Crushed apremilast for the treatment of oral lichen planus

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Key words: apremilast; Mucosal disease; oral lichen planus; PDE-4 inhibitor.

INTRODUCTION

Oral lichen planus (OLP) is a chronic T-cell–mediated disease involving the stratified squamous epithelium of oral mucosal membranes.[1] Although the precise etiology of lichen planus is unknown, there have been many proposed associations with dental materials, medications, autoimmune diseases, and infectious agents.[1] Prompt treatment is important to prevent malignant transformation to oral squamous cell carcinoma, which can also show similar microscopic lichenoid features as OLP.[1,2] In this article, we report a case of refractory OLP that was successfully treated with crushed oral apremilast, a phosphodiesterase-4 (PDE-4) inhibitor.

Abbreviations used:

IFN-γ:	interferon gamma
IL:	interleukin
OLP:	oral lichen planus
PDE-4:	phosphodiesterase-4
TNF-α:	tumor necrosis factor-alfa

CASE REPORT

A 36-year-old woman was referred to dermatology clinic with a 6-month history of painful oral lesions. She first noticed white lesions on her buccal mucosa with recent involvement of the lower portion of her lip. She had tried triamcinolone dental paste without improvement. Physical examination revealed thin, lacy, eroded plaques on the bilateral buccal mucosa and lower portion of her lip (Fig 1, *A*). Biopsy of the buccal mucosa demonstrated a lichenoid infiltrate with hyperkeratosis and squamous hyperplasia, consistent with a diagnosis of OLP. She was treated with 0.1% triamcinolone dental paste, 0.05% fluocinonide gel, and oral hydroxychloroquine 200 mg daily for 2 months without improvement. A definitive diagnosis of OLP was made after exclusion of other similar entities, including chronic ulcerative stomatitis, given the patient's lack of response to hydroxychloroquine and other lichenoid reactions, such as oral lichenoid drug reaction, lichenoid contact hypersensitivity reaction, and connective tissue diseases because of lack of relevant triggers, associated symptoms, and physical examination findings.[2]

The patient was hesitant to start any additional systemic treatments, and thus, she was prescribed oral tacrolimus "swish and spit" as previously described.[3] Over 3 months, the buccal lesions improved but the lip lesions and oral pain persisted. Treatment with crushed apremilast was initiated as follows: crush and dissolve 60 mg apremilast in 500 mL of water to create a solution that can then be applied to the lips with gauze and used as "swish and spit" twice daily. After 5 months, the patient had complete resolution of her lip lesions and significant improvement in her oral pain without any associated side effects (Fig 1, *B*).

DISCUSSION

Treatment of OLP can be challenging given its refractory nature. Several studies have demonstrated improvement in OLP disease activity and associated pain with oral apremilast.[4,5] Apremilast is a PDE-4 inhibitor that is Food and Drug Administration-

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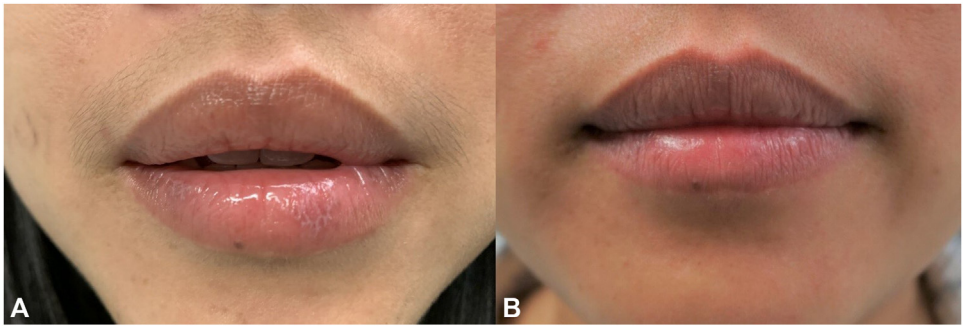

Fig 1. Clinical images before and after treatment with crushed apremilast. **A,** Lacy reticular white plaques on the lips before treatment. **B,** Resolution after 5 months.

approved for plaque psoriasis, psoriatic arthritis, and oral ulcers associated with Behcet disease. As a PDE-4 inhibitor, apremilast increases intracellular cyclic adenosine monophosphate and has a broad effect on many immunomodulatory responses, including decreasing production of tumor necrosis factor-alfa (TNF-α), interferon gamma (IFN-γ), and interleukins (IL-2, IL-8, IL-12, and IL-23).[6-8] In OLP, $CD8^+$ T cells recognize a major histocompatibility complex-I antigen on basal keratinocytes. Subsequently, IFN-γ and IL-2 play a role in activating migrated $CD8^+$ T cells, which then cause basal keratinocyte apoptosis through TNF-α, granzyme B, and Fas-FasL interactions. Furthermore, cytokines, including IFN-γ and TNF-α, can upregulate expression of vascular adhesion molecules, which have been shown to have increased expression in OLP and play a role in T-cell migration to lesional tissue.[1,9] Therefore, a reduction in these cytokines may decrease the cytotoxic T-cell response seen in OLP and thus, lead to disease improvement.[10]

Our patient with refractory OLP expressed a strong desire to avoid systemic agents, and thus, crushed apremilast was started both topically and through the "swish and spit" method. Although crushing of apremilast is not advised per the manufacturer, there have not been reports of negative consequences of utilizing crushed apremilast. In this patient, treatment with crushed apremilast resulted in symptom improvement and was tolerated without side effects. For patients who prefer to avoid systemic treatment for persistent or refractory OLP, crushed apremilast may be an option. Further studies evaluating the efficacy and safety of crushed apremilast in the treatment of OLP are needed.

Conflicts of interest

None disclosed.

REFERENCES

1. Gupta S, Jawanda MK. Oral lichen planus: an update on etiology, pathogenesis, clinical presentation, diagnosis and management. *Indian J. Dermatol*. 2015;60(3):222-229.
2. Cheng YS, Gould A, Kurago Z, Fantasia J, Muller S. Diagnosis of oral lichen planus: a position paper of the American Academy of Oral and Maxillofacial Pathology. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol*. 2016;122(3):332-354.
3. Olivier V, Lacour JP, Mousnier A, Garraffo R, Monteil RA, Ortonne JP. Treatment of chronic erosive oral lichen planus with low concentrations of topical tacrolimus: an open prospective study. *Arch. Dermatol*. 2002;138(10):1335-1338.
4. AbuHilal M, Walsh S, Shear N. Treatment of recalcitrant erosive oral lichen planus and desquamative gingivitis with oral apremilast. *J. Dermatol. Case Rep*. 2016;10(3):56-57.
5. Bettencourt M. Oral lichen planus treated with apremilast. *J Drugs Dermatol*. 2016;15(8):1026-1028.
6. Schafer PH, Parton A, Gandhi AK, et al. Apremilast, a cAMP phosphodiesterase-4 inhibitor, demonstrates anti-inflammatory activity in vitro and in a model of psoriasis. *Br. J. Pharmacol*. 2010;159(4):842-855.
7. Nassim D, Alajmi A, Jfri A, Pehr K. Apremilast in dermatology: a review of literature. *Dermatol. Ther*. 2020;33(6):e14261.
8. Houslay MD, Adams DR. PDE4 cAMP phosphodiesterases: modular enzymes that orchestrate signalling cross-talk, desensitization and compartmentalization. *Biochem. J*. 2003;370(Pt 1):1-18.
9. Regezi JA, Dekker NP, MacPhail LA, Lozada-Nur F, McCalmont TH. Vascular adhesion molecules in oral lichen planus. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1996;81(6):682-690.
10. Sugerman PB, Savage NW, Walsh LJ, et al. The pathogenesis of oral lichen planus. *Crit Rev Oral Biol Med*. 2002;13(4):350-365.