CORRESPONDENCE

# Apremilast in Treatment-Refractory Recurrent Aphthous Stomatitis

**TO THE EDITOR:** Recurrent aphthous stomatitis is a chronic, painful ulcerative disease of the oral mucosa that may be resistant to treatment. Its clinical heterogeneity has complicated classification of the disorder, but variants in cytokine genes, including tumor necrosis factor $\alpha$ (TNF-$\alpha$), have been reported and suggest a role for cytokines in the pathogenesis of the disorder.[1] Depending on disease severity, treatment may include topical and systemic glucocorticoids, colchicine, dapsone, and TNF-$\alpha$ inhibitors, and there have been case reports of responses to apremilast.[2-4] Apremilast is an oral phosphodiesterase-4 inhibitor that inhibits production of proinflammatory cytokines, including TNF-$\alpha$, and is approved for the treatment of psoriasis and psoriatic arthritis. A phase 2 trial[5] and a phase 3 trial by Hatemi et al. (the results of which are reported in this issue of the *Journal*) have shown efficacy of apremilast in treating the oral ulcers in patients with Behçet's disease.

We report a retrospective series of five patients with recurrent aphthous stomatitis who were treated with apremilast (standard induction over a period of 5 days, followed by a dose of 30 mg twice daily) for 2 to 24 months (mean, 11.4 months) (Table 1). Details regarding treatment administration are provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org. The lesions in these patients had been refractory to conventional treatment with topical glucocorticoids and colchicine. Alternative diagnoses, including Behçet's disease, inflammatory bowel disease, and infection, were evaluated and were ruled out on the basis of history, bacterial and viral swabs, colonoscopy with biopsies, the absence of HLA-B51 in three patients, and negative pathergy testing in two patients. Biopsies of active lesions revealed ulceration with neutrophil-rich infiltration in four patients. Written informed consent was provided by all the patients for off-label treatment with apremilast, and the study was approved by the regional ethics review board. All the authors vouch for the accuracy of the data and for the reporting of adverse events that occurred in the patients who were treated with apremilast.

Patients were evaluated by means of the Physician Global Assessment (PGA) at baseline and follow-up; the assessment uses a five-point scale, with scores ranging from 0 (clear) to 1 (almost clear), 2 (mild), 3 (moderate), and 4 (severe). Follow-up visits for safety and efficacy evaluations occurred within 2 to 6 weeks after the start of therapy and at various times thereafter.

Over a period of 2 to 6 weeks of apremilast therapy at a dose of 30 mg twice daily, a complete response (PGA score of 0) was observed in four of the five patients, and the fifth patient had a PGA score of 1 (almost clear) (Table 1 and Fig. S1 in the Supplementary Appendix). After 1 year of treatment, Patient 4 could reduce the apremilast dose to 30 mg once daily with persistent control, whereas the other three patients had control maintained with the use of 30 mg of apremilast twice daily. At 24 months of continued treatment, a PGA score of 1 was maintained in four of five patients. Treatment was associated


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**Table 1. Selected Demographic and Treatment-Related Characteristics of Five Patients with Recurrent Aphthous Stomatitis.***

| Patient No., Sex, and Age | Disease Onset and Form | Coexisting Conditions | Concomitant Medication | Previous Therapies | Duration of Previous Systemic Treatment | PGA Score | | Time to Clearance | Duration of Apremilast Therapy | PGA Score at Last Follow-up† |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Before Apremilast | At Clearance | | | |
| | | | | | *mo* | | | *wk* | *mo* | |
| 1, Female, 41 yr | Childhood; minor | Arterial hypertension, cardiomyopathy, endometriosis, depression | Bisoprolol, venlafaxine | Topical glucocorticoids, topical chlorhexidine, colchicine | 6 | 4 | 1 | 2 | 7 | 1 |
| 2, Female, 51 yr | 2014; minor | Arterial hypertension, bronchial hyperreactivity, soft-tissue rheumatism | Atenolol, chlorthalidone, dexlansoprazole, gum karaya, vitamin $D_3$ | Topical glucocorticoids, topical chlorhexidine, colchicine | 3 | 3 | 0 | 4 | 4 | 1 |
| 3, Female, 66 yr | 2003; minor | Polyarthralgia, osteopenia, adrenal adenoma | Acetaminophen | Topical glucocorticoids, colchicine, dapsone, prednisone, adalimumab, azathioprine, acitretin, cyclophosphamide, cyclosporine | 28 | 3 | 0 | 4 | 2 | NA |
| 4, Male, 65 yr | 2014; major | None | None | Topical glucocorticoids, prednisone, antibiotics, thalidomide, colchicine | 8.5 | 4 | 0 | 6 | 24 | 1 |
| 5, Male, 37 yr | 2008; major | Contact dermatitis reaction to rubber gloves | None | Topical glucocorticoids, prednisone, topical lidocaine, doxycycline, colchicine | 5 | 4 | 0 | 4 | 20 | 1 |

* The Physician Global Assessment (PGA) uses a five-point scale, with scores ranging from 0 (clear) to 1 (almost clear), 2 (mild), 3 (moderate), and 4 (severe). Clearance was defined as a score of 0 or 1 and was observed in all five patients at some point in weeks 2 through 6. NA denotes not applicable (because the patient discontinued treatment at 2 months).
† The last follow-up visit occurred during months 2 to 24 and corresponds to the duration of apremilast therapy.

with intermittent gastrointestinal side effects in all patients (Table S1 in the Supplementary Appendix). Persistent headache and weight loss, which led to treatment discontinuation, developed in one patient.

In conclusion, in an uncontrolled series involving five patients at one institution, apremilast therapy reduced disease activity in treatment-refractory recurrent aphthous stomatitis. The small number of patients and retrospective nature of our study limit its generalizability. Trials of apremilast for treatment-resistant recurrent aphthous stomatitis may be appropriate.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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# Selinexor for Refractory Multiple Myeloma

**TO THE EDITOR:** In the article by Chari et al. (Aug. 22 issue)[1] on oral selinexor for multiple myeloma, we noticed that one of the most common grade 3 or 4 adverse events was hyponatremia (serum sodium level, <130 mmol per liter) (in 22% of the patients). This appears to be a class effect of selinexor, because other studies of this agent had similar incidences of hyponatremia, ranging from 7 to 26%.[2-5] The incidence of hyponatremia was higher in studies involving patients with multiple myeloma than in studies involving patients with solid tumors. No workup was performed or no cause was found in many of the studies. In patients with multiple myeloma, hyponatremia is not a common clinical finding. A direct effect on water transport through nuclear-export modulation by selinexor cannot be ruled out.

Involvement of nephrology consultation in ongoing trials might be useful to investigate the mechanism of this adverse event. Measurement of serum and urine osmolality along with urine electrolyte levels would help in assessment of the cause and pathophysiology of the hyponatremia. This will then allow for preventive strategies in further trials and clinical practice.

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Dr. Jhaveri reports serving as a consultant for Astex Pharmaceuticals. No other potential conflict of interest relevant to this letter was reported.

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