# Topical cyclosporine in a bioadhesive for treatment of oral lichenoid mucosal reactions

## An open label clinical trial

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Oral lichenoid reactions may present as chronic symptomatic mucosal reactions. Lichen planus-like reactions include those associated with drug reactions, graft-versus-host disease after bone marrow transplantation, and idiopathic lichen planus. The mainstay of management is topical steroids; in resistant cases, topical and systemic corticosteroids may be used. We evaluated the use of cyclosporine administered in an adhesive hydroxypropyl cellulose base in patients with oral lichenoid reactions that remained active despite the prior use of high-potency topical steroids and in some cases despite the combined use of topical and systemic immunosuppression. Signs and symptoms of ulcerative oral graft-versus-host-disease improved more than 50% in three of four patients with oral graft-versus-host disease treated with the addition of topical cyclosporine. However, in patients with persistent oral lichen planus less effect was seen with 7 of 14 patients demonstrating a partial reduction in signs and symptoms. The topical use of cyclosporine in a bioadhesive base may represent a useful adjunctive approach in management of oral lichenoid reactions, although dose escalation and placebo-controlled studies are needed. **(Oral Surg Oral Med Oral Pathol Oral 1996;82:532-6)**

Cyclosporine has been used in management of T-lymphocyte–mediated conditions including inflammatory diseases, immunologically mediated graft rejection, graft-versus-host disease (GVHD), and inflammatory diseases. The mechanism of action may be due to inhibition of T-cell activation that may be involved in inflammatory and immune diseases including lichen planus.[1-3] Activated T-cells produce γ-interferon that increases the expression of ICAM-1 and HLA-DR by keratinocytes, which may result in the adhesion of T-lymphocytes promoting an inflammatory reaction.[3]

Systemic and topical cyclosporine has been studied in dermatology for treatment of a variety of conditions. In psoriasis, which may represent a T-cell–mediated condition, systemic therapy has been shown to be effective; however, topical application shows limited effect.[4, 5] Limited effect of topical cyclosporine has also been seen in management of contact dermatitis and atopic dermatitis.[6] The lack of penetration of topical cyclosporine through intact skin has been implicated in this limited efficacy.

Topical cyclosporine has been shown to be effective in a variety of oral mucosal disorders such as lichen planus, aphthous stomatitis, pemphigoid, and pemphigus.[7-11] In lichen planus, a disease that shares clinical features of lichenoid oral GVHD, oral rinsing with cyclosporine has produced clinical or histopathologic improvement in several studies.[3, 7, 8, 12-15]

Low systemic absorption of topical cyclosporine has been demonstrated in blood studies in some patients; no systemic side effects were reported.[3, 7, 14] Cyclosporine measured in biopsy specimens indicate that drug absorption through the mucosa is needed for a beneficial effect, and low systemic levels suggest a local action of the drug.[7] Pre- and posttherapy biopsies have revealed decreased T-cell infiltrate and reduced expression of ICAM-1 and HLA-DR after topical cyclosporine.[3] In a clinical study of oral GVHD, management was related to local effects as no consistent changes in systemic levels of cyclosporine were demonstrated.[16] The dose of cyclosporine applied topically may be important. One study used a low dose of cyclosporine rinse (100 mg/ml, 2 ml rinse, 15 minutes three times per day) with no improvement[12]; whereas a higher dose (100 mg/ml, 5 ml, three times a day) in a controlled double-blind

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study was effective.[14] No systemic side effects or laboratory abnormalities have been identified with topical cyclosporine when used in treatment of oral conditions, and only low or undetectable levels of systemic cyclosporine have been seen.

Topical cyclosporine has been studied in treatment of oral lichen planus[3, 7, 8, 12-18] with improvement reported in several publications.[3, 7, 8, 12-15] Eisen et al.[7] provided topical cyclosporine in a double-blind placebo-controlled design for eight patients. Balato et al.[15] demonstrated improvement in oral erosive lichen planus after topical application of cyclosporine (100 mg/day) that was maintained at a lower dose (50 mg/day) for a second month. The recent study of oral lichen planus by Harpenau et al.[14] compared topical cyclosporine (500 mg, rinsed 5 minutes) with placebo and showed statistically significant improvement in erythema, ulceration, and decreased pain scores with the use of cyclosporine. However, limited effect has been reported in other studies.[13, 17, 18] A study of cyclosporine (Sandimmune 0.05%) in an ointment of 40% hypromellose in soft paraffin to a concentration of 0.025% in patients with recalcitrant lichen planus showed only partial response in less than half of the patients.[13]

Zilactin (Zila Pharmaceuticals, Phoenix, Ariz.) forms a unique topical film form composed of hydroxypropyl cellulose that contains salicylic, boric, and tannic acids. The solubility of hydroxypropyl cellulose is altered by the formation of esters with these three acids and results in the bioadhesive film.[19] Zilactin has been shown to bind to mucosa and to provide pain relief in symptomatic oral ulcers.[20] The application has been reported to form a durable film when applied to mucosa, and when dried after application it did not adhere to adjacent contacting tissues. Moisture control during application was found important in duration of adherence of Zilactin.

The purpose of this open clinical trial was to assess the potential of cyclosporine in Zilactin for management of persisting oral lichenoid reactions.

## PATIENTS AND METHODS

Patients were enrolled in an open clinical trial if they had an oral lichenoid mucosal condition that was unsuccessfully managed with therapy including topical corticosteroids and, in some cases, topical and systemic corticosteroids. These patients included 14 biopsy-confirmed cases of idiopathic lichen planus in immunocompetent hosts. The remaining four cases represented lichenoid oral GVHD, diagnosed by medical history, clinical features, and histopathologic diagnosis of GVHD of the oral mucosa in one case, the skin in one case, and of skin and gut in two cases. The patients with lichenoid oral GVHD were recipients of allogeneic bone marrow transplants who were referred for treatment for persistent oral GVHD despite systemic therapy (prednisone and cyclosporine) and topical corticosteroids. All patients had been either prescribed high-potency topical steroids (four patients) or systemic steroids for therapy for a minimum of 2 months.

The oral status was examined and recorded as previously described.[21, 22] Each area of the oral cavity was evaluated for the presence and severity of erythema, lichenoid pattern, and ulceration. The maximum size of the ulcer (length × width) and the total area of ulceration were recorded. The variable of lichenoid pattern, a recognized component of oral GVHD, was included in the assessment as described by Schubert et al.[23, 24] Symptoms were assessed with the aid of visual analogue scales. A global assessment was provided by the patient and provider.

Cyclosporine (100 mg/ml, Sandimmune, Sandoz Pharmaceuticals, East Hanover, N.J.) was added to the alcohol phase of Zilactin to a final concentration of 0.5 mg/dl before completion of the manufacturing process. The patients were instructed to apply the medication four times daily. For bone marrow transplantation patients, there were no changes in systemic medications during the trial. For patients with lichen planus, topical and systemic corticosteroids were not provided during the trial with cyclosporine.

Patients were assessed before starting cyclosporine and then reassessed after 2 to 4 weeks. All patients were followed for a minimum of 1 month.

## RESULTS

Patient demographics, oral findings and symptoms, and the effect of topical cyclosporine are shown in Table I. For patients with lichenoid oral GVHD, the mean maximum ulcer size was reduced from 0.69 $cm^2$ to 0.24 $cm^2$, the mean total ulcer area decreased from 1.88 $cm^2$ to 0.25 $cm^2$, the mean severity of erythema reduced from 2.8 to 1.5 (on a 0 to 3 scale) and the area of mucosa with clinical striations was changed from 38 to 27 cm. The overall clinical improvement as judged by the provider was 75%, and the patient assessment was an improvement of 90%. In patients with lichen planus, the mean maximum ulcer size was minimally reduced from 0.24 $cm^2$ to 0.19 $cm^2$, the mean total ulcer area decreased from 0.38 $cm^2$ to 0.27 $cm^2$, the mean severity of erythema reduced from 2.5 to 1.9, and the area of mucosa with clinical striations was little changed from 32 to 29 cm.

Ten patients reported a bad taste that persisted for a short duration after the topical application, but none of the patients stopped the use of the test preparation

**Table I.** Cyclosporine/Zilactin open label clinical trial on oral lichenoid reactions

| | | *Pretreatment* | | | | | | *Posttreatment* | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Lichen Planus* | | | | | *Ulcer (mm)* | | | | | *Ulcer (mm)* | | | *Overall effect* | |
| *Patient number* | *Age* | *Sex* | *Stria (cm)* | *Erythema* | *Largest* | *Total* | *Discomfort (eating)* | *Stria (cm)* | *Erythema* | *Largest* | *Total* | *Discomfort (eating)* | *Patient (%)* | *Dentist (%)* |
| 1 | 36 | M | 26 | 3 | 11 | 22 | 6 | 25 | 3 | 10 | 20 | 5 | 0 | 10 |
| 2 | 46 | F | 10 | 3 | 21 | 62 | 7 | 11 | 2 | 15 | 45 | 3 | 50 | 20 |
| 3 | 67 | M | 20 | 2 | 20 | 60 | 4 | 20 | 2 | 20 | 60 | 4 | 0 | 0 |
| 4 | 47 | M | 7 | 3 | 4 | 12 | 5 | 8 | 3 | 5 | 15 | 5 | 20 | 0 |
| 5 | 68 | F | 30 | 3 | 55 | 22 | 9 | 35 | 3 | 60 | 24 | 8 | 0 | 0 |
| 6 | 70 | F | 25 | 2 | 10 | 10 | 9 | 22 | 2 | 10 | 10 | 8 | 10 | 10 |
| 7 | 51 | F | 45 | 3 | 35 | 70 | 6 | 46 | 3 | 33 | 66 | 6 | 0 | 0 |
| 8 | 55 | M | 20 | 2 | 70 | 70 | 4 | 15 | 1 | 40 | 40 | 2 | 50 | 40 |
| 9 | 57 | M | 42 | 2 | 9 | 9 | 5 | 42 | 1 | 9 | 9 | 5 | 0 | 0 |
| 10 | 50 | M | 25 | 1 | 0 | 0 | 2 | 23 | 0 | 0 | 0 | 1 | 50 | 50 |
| 11 | 40 | F | 6 | 3 | 20 | 25 | 3 | 6 | 2 | 20 | 25 | 3 | 0 | 0 |
| 12 | 72 | F | 11 | 2 | 3 | 5 | 3 | 10 | 1 | 0 | 0 | 3 | 10 | 25 |
| 13 | 39 | M | 85 | 3 | 60 | 114 | 5 | 80 | 2 | 50 | 60 | 3 | 50 | 30 |
| 14 | 65 | M | 100 | 3 | 24 | 48 | 4 | 68 | 1 | 0 | 0 | 0 | 90 | 70 |
| Mean totals | 54.5 | — | 32 | 2.5 | 24 | 38 | 5 | 29 | 1.9 | 19 | 27 | 4 | 24 | 18 |
| Graft-versus-host disease | | | | | | | | | | | | | | |
| 15 | 29 | M | 62 | 3 | 24 | 100 | 8 | 48 | 1 | 16 | 18 | 2 | 90 | 90 |
| 16 | 22 | F | 26 | 3 | 100 | 400 | 4 | 20 | 2 | 20 | 20 | 1 | 90 | 80 |
| 17 | 33 | M | 20 | 2 | 30 | 40 | 7 | 20 | 2 | 12 | 12 | 2 | 90 | 40 |
| 18 | 45 | F | 45 | 3 | 120 | 213 | 8 | 20 | 1 | 48 | 48 | 1 | 90 | 90 |
| Mean totals | 32 | — | 38 | 2.8 | 69 | 188 | 7 | 27 | 1.5 | 24 | 25 | 1.5 | 90 | 75 |

as a result of the taste complaints. Three patients reported discomfort for a short duration (seconds to minutes), and one of the patients did not continue with applications after 1 month because of the sensitivity and the lack of recognition of benefit.

## DISCUSSION

This clinical trial was an open label nonblinded evaluation of topical cyclosporine in Zilactin for management of refractory oral lichenoid reactions. All patients had failed to respond to topical or topical and systemic steroids. During the period of evaluation the only oral treatment was topical cyclosporine.

Improvement that was seen included decreased oral discomfort in 67% of patients and improvement in mucositis in 65% of patients. The maximum size of the mucosal ulceration was decreased in nine patients, the total area of ulcerated mucosa was reduced in nine patients, and erythema improved in 65% of the subjects studied. The presence of oral mucosal striations was minimally changed with topical cyclosporine. Patients with oral GVHD appeared to improve more than those with refractory lichen planus. The improvement in GVHD supports a previous study.[16] The greater improvement in oral lichenoid GVHD than lichen planus may be related to a reduced saliva volume in GVHD, leading to more effective application, as saliva wetting the mucosa may reduce the duration of adherence Zilactin to the mucosa. This finding may also suggest that the etiologic mechanisms of oral lichenoid GVHD may differ from those in lichen planus.

The patients' assessment of their status appeared to be related more to symptoms than to the appearance of the oral mucosa. The overall clinical impression of oral lichenoid GVHD was improved in all four patients in the trial. We have previously reported that oral cyclosporine suspension was effective in the majority of patients with symptomatic oral GVHD that persisted despite systemic immunosuppressive therapy and topical corticosteroids and that oral disease flared in two of three of the patients with high-grade responses after they stopped the topical use of cyclosporine.[16] In the patients with lichen planus, a response of 50% or more was seen in two patients (14%), less than 50% reduction in 43% of patients, and no improvement in 43% of patients. This is consistent with the conflicting reports of topical cyclosporine in treatment of lichen planus.[3, 7, 8, 12-15, 17, 18] Differences in results of topical cyclosporine may be due to differences in the design of the studies, small sample size in most trials, variable frequency of application, variable concentrations of cyclosporine used, and differences in the carrier used for application.

In our trial, we considered spontaneous remission to be unlikely because all of these patients had refractory oral signs and symptoms despite continuing aggressive topical corticosteroid application, and in four cases topical and systemic prednisone had been prescribed for recalcitrant symptomatic lichen planus.

Prior studies have not identified changes in the systemic levels of cyclosporine with topical use; improvement was felt to be due to direct drug contact with the oral mucosa. This finding supports the hypothesis that cyclosporine applied topically can produce a local effect in oral T-cell–mediated conditions.[1-3, 9-12, 14, 16] Another possible mechanism may be the occlusive or protective effect of the bioadhesive that could prevent continued challenge of the oral mucosa by local agents that may trigger or aggravate the inflammatory reaction.

Initial management of symptomatic oral lichenoid reactions includes removal of stimuli if identified, avoiding local tissue irritants, and application of topical anti-inflammatory agents. The primary modality for management has been that of topical steroids. However, there are cases in which even high potency topical steroids are ineffective in controlling symptoms and mucosal ulceration. In these cases systemic agents are considered, however, even with topical and systemic corticosteroids resistant cases occur. Cyclosporine has been shown to be an effective systemic agent in management of oral GVHD including patients with oral manifestations; it has been identified as a treatment approach for patients with lichenoid oral GVHD with topical application by means of rinsing and holding the oral solution. A means of application to localized sites that persists and maintains the contact of the drug, such as assessed here, may be of advantage. Cyclosporine is an expensive medication, however, use of a low concentration product that results in extended contact time with the area of involvement may provide therapeutic effects.

This open clinical trial is limited by its assessment of few cases and the lack of double-blind design. Clinically and histologically oral GVHD and lichen planus appear similar, however, it is possible that there are differences in the underlying causes of these conditions. The preliminary results of this open label clinical trial suggest that further study is appropriate. In symptomatic cases of lichenoid reactions, symptoms were reduced in 55% of the patients, with a mean decrease of 5/10 on a visual analogue scale. However, when only the patients with lichen planus were considered, the reduction in symptoms was 20%. Lichenoid striations were minimally affected in all patients. In 65% of patients with GVHD, reduction in erythema by approximately by half and reduction in ulceration by half was seen, but limited reduction was seen in these variables in the lichen planus group. As in previous studies there was no indication of side effects from topical application although some patients reported a bad taste and minor sensitivity on initial application. In only one case did the sensitivity with application lead to discontinued topical use by the patient. In cases where taste complaints were present, all patients continued application throughout the duration of the trial. On the basis of these preliminary findings, double-blind clinically controlled trials appear warranted. In addition, an escalating dose trial will be valuable to identify the minimum effective concentration of the cyclosporine.

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CORRECTION

The article "Oral stent as treatment adjunct for oral submucous fibrosis," which appeared in the February 1996 issue (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996;82:148-50), was written by Phuc Vinh Le, DDS, Mervyn Gornitsky, BSc, DDS, FDCD(C), and Gerard Domanowski, MD.