

Use of Apremilast for Aphthous Ulcers in a Patient With Behçet's Syndrome

Arjun Saini MS, Cynthia Ferguson PA, Kimberly Salkey MD
Eastern Virginia Medical School, Norfolk, VA

INTRODUCTION

Behçet's syndrome is an inflammatory disease characterized by aphthous oral ulcers and several systemic manifestations, which include genital ulcers, ocular disease, skin lesions, arthritis, and vascular disease. Recurrent oral ulcers can be disabling and have a considerable impact on quality of life.[1] There is no laboratory diagnostic test for Behçet's syndrome so the diagnosis is usually made based on clinical criteria, which includes recurrent oral ulcers and at least two of the following clinical features: reccurent genital apthae; uveitis or retinal vasculitis; skin lesions that are classified as erythema nodosum (EN)-like lesions, acneiform lesions, pustulosis, or pseudofolliculitis; and a positive pathergy test.[2] The pathogenesis of the oral ulceration in Behçet's syndrome is poorly understood, but the most widely held hypothesis of disease pathogenesis is that of a profound inflammatory response triggered by an infectious agent in a genetically susceptible host. Supporting this is the consistent association of disease susceptibility with polymorphisms in the human leukocyte antigen complex, particularly HLA-B*51.[3]

Treatment guidelines are based around trying to control the frequency with which oral apthae develop.[4] Anecdotal treatment for Behçet's syndrome exists, which includes oral colchicine, azathioprine, prednisone, and cyclosporine, however, the efficacy of these drugs is not well validated.[2,5–7] Apremilast is an orally effective small molecule that inhibits phosphodiesterase 4, thereby lowering intracellular cyclic AMP, particularly in immune cells.[1] With apremilast treatment, levels of proinflammatory cytokines, such as TNF-α, interleukin-23, and interferon-γ are decreased, and levels of anti-inflammatory cytokines, such as interleukin-10, are increased. This suggests that apremilast may be a promising agent for the treatment of chronic inflammatory conditions.[8] Apremilast has been shown to have clinically significant results in the management of psoriasis and psoriatic arthritis.[9] A phase 2 clinical trial has shown some promise using apremilast in the management of oral ulcers in Behçet's syndrome.[1] We demonstrate a patient who has had complete elimination of oral ulcers and has successful remission of oral ulcers after using apremilast.

CASE OVERVIEW

A 49-year-old woman presented with a 23-year history of polyarticular joint pain and recurrent oral ulcers. Over the 23 years, the joint pain has included her hips, hands, upper and lower back, shoulders, wrists, and elbows. Her oral ulcers had been controllable with only one or two outbreaks per year; however, in the last few years, the sores have been almost constant, affecting her ability to eat and resulting in a 23 pound weight loss. A biopsy of one of the ulcers was performed, which demonstrated changes consistent with the diagnosis of Behçet's syndrome. Triamcinolone paste and viscous lidocaine were prescribed as numbing agents to help control the pain of the ulcers so she could eat. She began noticing headaches in the occipital area, and she began having pain in her cervical spine. She has also reported having a few episodes of a red facial rash with occasional outbreaks on her legs; however, she has no history of any genital lesions.

Over the years she has tried many treatment strategies, which did not fully resolve her oral ulcers. Initially, oral colchicine 0.6 mg taken twice daily was used. The patient reported having less frequent episodes of oral ulcers on colchicine but never completely resolved them. She has been on several courses of oral corticosteroids (prednisone) with doses ranging from 20 mg per day to 60 mg per day. The prednisone helped control the oral ulcers but also never completely resolved them. The prednisone was stopped, and she was started on azathioprine and titrated up 175 mg per day, which also did not completely resolve the oral ulcers and she started to notice more pain in her PIP and DIP joints.

After review of a phase two clinical trial using apremilast to treat Behçet's syndrome showing some success in treating oral ulcers,[1] treatment was initiated with apremilast, which was titrated up to 30 mg per day. Once it was determined that apremilast was well tolerated, apremilast was titrated up to 60 mg per day and the azathioprine was decreased to 125 mg per day. After one month of apremilast, the patient had no oral ulcers and has not had a new episode of oral ulcers since two weeks after starting the apremilast.

DISCUSSION

The pathophysiology of Behçet's syndrome is not completely understood and the efficacy of many of the first line treatment options is still under debate.[5] Apremilast is a phosphodiesterase 4 inhibitor that has been shown to decrease the levels of pro-inflammatory cytokines such as TNF-α, interleukin-23, and interferon-γ and increase the levels of anti-inflammatory cytokines such as interlukin 10.[8] These alterations in cytokine levels

suggest that apremilast could be useful for managing chronic inflammatory diseases. The complete elimination of oral ulcers in our patient demonstrates the ability of apremilast to be useful in helping to manage refractory cases of recurrent oral ulcers in Behçet's syndrome. As with any agents that are immunomodulatory, the possible adverse effects of apremilast should be closely monitored and further studies would be needed to evaluate the long-term effects of continuous use of apremilast for Behçet's syndrome. The successful treatment of refractory oral ulcers with apremilast may also help to shed some light on the pathogenesis of Behçet's syndrome with further study.

DISCLOSURE

There are no potential financial conflicts of interest from any of the above authors relevant to the submitted manuscript.

REFERENCES

1. 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. doi:10.1056/NEJMoa1408684
2. Taylor J, Glenny A-M, Walsh T, et al. Interventions for the management of oral ulcers in Behçet's disease. *Cochrane Database Syst Rev.* 2014;(9):CD011018. doi:10.1002/14651858.CD011018.pub2
3. Marshall SE. Behçet's disease. *Best Pract Res Clin Rheumatol.* 2004;18(3):291-311. doi:10.1016/j.berh.2004.02.008
4. Hatemi G, Silman A, Bang D, et al. EULAR recommendations for the management of Behçet disease. *Ann Rheum Dis.* 2008;67(12):1656-1662. doi:10.1136/ard.2007.080432
5. Saenz A, Ausejo M, Shea B, Wells GA, Welch V, Tugwell P. Pharmacotherapy for Behçet's syndrome. In: *Cochrane Database of Systematic Reviews.* John Wiley & Sons, Ltd; 1998. doi:10.1002/14651858.CD001084
6. Davatchi F, Abdollahi BS, Banihashemi AT, et al. Colchicine versus placebo in Behçet's disease: randomized, double-blind, controlled crossover trial. *Mod Rheumatol.* 2009;19(5):542-549. doi:10.3109/s10165-009-0200-2
7. Hatemi G, Silman A, Bang D, et al. Management of Behçet disease: a systematic literature review for the European League Against Rheumatism evidence-based recommendations for the management of Behçet disease. *Ann Rheum Dis.* 2009;68(10):1528-1534. doi:10.1136/ard.2008.087957
8. Wittmann M, Helliwell PS. Phosphodiesterase 4 inhibition in the treatment of psoriasis, psoriatic arthritis and other chronic inflammatory diseases. *Dermatol Ther.* 2013;3(1):1-15. doi:10.1007/s13555-013-0023-0
9. Papp K a., Kaufmann R, Thaçi D, Hu C, Sutherland D, Rohane P. Efficacy and safety of apremilast in subjects with moderate to severe plaque psoriasis: results from a phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison study. *J Eur Acad Dermatol Venereol.* 2013;27(3):e376-e383. doi:10.1111/j.1468-3083.2012.04716.x

AUTHOR CORRESPONDENCE

Arjun Saini MS

E-mail:..... sainiad@evms.edu