CASE REPORT

Apremilast for treatment of recalcitrant aphthous stomatitis

Fabian Schibler, MD, Kristine Heidemeyer, MD, Hans-Willhelm Klötgen, MD, Keshavamurthy Vinay, MD, and Nikhil Yawalkar, MD
Bern, Switzerland

Key words: apremilast; phosphodiesterase-4 inhibitor; recurrent aphthous stomatitis.

OBSERVATION

Recurrent aphthous stomatitis (RAS) is a common cause of recurrent oral ulcers, which often leads to significant impairment of a patient’s quality of life. The underlying pathogenic mechanism remains unclear, and no treatment modality is uniformly effective. In this report, we describe the use of apremilast, an oral phosphodiesterase-4 inhibitor in treatment of recalcitrant RAS.

REPORT OF A CASE

A gentleman in his 60s, presented to the outpatient clinic for evaluation of recurrent painful oral ulcers present for the last 3 years. On examination, multiple, variable sized, round-to-oval circumscribed ulcers with an erythematous halo and a yellowish floor were seen to involve the hard and soft palate (Fig 1, A). There was no history suggestive of Behçet disease. Histologic examination found a superficial ulceration with a mixed inflammatory infiltrate. No significant immune deposits were seen on direct immunofluorescence. Oral swabs/cultures were negative for Candida albicans and human herpes simplex virus 1 and 2. Based on clinical, histologic and immunologic features, a diagnosis of major RAS was made.

After not responding to topical and systemic corticosteroids (20 mg/d of prednisolone for 2 weeks), antibiotics (2 g/d of amoxicillin/clavulanic acid for 2 weeks), and colchicine (1 mg/d for 6 months), apremilast monotherapy was initiated at a dose of 10 mg once daily. The dose was gradually titrated to a maintenance dose of 30 mg twice daily. There was complete clearance of all lesions within 6 weeks (Fig 1, B). The patient has been on treatment with apremilast, 30 mg twice daily for 12 months, and no relapse has been observed so far. Apremilast was well tolerated except for minor gastrointestinal symptoms.

CONCLUSION

Apremilast is an orally administered small molecule that specifically inhibits phosphodiesterase-4 and modulates the immune system by increasing the levels of intracellular cyclic adenosine monophosphate and inhibiting interleukin (IL)-2, interferon-γ, IL-8, and tumor necrosis factor production. It is US Food and Drug Administration approved for treatment of psoriasis and psoriatic arthritis but has been used off label in treating various inflammatory diseases including atopic dermatitis, chronic cutaneous sarcoidosis, lichen planus, and Behçet disease. In a recent multicenter, placebo-controlled phase II study, apremilast was found to be effective in treating oral and genital ulcers of Behçet disease, with 71% of patients achieving complete clearance by week 12. Pentoxifylline, an oral phosphodiesterase inhibitor, has been reported previously to be marginally effective in treating RAS as a second-line therapy.

Abbreviations used:
IL: interleukin
RAS: recurrent aphthous stomatitis

From the Department of Dermatology, Inselspital, Bern University Hospital, University of Bern.
Funding sources: None.
Conflicts of interest: Nikhil Yawalkar has served as a consultant for Celgene and does not hold any shares or other financial interest in this company. The rest of the authors have not conflicts to declare.
Correspondence to: Fabian Schibler, MD, Department of Dermatology, Inselspital, Bern University Hospital and University of Bern, Bern 3010, Switzerland. E-mail: fabian.schibler@insel.ch.
JAAD Case Reports 2017;3:410-1.
2352-5126 © 2017 by the American Academy of Dermatology, Inc. Published by Elsevier, Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
http://dx.doi.org/10.1016/j.jdcr.2017.06.017
However, to the best of our knowledge, treatment of RAS with apremilast has not been reported thus far. It appears to be an effective agent through reducing proinflammatory cytokines tumor necrosis factor-α, IL-23, and interferon-γ and increasing anti-inflammatory cytokines like IL-10. Apremilast has shown a good safety profile with most frequent side effects being nausea, vomiting, diarrhea, upper respiratory tract infection, nasopharyngitis, and headache. Cases of diarrhea and nausea occur in approximately 17% of patients and are generally mild to moderate in severity. The side effects usually begin during the first 2 weeks of apremilast treatment and resolve within 4 weeks. Treatment strategies include adequate hydration, taking medication with small and more frequent meals, and avoiding caffeine, dairy, and artificial sweeteners. Further options include bulk-forming agents, bismuth subsalicylate, and loperamide.

Our case shows a rapid and substantial response of recalcitrant aphthous lesions to apremilast. However, further studies are needed to prove its efficacy and safety.

REFERENCES
1. 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.
2. Samrao A, Berry TM, Goreshi R, Simpson EL. A pilot study of an oral phosphodiesterase inhibitor (apremilast) for atopic dermatitis in adults. Arch Dermatol. 2012;148(8):890-897.
3. Baughman RP, Judson MA, Ingledue R, Craft NL, Lower EE. Efficacy and safety of apremilast in chronic cutaneous sarcoidosis. Arch Dermatol. 2012;148(2):262-264.
4. Paul J, Foss CE, Hirano SA, Cunningham TD, Pariser DM. An open-label pilot study of apremilast for the treatment of moderate to severe lichen planus: a case series. J Am Acad Dermatol. 2013;68(2):255-261.
5. Hatemi G, Melikoglu M, Tunc R, et al. Apremilast for Behçet’s syndrome—a phase 2, placebo-controlled study. N Engl J Med. 2015;372(16):1510-1518.
6. Thornhill MH, Baccaglini L, Theaker E, Pemberton MN. A randomized, double-blind, placebo-controlled trial of pentoxifylline for the treatment of recurrent aphthous stomatitis. Arch Dermatol. 2007;143(4):463-470.
7. Crowley J, Thaci D, Joly P, et al. Long-term safety and tolerability of apremilast in patients with psoriasis: Pooled safety analysis for ≥ 156 weeks from 2 phase 3, randomized, controlled trials (ESTEEM 1 and 2). J Am Acad Dermatol. 2017;77(2):310-317.e1.