especially in large lesions, it can be applied as an alternative or adjunct to surgical procedures. It is an effective treatment method, because, without the need for major surgical procedures and providing patient comfort.

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### Abstract

Many lesions of the oral region are treated with surgical methods such as curettage and resection. Chemotherapy and radiation therapy with or without surgical intervention can be used as an adjunct in some cases. Intralesional steroid injection is a conservative procedure which is already used in various regions of the body and

### INTRODUCTION

Corticosteroids are one of the most widely used drugs due to their anti-inflammatory, anti-allergic and immunosuppressive effects. Today they are used as systemic, topical, intra-articular and intralesional in the clinic. They were first used systemically in a patient with severe rheumatoid arthritis in 1948 by Hench *et al*<sup>[1]</sup>.

Consequently a further 15 patients were successfully treated. In 1950, their discovery of the effect of cortisone brought Hench, Edward and Reichstein the Nobel Prize in Medicine and Physiology<sup>[2]</sup>. Beneficial effects of intra-articular corticosteroid (hydrocortisone acetate) injection was first published in 1951<sup>[3]</sup>. In 1956, prednisolone was introduced by Rothermich and Phillips<sup>[4]</sup> as an satisfactory and more potent alternative for intra-articular injections. Boland and Liddle<sup>[5]</sup> compared methylprednisolone with prednisolone and found them equally effective. Triamcinolone acetonide was applied in the treatment of dermatoses by Robinson<sup>[6]</sup> in 1958. Later, triamcinolone hexacetonide was reported to be a potent synthetic corticosteroid for intra-articular usage<sup>[7]</sup>. In the 1970s, corticosteroids were administered in intra-osseous lesions such as bone cysts<sup>[8-10]</sup>. Intralesional steroid injection (ISI) has been performed in both of bone and mucosal lesions of oral and maxillofacial region since 1980. Currently, this method is widely accepted as an alternative or aid to surgical treatment especially in large reactive lesions.

In this review, we review the hard and soft tissue lesions of oral region that can be treated with intralesional steroid injections. Under the each disease's title, we also discuss the action mechanism of steroids.

## DISEASES THAT CAN BE TREATED WITH ISI

### Bone lesions

Localized langerhans cell histiocytosis (eosinophilic granuloma) and central giant cell granuloma.

### Soft tissue lesions

Soft tissue lesions include oral submucous fibrosis; oral lichen planus; oral lichen sclerosis; lymphatic malformations; and orofacial granulomatosis.

## LOCALIZED LANGERHANS CELL HISTIOCYTOSIS (EOSINOPHILIC GRANULOMA)

Langerhans' cell histiocytosis (LCH), formerly known as histiocytosis-X, is a disease characterized by cell proliferation exhibiting phenotypic characteristics of Langerhans cells<sup>[11]</sup>. There are three clinical forms of the disease: Letterer-Siwe disease, Hand-Schüller-Christian syndrome and Localized Langerhans Cell Histiocytosis (LLCH) or eosinophilic granuloma<sup>[12]</sup>.

Letterer-Siwe disease is an acute disseminated form of LCH and characterized by hepatosplenomegaly, lymphadenopathy, anemia, skin rash, and bone lesions with dissemination. It usually affects young children and follows an acute or sub-acute course.

Chronic disseminated form of the LCH is called Hand-Schüller-Christian syndrome and it is usually associated

with a triad of exophthalmos, diabetes insipidus and punched-out bone lesions. This form of the disease typically affects the patients in the second and third decades or older age<sup>[13]</sup>.

LLCH, a localized disease. It accounts for 60%-70% of LCH cases and it can be found as solitary or multifocal bone defects. While mandible, skull and ribs are most often affected in children, long bones and vertebrae are more frequently involved in adults. The disease peaks in the first three decades and males are affected twice as females<sup>[14]</sup>. Possible symptoms are swelling, pain and tenderness over the lesion's site. General malaise, fever, headache, toothache, bleeding, loose teeth and sensory disturbances may accompany as well. It is also possible not to see any symptoms<sup>[15]</sup>. The lesions appear as radiolucent areas with well-demarcated borders in radiographic views. Pathologic fractures may arise due to resorption of the overlying cortical bone<sup>[16]</sup>. Treatment options of LLCH include resection or curettage, chemotherapy, radiotherapy or a combination of them<sup>[17]</sup>. Spontaneous healing has been reported, too<sup>[18]</sup>.

### Treatment of the LLCH with ISI

Currently there is not a clear treatment protocol for the ISI in the LLCH. Previously a few studies have been reported. In 1980, Cohen *et al*<sup>[19]</sup> first employed this technique in eosinophilic granulomas of the bones. While they did a single dose of methylprednisolone directly into the lesions in various parts of the body, in mandibular lesions they did a second injection. Jones *et al*<sup>[16]</sup> applied single intralesional dose of 165 mg methylprednisolone to a mandibular LCH and reported complete resolution of the lesion after 8 mo. Others<sup>[20]</sup> have described a case with multifocal LCHs in the mandible, who failed to respond to radiotherapy and systemic therapy with prednisone and etoposide. On a weekly basis, the authors injected 2 mL of 25 mg/mL triamcinolone into the lesion for six times. Complete remission was reached by the 15 mo. Putters *et al*<sup>[21]</sup> treated three LLCH cases of the mandible in a one-stage procedure. They performed intralesional injections of 80, 40, and 80 mg of methylprednisolone succinate, respectively. The lesions showed radiologically and clinically complete remission after 6 mo. In another case<sup>[22]</sup>, 200 mg of intralesional methylprednisolone injection was used in a mandibular lesion and complete resolution had been achieved after 17 mo. Esen *et al*<sup>[23]</sup> reported a case of LLCH of the mandible, which also caused a non-displaced pathologic fracture. They started repeated ISIs and the fracture line disappeared within 14 mo without using any reduction or fixation methods. By the end of the 36-mo follow-up, the lesion was entirely healed. In a later paper<sup>[24]</sup>, two patients were treated in one-stage procedures with intralesional methylprednisolone injections. The lesions healed clinically and radiologically 35 and 15 mo after treatment.

### Action mechanism of steroids

Many questions remain to be clarified to understand the therapeutic effects of corticosteroids in LLCH. It is unknown whether they suppress T lymphocytes, the Langerhans cells, eosinophils or stimulate osteogenesis. It has been suggested<sup>[8,25]</sup> that corticosteroid microcrystals can break the connective tissue of the cystic wall and allow secondary osteogenic repair or IL-1 is inhibited by steroids. Even though these hypotheses may explain the improvement in bone cysts, it does not apply to LLCH, because there is no membrane covering the lesion.

As evident from the literature, ISI is a successful method in cases of LLCH. It is an effective treatment method, because, without the need for major surgical procedures and providing patient comfort.

## CENTRAL GIANT CELL GRANULOMA

The central giant cell granuloma (CGCG) was first described by Jaffe<sup>[26]</sup> in 1953. CGCG occurs almost solely within the jaws and it is a benign proliferation of fibroblasts and multinucleated giant cells. It typically presents as a solitary radiolucent lesion of the mandible or maxilla. The lesions occur twice as often in the mandible than in the maxilla. It is predominantly found in young adults before the age 30 with a female preponderance<sup>[27]</sup>. Based on its clinical behavior, CGCG has been classified as non-aggressive and aggressive lesion. Non-aggressive lesions tend to grow slowly and do not perforate the cortical bone. Recurrence usually is not seen after treatment. Aggressive lesions are characterized by rapid growth, pain, expansion or perforation of the cortical bone, root resorption, and a high recurrence tendency<sup>[28]</sup>. The traditional treatment of CGCG is curettage or resection depending on the lesion's behavior, size, location, and radiographic appearance. Non-surgical treatment methods are systemic administration of calcitonin, intralesional injection of corticosteroids and administration of  $\alpha$ -interferon<sup>[29-32]</sup>.

### Treatment of the CGCG with ISI

The treatment of CGCG with corticosteroids was first reported by Jacoway *et al*<sup>[33]</sup> in 1988. They suggested is a 50/50 mixture of 2% lidocaine with 1:100000 epinephrine and triamcinolone acetonide (TA) to inject 2 mL/1 cm of lesion as seen on a panoramic radiography and to repeat this six times at weekly intervals. Later, Terry and Jacoway<sup>[34]</sup> presented four patients treated with steroids in 1994. A weekly done ISI during six weeks resulted in a complete resolution in three patients, while one patient needed additional surgery. Kermer *et al*<sup>[35]</sup> published another case of CGCG treated with corticosteroids in the same year. Rajeevan and Soumithran<sup>[36]</sup> reported that intralesional triamcinolone acetonide was administered to a 17-year-old girl who had CGCG in 1998. They indicated that almost healing the lesion of the left mandible was observed after the

sixth month. In 2000, Khafif *et al*<sup>[37]</sup> applied the same protocol to a 36-year-old female patient who had a CGCG of maxilla and they reported that a complete remission was seen after two years. Kurtz *et al*<sup>[38]</sup> also used ISI to a 10-year-old CGCG patient in 2001. They reported that the proper healing was seen after 5 years. In 2002, Carlos *et al*<sup>[39]</sup> added four new cases to the literature. They reported that the lesions showed clinically and radiologically recovery approximately 6-7 years after treatment except for one case in which partial remission was observed. Abdo *et al*<sup>[40]</sup> reported that a recurrent CGCG in a 14-year-old girl in the anterior region of the mandible was treated successfully by ISI in 2005. Sezer *et al*<sup>[41]</sup> also reported that an 11-year-old boy with a CGCG is successfully treated with intralesional corticosteroid injections after 3 years follow-up in the same year. Comert *et al*<sup>[42]</sup> preferred to use prednisolone in their patient who had CGCG of the maxilla. They reported that a partial recovery was achieved and a limited surgery could be performed. Wendt *et al*<sup>[43]</sup> employed ISI for a maxillary CGCG with a 1:1 triamcinolone acetonide (10 mg/mL) and 0.5% bupivacaine. The solution was injected into the lesion for a period of 11 wk. After 6-years follow-up, the treatment was found to be successful clinically and radiographically. Mohanty and Jhamb<sup>[44]</sup> performed same protocol and reported that two patients were successfully treated with triamcinolone acetonide injections. Nogueira *et al*<sup>[45]</sup> contributed to literature with 21 new cases in 2010 using ISI with triamcinolone hexacetonide. Two patients did not responded to the treatment and surgical resection was needed; a moderate improvement noted in four patients (curettage in two patients) and 15 of the cases showed good response (curettage in one patient). Shirani *et al*<sup>[46]</sup> performed ISI in an aggressive and extensive case and they could not get the answer to the treatment. Ferretti *et al*<sup>[47]</sup> applied the same protocol to 16-year-old female patient who had CGCG and they reported that a complete remission was seen after 4 years follow up. Rachmiel *et al*<sup>[48]</sup> performed combination therapy consisting of ISI, calcitonin nasal spray and curettage in a 24-year-old female patient and found that no recurrence after 5-year follow-up. da Silva *et al*<sup>[49]</sup> treated a 36-year-old male with a CGCG crossing the midline of mandible with ISI combined with alendronate sodium for the control of systemic bone resorption. They reported that no recurrence or side effects at the end of four years. Finally, Fonseca *et al*<sup>[50]</sup> reported that intralesional triamcinolone acetonide was administered to a 15-year-old boy who had CGCG. They indicated that partial resolution of the lesion was observed after the sixth month.

### Action mechanism of steroids

There are several theories about the action mechanism of ISI in the CGCG. Osteoclasts achieve bone resorption by secreting lysosomal proteases. These agents mediate the process by creating an extracellular medium. It

has been showed<sup>[51,52]</sup> that 17 $\beta$ -estradiol (E2) could directly inhibit osteoclastic bone resorption. Moreover, at concentrations effective for inhibiting bone resorption, E2 could also induces osteoclast apoptosis.

On the basis of the aforementioned experimental evidence the mechanism of corticosteroids in the treatment of these lesions is suggested as inhibition of the extracellular production of lysosomal proteases and steroidal apoptotic action on osteoclast-like cells. These two mechanisms could cause cessation of bone resorption<sup>[39]</sup>.

According to literature, ISI is an effective method in patients with CGCG. However, it is not always possible to obtain a positive response to the treatment in the multilobular or aggressive lesions. Hence, in such cases, it is necessary to apply surgical or combined treatment methods. In addition, serum calcium, phosphorus and parathyroid hormone levels should be examined on suspicion of hyperparathyroidism after definitive diagnosis result of the incisional biopsy. It should be noted that the images of brown tumor and CGCG can't be distinguished histologically. And before starting the ISIs, possible diabetes mellitus and the presence of peptic ulcers or any infection should be questioned.

## ORAL SUBMUCOUS FIBROSIS

Oral submucous fibrosis (OSF) is a chronic disease of the oral mucosa. It affects the pharynx, oral cavity, upper third of the esophagus and it is characterized by inflammation and a progressive fibrosis of sub-epithelial tissues<sup>[53]</sup>. Connective tissue fibers of the lamina propria and deeper parts change, which in turn lead to mucosal stiffness and limitation in mouth opening<sup>[54]</sup>. OSF is considered as high-risk precancerous disease<sup>[53-55]</sup>. Several factors contributing to OSF include general nutritional or vitamin deficiencies and hypersensitivity to various dietary constituents. The primary factor appears to be chewing of the areca (betel) nut. Genetic factors are thought to be involved in the etiology. It has been reported that a polymorphism of the promoter region of the matrix metalloproteinase 3 gene is common in OSF and may contribute to development of the disease<sup>[27]</sup>. The potential morbidities of OSF are restriction of mouth opening, difficulty with swallowing, mastication, speech, and a burning sensation as well. It has a mortality potential because of the possibility of transformation into squamous cell carcinoma<sup>[55]</sup>. Both nonsurgical and surgical treatment options have been suggested. Nonsurgical options are ISIs, hyaluronidase and interferon gamma. Surgery primarily targets to improve the mouth opening and comprises the excision of the fibrous bands, skin grafts and splitting of the temporalis tendon.

### Treatment of the OSF with ISI

Treatment is generally intended to increase the mouth opening and to decrease the burning sensation. For

early-stage submucous fibrosis cases, the results are better with non-surgical methods. In intralesional applications, the triamcinolone acetonide is the most preferred agent but different substances are also applied such as salvianolic acid B (SA-B) and lycopene. As far as we know, Gupta and Sharma<sup>[56]</sup> were the first who successfully treated the OSF with local injections of chymotrypsin, hyaluronidase, and dexamethasone. Later, sub-mucosal steroid injection and hyaluronidase or topical vitamin A, topical steroid application and oral iron preparations were applied by Borle and Borle<sup>[57]</sup> in 326 patients with oral submucous fibrosis. Khanna *et al.*<sup>[58]</sup> presented 100 patients in their clinical study in which the author implemented intralesional injection of triamcinolone acetonide in patients with very early and early-stage of OSF cases while they performed surgical intervention in advanced cases. Satisfactory results were reported in long-term follow up. Kumar *et al.*<sup>[59]</sup> applied the lycopene and lycopene combined with ISI of betamethasone in OSF patients. They reported that positive clinical response was obtained in both study groups when compared with placebo. Singh *et al.*<sup>[60]</sup> compared the efficacy of hydrocortisone acetate and hyaluronidase at weekly interval vs triamcinolone acetonide and hyaluronidase at 15 d interval. They notified no significant differences in symptom or sign scores and any histopathological improvement between the groups. The authors conclude that treatment regimen of triamcinolone acetonide and hyaluronidase was more convenient to the patients because of less number of visits required and of cost efficiency. No side effects were seen<sup>[60]</sup>. Rao<sup>[61]</sup> treated the patients with OSF using alpha lipoic acid in addition to the ISI of betamethasone and hyaluronidase. He reported that the alpha lipoic acid group exhibited better relief of symptoms as compared to the controls and he concluded that the use of an antioxidant, alpha lipoic acid, along with conventional therapy of ISI is effective in the management of OSF. Jiang *et al.*<sup>[55]</sup> investigated that the effectiveness of triamcinolone acetonide and (SA-B) intralesional combined injection in the treatment of oral submucous fibrosis (OSF) and they concluded that the triamcinolone acetonide + SA-B intralesional injections improved mouth open and burning sensation in these OSF patients. Shetty *et al.*<sup>[62]</sup> examined the efficacy of spirulina as an antioxidant adjuvant to corticosteroid injection in management of oral submucous fibrosis. They treated the OSF patients in a group with spirulina+ betamethasone and placebo capsules + betamethasone in other group. They reported that the mouth opening and burning sensation was found to be statistically very highly significant in favor of the spirulina group.

Some complications can be seen after the procedure in the OSF cases. Chen *et al.*<sup>[63]</sup> observed facial candida albicans cellulitis in a diabetes mellitus patient with oral submucous fibrosis after ISI treatment. Therefore, it should be noted that some complications can arise due

to the predisposing factors such as immunodeficiency (HIV), immune-suppression (systemic treatments with corticosteroids), chronic illness, obesity, diabetes, malnutrition, vitamin deficiency, alcohol misuse, tobacco smoking and intravenous drugs abuse.

### Action mechanism of steroids

According to the hypothesis of Tsai *et al.*<sup>[64]</sup>, some alkaloids (arecoline, arecaidine) inhibit fibroblast phagocytosis and this contributes for the development of OSF. ISIs could cause an enhancement of fibroblast collagen phagocytosis. Juxta-epithelial inflammatory cell infiltration and then progressive hyalinization of the lamina propria and deeper connective tissues are associated with early OSF<sup>[55,65,66]</sup>. Use of ISI have been directed to chronic juxta-epithelial inflammation<sup>[55-57,60]</sup>. The steroids can prevent or suppress inflammatory reactions, so they fight with fibrosis by decreasing fibroblastic proliferation and collagen deposition<sup>[55,65,66]</sup>. Therefore, it can be more successful when the steroid injections administered in the early stages of the disease. According to the literature, triamcinolone acetonide or betamethasone appears to be a suitable choice.

## ORAL LICHEN PLANUS

Oral lichen planus (OLP) is a chronic mucocutaneous disease of unknown cause, with oral lesions occurring most commonly in women over 30 years of age. Incidence of OLP is between 0.2% and 2% in the population. Different types of OLP have been described as reticular, plaque form, erosive, atrophic, or bullous. Intraorally, the buccal mucosa, tongue and the gingiva are commonly involved although other sites may be rarely affected. Oral mucosal lesions present alone or with concomitant skin lesions. The most common type is the reticular form which is characterized by numerous interlacing white keratotic lines or striae that produce an annular or lacy pattern<sup>[27,67]</sup>. The plaque form of OLP tends to resemble leukoplakia clinically but has a multifocal distribution. In the erosive form, the central area of the lesion is ulcerated. A fibrinous plaque or pseudomembrane covers the ulcer. The erythematous or atrophic type appears as red patches with very fine white striae. It may be seen in conjunction with reticular or erosive variants. Patients complain of pain, burning, sensitivity and generalized discomfort in particularly erosive and atrophic types<sup>[27,67]</sup>. The risk of malignant transformation varies between 0.4% and 5% over periods of observation from 0.5 to 20 years<sup>[68]</sup>. A few studies have reported that the malignant potential of OLP and hepatitis C virus infection apparently increased the risk for oral squamous cell carcinoma<sup>[69-71]</sup>. Patients with reticular and other asymptomatic OLP lesions usually require no active treatment but symptomatic lesions may also need treatment. Nonsurgical treatments are systemic drug therapy, topical corticosteroids-calcineurin

inhibitors - retinoids, injection of steroids and ultraviolet irradiation. The other methods are surgery, laser therapy and cryosurgery<sup>[67]</sup>.

### Treatment of the OLP with ISI

According to literature, intra- and sublesional treatment of OLP with triamcinolone acetonide was reported by Sleeper<sup>[72]</sup> for the first time in 1967. The author reported that after 72 h, examination of the lesions showed 45% to 50% involution with corresponding relief of symptoms. In three cases the entire lesion disappeared in two weeks. In the other four cases with larger lesions, approximately 10% to 15% of the lesion remained, but the patients were completely symptom free. In 1974, Randell and Cohen<sup>[73]</sup> applied dexamethasone in patients with OLP and they reported successful results. Then Zegarelli<sup>[74,75]</sup> performed ISI with triamcinolone acetonide and methylprednisolone in patients with erosive or ulcerative OLP. Xia *et al.*<sup>[76]</sup> studied with 45 patients with clinical and histologically confirmed ulcerative OLP. Each participant received 0.5 mL intralesional triamcinolone acetonide injection (40 mg/mL) on one side and other side was left as control. The treated areas gave rapid relief of signs and symptoms, while the control areas showed minimal decrease. Thirty-eight (84.4%) patients demonstrated complete response in ulceration size. No complications were noted with triamcinolone acetonide injections. They concluded that intralesional triamcinolone acetonide injection in ulcerative OLP is effective and safe in achieving lesion and pain regression. Xiong *et al.*<sup>[77]</sup> compared the intralesional polysaccharide nucleic acid fraction of bacillus Calmette-Guerin (BCG-PSN) and triamcinolone acetonide in patients with erosive OLP. They randomly assigned 56 OLP patients receive either intralesional injection of 0.5 mL BCG-PSN every other day ( $n = 31$ ) or 10 mg triamcinolone acetonide (a positive-controlled group,  $n = 25$ ) every week for 2 wk. After the cessation of treatment, patients were followed up for 3 mo. After 2-wk treatment, 27 of 31 BCG-PSN-treated patients (87.1%) and 22 of 25 TA-treated patients (88.0%) healed. There were no statistical differences between the two groups in erosive areas and pain scores. They concluded that topical intralesional BCG-PSN injection is as effective as triamcinolone acetonide for erosive OLP. Lee *et al.*<sup>[78]</sup> investigated intralesional injection vs mouth rinse of triamcinolone acetonide in 40 patients with OLP in terms of pain and burning sensation. They concluded that the efficacies of both treatments were similar. The rate of adverse effects was significantly lower for intralesional injection of triamcinolone acetonide than mouth rinse of TA. In another clinical study, intralesional triamcinolone acetonide plus oral prednisolone was applied by Kuo *et al.*<sup>[79]</sup> in 50 patients with erosive OLP. They reported that although the patients showed complete response in 90% of cases after three weeks, recurrence of erosive or ulcerative lesion was observed after 3-24 (mean 12) mo of follow-up in all of these cases. Liu *et al.*<sup>[80]</sup> analyzed

the efficacy and safety of intralesional betamethasone in the treatment of erosive OLP. They implemented intralesional betamethasone 1.4 mg to the experimental group and 8 mg intralesional triamcinolone acetonide to the control group once a week for two weeks in 61 patients with erosive OLP. They found that 93.1% of participants were healed after two intralesional injections of 1.4 mg betamethasone, and 66.7% of participants were healed after two intralesional injections of 8 mg triamcinolone acetonide and authors concluded that intralesional betamethasone was a more effective way to treat erosive OLP.

According to the literature, triamcinolone acetonide is the most preferable agent as intralesional injection in patients with OLP. Recently, betamethasone seems to be also effective. General usage of triamcinolone acetonide is to dilute 10 to 20 mg in 0.5 mL saline or 2% lidocaine, then to inject into the lesion once 1 wk for 2 times<sup>[81]</sup>. Injections are administered into the connective tissue below the erosive lesion from the adjacent normal mucosa. The treatment is absolutely required in patients with erosive and erythematous types due to the daily life is affected by pain and burning sensation. Generally, patient comfort is provided and the lesions disappeared within one to two weeks after ISI. However, recurrence of the lesions may occur on the long-term follow-up. Disadvantages include mucosal atrophy, difficulty to deposit sufficient quantities into gingival lesions and painful injection<sup>[82]</sup>.

### Action mechanism of steroids

While the etiology of OLP is not clear, it has been suggested that it could be caused by a immune response with an inflammatory cell population composed of T lymphocytes<sup>[83,84]</sup>. When the steroids are injected directly into the connective tissue below the lesions, they can suppress T cells and show a strong anti-inflammatory and immunosuppressive effect<sup>[80]</sup>.

## OTHER DISEASES

Other oral diseases treated with ISI are very limited in the literature. Azevedo *et al.*<sup>[85]</sup> used intralesional injection of triamcinolone acetonide in patients with oral lichen sclerosis. The authors reported that the patients showed improvement and elasticity of oral tissues enhanced. Luo and Gun<sup>[86]</sup> found that intralesional injection of pingyangmycin with triamcinolone acetonide was more effective than pingyangmycin alone for management of lymphatic malformations in oral and maxillofacial region. Anjomshoaa *et al.*<sup>[87]</sup> performed intralesional injections of triamcinolone acetonide in a patient with follicular lymphoid hyperplasia. In addition, they reported that complete resolution of the lesion was obtained at 7-mo follow-up. Another disease in which ISI could be effective is orofacial granulomatosis (OFG). It is an uncommon disease, usually presents as recurrent or persistent swelling of the soft tissues

in the orofacial region, predominantly on lips, causing significant cosmetic and functional problems<sup>[88,89]</sup>. The reason of this disease is unknown. OFG may also be part of the triad of Melkersson-Rosenthal syndrome (MRS) and some consider it a monosymptomatic form of MRS<sup>[90,91]</sup>. Sakuntabhai *et al.*<sup>[92]</sup> used high-volume intralesional triamcinolone acetonide injections (3 to 10 mL of 10 mg/mL) and they reported that intralesional triamcinolone injections reduced lip swelling. However, Mignogna *et al.*<sup>[91]</sup> performed small volume, high concentrate, delayed release, intralesional injection of triamcinolone acetonide in patients with OFG. They reported that all patients remained without recurrences or with cosmetically acceptable slight lip enlargement for a mean time of 19 mo and this method was very affective and it did not require nerve blockage. The same researchers investigated the long-term outcome in patients treated with intralesional triamcinolone acetonide injections and reported that complete clinical remission were obtained in all patients for a mean time of  $56.3 \pm 18.2$  mo<sup>[93]</sup>. Several other clinical studies have reported that injections of intralesional steroids are clinically successful method in patients with OFG<sup>[88,89,94]</sup>.

Exogenous corticosteroids are usually classified based on their relative glucocorticoid and mineralocorticoid potency as well as duration of their effects. The most potent glucocorticoids are also the most potent suppressors of the hypothalamic pituitary adrenal axis. While short-acting steroids (e.g., Cortisol) are effective for less than 12 h, intermediate-acting steroids (Prednisone, Prednisolone, Methylprednisolone and Triamcinolone) can stay active for 12-36 h and long-acting steroids (Betamethasone, Dexamethasone and Flumethasone) are effective for more than 36 h<sup>[95]</sup>. Most prominent properties of corticosteroids are their anti-inflammatory, anti-allergic and analgesic effects. Glucocorticoids help keeping normal vascular permeability and stabilize lysosomal and cellular membranes. On the other hand, in acute inflammation, they decrease vascular permeability and inhibit the migration of polymorphonuclear lymphocytes into tissues. They also induce apoptosis in normal lymphoid cells; inhibit the clonal expansion of T and B lymphocytes; and reduce the eosinophils, basophils, and monocytes in the circulation. Glucocorticoids have different effects on neutrophils. They hinder margination of neutrophils and increase the release of mature neutrophils from the bone marrow.

However, they may also decelerate wound healing<sup>[95]</sup>. Long-term use of corticosteroids can cause osteoporosis, hypertension, electrolyte imbalance, hyperglycemia, delayed wound healing, and a tendency for infections. There are some contraindications for steroids such as history of allergy, peptic ulcer, Cushing syndrome, uncontrolled diabetes, renal failure, anticoagulation usage, fungal diseases and varicella zoster infection<sup>[96]</sup>. Although intralesional injection can be performed easily, several precautions should be taken during the

processing. The injection must always be made using sterile procedures and anatomy of the area should be known. Adjacent nerves should be kept away and intravenous injections should be avoided because of the possibility of systemic effects such as adrenal suppression<sup>[96]</sup>.

## CONCLUSION

ISI is one of the most preferable non-surgical methods for the treatment of mucosal or bone reactive lesions occurred in oral and maxillofacial region. The accumulating evidence suggests that ISI is well tolerated by patients, the likelihood of postoperative complications is less than those of other methods and patient complaints diminish rapidly. Especially in large lesions, it can be applied as an alternative or adjunct to surgical procedures. This method is also minimally invasive and relatively inexpensive.

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