ORIGINAL ARTICLE

Apremilast for Behçet's Syndrome — A Phase 2, Placebo-Controlled Study

Gulen Hatemi, M.D., Melike Melikoglu, M.D., Recep Tunc, M.D., Cengiz Korkmaz, M.D., Banu Turgut Ozturk, M.D., Cem Mat, M.D., Peter A. Merkel, M.D., Kenneth T. Calamia, M.D., Ziqi Liu, Ph.D., Lilia Pineda, M.D., Randall M. Stevens, M.D., Hasan Yazici, M.D., and Yusuf Yazici, M.D.

ABSTRACT

BACKGROUND

Oral ulcers, the hallmark of Behçet's syndrome, can be resistant to conventional treatment; therefore, alternative agents are needed. Apremilast is an oral phosphodiesterase-4 inhibitor that modulates several inflammatory pathways.

METHODS

We conducted a phase 2, multicenter, placebo-controlled study in which 111 patients with Behçet's syndrome who had two or more oral ulcers were randomly assigned to receive 30 mg of apremilast twice daily or placebo for 12 weeks. This regimen was followed by a 12-week extension phase in which the placebo group was switched to apremilast and a 28-day post-treatment observational follow-up phase. The patients and clinicians were unaware of the study assignments throughout the trial. The primary end point was the number of oral ulcers at week 12. Secondary outcomes included pain from these ulcers (measured on a 100-mm visual-analogue scale, with higher scores indicating worse pain), the number of genital ulcers, overall disease activity, and quality of life.

RESULTS

The mean (±SD) number of oral ulcers per patient at week 12 was significantly lower in the apremilast group than in the placebo group (0.5±1.0 vs. 2.1±2.6) ($P<0.001$). The mean decline in pain from oral ulcers from baseline to week 12 was greater with apremilast than with placebo (–44.7±24.3 mm vs. –16.0±32.5 mm) ($P<0.001$). Nausea, vomiting, and diarrhea were more common in the apremilast group (with 22, 9, and 12 incidents, respectively, among 55 patients) than in the placebo group (with 10, 1, and 2 incidents, respectively, among 56 patients), findings that were similar to those in previous studies of apremilast. There were two serious adverse events in patients receiving apremilast.

CONCLUSIONS

Apremilast was effective in treating oral ulcers, which are the cardinal manifestation of Behçet's syndrome. This preliminary study was neither large enough nor long enough to assess long-term efficacy, the effect on other manifestations of Behçet's syndrome, or the risk of uncommon serious adverse events. (Funded by Celgene; ClinicalTrials.gov number, NCT00866359.)

From the Istanbul University Cerrahpasa Medical School, Istanbul (G.H., M.M., C.M., H.Y.), Selçuk University, Konya (R.T., B.T.O.), and Eskişehir Osmangazi University, Eskişehir (C.K.) — all in Turkey; the University of Pennsylvania, Philadelphia (P.A.M.); the Mayo Clinic College of Medicine, Jacksonville, FL (K.T.C.); Celgene, Warren, NJ (Z.L., L.P., R.M.S.); and the New York University Hospital for Joint Diseases, New York (Y.Y.). Address reprint requests to Dr. Yazici at the NYU School of Medicine, NYU Hospital for Joint Diseases, 333 E. 38 St., New York, NY 10016, or at yusuf.yazici@nyumc.org.

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The mucocutaneous lesions of Behçet's syndrome include oral ulcers, genital ulcers, and papulopustular and nodular lesions. Recurrent oral ulcers can be disabling and have a substantial effect on quality of life.

The current first-line therapy for the mucocutaneous lesions of Behçet's syndrome includes colchicine and topical agents (e.g., glucocorticoids).[1] The efficacy of colchicine has been debated.[2-4] For lesions that are resistant to these treatments, azathioprine, interferon-α, thalidomide, and tumor necrosis factor α (TNF-α) antagonists are prescribed. There remains a need for a safe and effective treatment, and any new drug that is effective against oral ulcers (the hallmark lesion of Behçet's syndrome) may be a candidate for the treatment of other aspects of the disease.

Apremilast is an orally effective small molecule that specifically inhibits phosphodiesterase-4 and thereby increases levels of intracellular cyclic AMP, particularly in immune cells, with consequent effects on several inflammatory pathways.[5] With apremilast treatment, levels of proinflammatory cytokines, such as TNF-α, interleukin-23, and interferon-γ, are decreased, and levels of antiinflammatory cytokines, such as interleukin-10, are increased. These observations suggest that apremilast may be a promising agent for the treatment of chronic inflammatory conditions.[6] Statistically significant and clinically meaningful results have been obtained in patients with psoriasis and psoriatic arthritis.[7-9]

The goal of this study was to evaluate the efficacy and safety of apremilast in the treatment of oral ulcers in patients with Behçet's syndrome by assessing the change in the number of ulcers and the pain from the ulcers. Effects on the number of genital ulcers and overall disease activity were also assessed.

Methods

Study Design and Oversight

In this phase 2, double-blind, placebo-controlled, parallel-group study, each patient had to undergo screening no more than 90 days before the start of the study medication. Patients were then randomly assigned in a 1:1 ratio to receive 30 mg of apremilast twice daily or placebo twice daily for 12 weeks. At the end of the 12-week, placebo-controlled phase, all participants received apremilast in a 12-week active-treatment phase (during which they remained unaware of their original group assignment). All participants, regardless of whether they had completed the study, were observed during a 4-week follow-up phase. We enrolled patients from October 2009 through October 2011.

Six university hospitals — three in Turkey and three in the United States — participated in the study. The protocol and the amendments to the protocol were reviewed and approved by the institutional review board or local ethics committee at each study site, the central ethics committee of the Ministry of Health in Turkey, and the Food and Drug Administration. The study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines; all patients provided written informed consent before undergoing any study-related procedures.

The study was designed by the last two authors and the study sponsor, Celgene, which funded the study and was involved in data processing, management, statistical analysis, and data interpretation together with the investigators. The first draft of the manuscript was written by the first author and underwent a critical revision by the last two authors without any professional writing assistance. All the other study authors also contributed to the revision. All the authors vouch for the completeness and accuracy of the data and analyses and the fidelity of the study to the protocol, which is available with the full text of this article at NEJM.org.

Patients

Patients were eligible for the study if they met the criteria of the International Study Group for Behçet's Disease,[10] were at least 18 years of age, had had at least one oral or genital ulcer within 28 days before screening, and had at least two oral ulcers at the time of randomization. (The original protocol called for eligible patients to have at least two ulcers during the 28-day prescreening period; the protocol change to allow screening of patients with at least one ulcer during the 28-day prescreening period was instituted to broaden the inclusion criteria; details are available in the Supplementary Appendix, available at NEJM.org).

Patients with active involvement of a major organ during the 12 months preceding study entry or who were pregnant or breast-feeding, had active infections, had a history of recurrent or chronic infections, or had indications of latent

tuberculosis were excluded (see the protocol for details).

RANDOMIZATION AND INTERVENTIONS

Randomization was stratified according to sex, because the disease course of Behçet's syndrome differs between men and women, with women generally having less severe disease; the response to drug treatment also differs according to sex.[3,11,12] Randomization was performed in blocks of 4.

To reduce the possibility of gastrointestinal adverse events, the dose of apremilast and of placebo was increased gradually during the first week (10 mg twice daily for 2 days, 20 mg twice daily for 3 days, and 30 mg twice daily from day 6 until the end of week 24). Once the full 30-mg dose was reached, a single dose reduction was allowed (to 20 mg of apremilast twice daily in the apremilast group and 20 mg of placebo twice daily in the placebo group) to ameliorate side effects thought to be due to the study drug. Patients were not allowed to receive concomitant medications directly related to Behçet's syndrome during the study; these restrictions did not apply during the post-treatment, observational follow-up period.

OUTCOMES

The primary efficacy end point was the number of oral ulcers at week 12. Secondary efficacy end points for the placebo-controlled phase included the change in pain from oral and genital ulcers from baseline to week 12, as measured on a 100-mm visual-analogue scale (with 0 representing no pain and 100 the worst pain ever experienced), and the change in disease activity from baseline to week 12. Disease activity was evaluated with the use of the Behçet's Disease Current Activity Form (on which scores range from 0 to 12, with higher scores indicating more active disease)[13] and the Behçet's Syndrome Activity Score (a scale on which scores range from 0 to 100, with higher scores indicating more active disease).[14] Quality of life was evaluated at baseline, week 12, and week 24 with the use of the Behçet's Disease Quality of Life scale (on which scores range from 0 to 30, with higher scores indicating greater impairment of quality of life)[15] and version 2 of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36, on which scores range from 0 to 100 for each component, with lower scores indicating greater impairment of quality of life).[16] (See the Supplementary Appendix for a description of each scale and their ranges.)

Secondary end points for the placebo-controlled phase also included the number of genital ulcers at week 12, the proportion of patients with a complete response with respect to oral ulcers (defined as the proportion of patients who had no oral ulcers at week 12), and the proportion of patients with a partial response (defined as the proportion of patients who had a reduction of 50% or more in the number of oral ulcers at week 12). Additional secondary end points included the area under the curve (AUC, expressed as the number of ulcers multiplied by the number of days) for oral ulcers, genital ulcers, and both during the 12-week, placebo-controlled phase (see the Supplementary Appendix).

Secondary efficacy end points for the active-treatment phase were the number of oral ulcers, pain from oral ulcers (as assessed on a 100-mm visual-analogue scale), the number of genital ulcers, pain from genital ulcers, and disease activity at week 24. Safety end points included the type, frequency, and severity of adverse events, the relationship of such events to apremilast, the number of patients who prematurely discontinued the study medication or whose dose was reduced owing to any adverse event, and the frequency of clinically significant changes in electrocardiographic findings, laboratory findings, or both.

STATISTICAL ANALYSIS

We calculated that with a sample size of 156 patients (78 in each group), the study would have 90% power to detect a difference of 0.65 in the mean number of oral ulcers per patient between the placebo group and the apremilast group at week 12, with a common standard deviation of 1.1, at a significance level of 0.05, and assuming a 20% dropout rate.[17] Owing to slow patient accrual, enrollment was stopped before this sample size was reached. The final sample of 111 patients was sufficient to provide 80% power to detect a between-group difference of 0.65 in the number of oral ulcers. All participants remained unaware of group assignments once the decision was made to stop enrollment (see the Supplementary Appendix for details).

Demographic and baseline characteristics were summarized with the use of descriptive statistics (numbers and means with standard deviations) to check for similarity at baseline. Efficacy analyses

were performed in the intention-to-treat population, which included all patients who underwent randomization and had at least one evaluation of an oral ulcer. A last-observation-carried-forward approach was used for patients who discontinued the study early. To confirm the robustness of the primary efficacy end point, we also performed a sensitivity analysis in which data from patients who did not undergo prespecified study assessments were imputed as indicating a lack of response. The number of oral ulcers and the extent of oral ulcer pain (as measured on the visual-analogue scale) at week 12 (or at early termination) were compared by means of an analysis-of-covariance model, in which treatment and sex were factors and the baseline value was the covariable, to extract the difference between the placebo group and the apremilast group. In addition, different modeling methods (e.g., a model with imputation of missing data as indicating no response and an SAS PROC mixed model) were used to perform sensitivity analyses to assess the consistency and robustness of the analysis results.

Table 1. Demographic and Baseline Characteristics.*

	Placebo (N=56)	Apremilast (N=55)
Age — yr		
Mean	34.7	34.3
Median	34.0	34.0
Sex — no. (%)		
Male	18 (32)	16 (29)
Female	38 (68)	39 (71)
Race — no. (%)†		
White	55 (98)	53 (96)
Black	0	2 (4)
Other	1 (2)	0
Region — no. (%)		
Turkey	53 (95)	50 (91)
United States	3 (5)	5 (9)
Duration of Behçet's disease — yr		
Mean	5.72	4.92
Median	2.97	4.44
Oral ulcers — no./patient	3.1±1.3	3.2±2.0
Pain of oral ulcers on 100-mm visual-analogue scale	51.7±22.6	54.3±26.2

* Plus–minus values are means SD. Apremilast was administered in a 30-mg dose twice daily. There were no significant between-group differences in baseline characteristics.
† Race was self-reported.

RESULTS

PATIENTS

A total of 111 patients underwent randomization: 55 received apremilast and 56 received placebo (Fig. S1 in the Supplementary Appendix). The demographic features and baseline characteristics of the participants in the two groups were balanced (Table 1). A total of 50 patients in the apremilast group (91%) and 45 in the placebo group (80%) completed the initial placebo-controlled phase of the study.

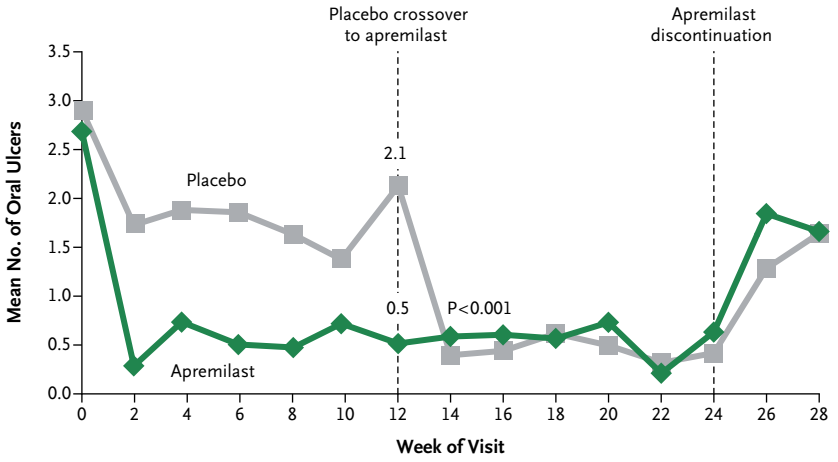
EFFICACY

Oral Ulcers

The mean (±SD) number of oral ulcers per patient at baseline was 3.1±1.3 in the apremilast group and 3.2±2.1 in the placebo group. The mean number of oral ulcers at week 12 was significantly lower in the apremilast group than in the placebo group (0.5±1.0 vs. 2.1±2.6, P<0.001). The median number of oral ulcers at week 12 was 0 (range, 0 to 6) in the apremilast group and 2 (range, 0 to 13) in the placebo group. The decrease in the number of oral ulcers was evident by week 2 in the apremilast group (Fig. 1) and was sustained throughout the full 24-week treatment phase. A good response was also observed after patients who had been receiving placebo were switched to apremilast at week 12 (Fig. 1). During the 4-week post-treatment observation phase that followed week 24, the mean number of oral ulcers started to increase within 2 weeks. The mean number of oral ulcers at week 12 in the per-protocol population was similar to that in the intention-to-treat population and was significantly lower in the apremilast group than in the placebo group (0.4±0.7 vs. 2.2±2.7, P<0.001). Consistent results were obtained when repeated-measures analyses were used.

The mean AUC for oral ulcers during the placebo-controlled phase was significantly lower in the apremilast group than in the placebo group (59.9±93.5 days vs. 155.5±96.1 days, P<0.001), indicating that the time-weighted average of the number of oral ulcers was lower in the apremilast group.

At baseline, the mean score for pain from oral ulcers, as measured on a 100-mm visual-analogue scale, was 54.3±26.2 in the apremilast group and 51.7±22.6 in the placebo group. The mean change from baseline to week 12 in pain from oral ulcers



No. at Risk															
Placebo	56	56	53	51	44	42	45	45	36	45	36	34	45	38	54
Apremilast, 30 mg	55	55	50	53	48	47	50	49	41	49	38	37	47	40	54
Mean No. of Oral Ulcers															
Placebo	2.9	1.7	1.9	1.9	1.6	1.4	2.1	0.4	0.4	0.6	0.5	0.3	0.4	1.3	1.6
Apremilast, 30 mg	2.7	0.3	0.7	0.5	0.5	0.7	0.5	0.6	0.6	0.6	0.7	0.2	0.6	1.9	1.7

Figure 1. Mean Number of Oral Ulcers Per Patient, According to Study Group.

The mean number of oral ulcers per patient was significantly lower in the apremilast group than in the placebo group during the placebo-controlled phase (baseline to week 12). At week 12, patients in the placebo group were switched to apremilast therapy, after which the mean number of oral ulcers in those patients decreased. After apremilast was discontinued at week 24, the mean number of oral ulcers started to increase within 2 weeks. A repeated-measures analysis performed with data from baseline to week 12 showed consistent results.

(with negative values indicating improvement) was significantly greater in the apremilast group than in the placebo group (−44.7±24.3 mm vs. −16.0±32.5 mm, P<0.001). Consistent results were obtained when repeated-measures analyses were used. The decrease in pain from oral ulcers over time paralleled the decrease in the number of oral ulcers starting at week 2, with the decrease in pain maintained throughout the treatment phase; the pain increased after apremilast was discontinued (Fig. 2). At week 24 (in a last-observation-carried-forward analysis), the mean change from baseline in pain from oral ulcers according to the visual-analogue scale was −42.2±32.2 mm in the group that was switched from placebo to apremilast and −44.8±29.8 mm in the group that received apremilast throughout the study. The mean score at week 24 on the visual-analogue scale for pain from oral ulcers was 9.6±21.1 mm among patients initially assigned to the placebo group and 9.7±20.3 mm among those initially assigned to the apremilast group.

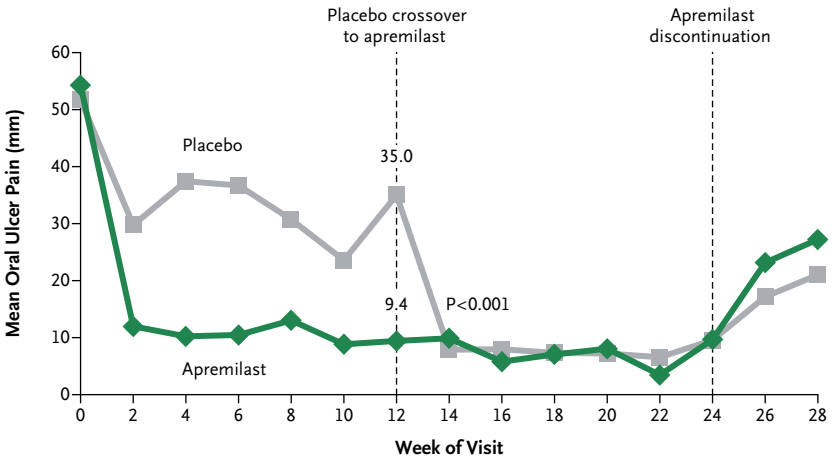
At week 12, the rate of complete response with respect to oral ulcers was 71% (39 of 55 patients) in the apremilast group as compared with 29% (16 of 56 patients) in the placebo group (P<0.001). The proportion of patients with at least a partial response (an improvement of ≥50%) was 89% (49 of 55 participants) in the apremilast group as compared with 50% (28 of 56 participants) in the placebo group (P<0.001).

Genital Ulcers

Ten patients in the apremilast group had genital ulcers at baseline; all were free from genital ulcers at week 12. In the placebo group, 3 of 6 patients with genital ulcers at baseline were free from genital ulcers at week 12 (P=0.04). The mean AUC for oral and genital ulcers from baseline to week 12 was 65.8±108.0 days in the apremilast group and 194.0±161.5 days in the placebo group. The mean AUC for genital ulcers alone was not calculated owing to the small number of participants with genital ulcers.

Disease Activity and Quality of Life

There was significant improvement in measures of disease activity and quality of life at week 12 in



No. at Risk															
Placebo	56	56	53	51	44	42	45	45	36	45	36	34	45	38	54
Apremilast, 30 mg	55	55	50	53	48	47	51	49	41	49	38	37	47	40	54

Mean Oral Ulcer Pain (VAS)															
Placebo	51.7	29.8	37.4	36.7	30.7	23.5	35.0	7.9	7.9	7.3	7.2	6.6	9.6	17.2	21.0
Apremilast, 30 mg	54.3	12.0	10.2	10.5	13.0	8.8	9.4	9.9	5.8	7.1	8.1	3.4	9.7	23.2	27.2

Figure 2. Mean Level of Pain from Oral Ulcers According to Study Group.

The decrease in pain from oral ulcers over time paralleled the decrease in the number of oral ulcers, starting at week 2, with the decrease in pain maintained throughout the treatment phase; the mean level of pain increased after apremilast was discontinued. Pain was measured on a 100-mm visual-analogue scale (VAS).

the apremilast group as compared with the placebo group (Table 2). The mean change from baseline to week 12 was significantly greater in the apremilast group than in the placebo group as measured by the Behçet's Disease Current Activity Form score (–1.5 vs. –0.1, P<0.001), Behçet's Syndrome Activity Score (–21.19 vs. –5.98, P<0.001), Behçet's Disease Quality of Life scale score (–4.5 vs. –1.6, P=0.04), and the summary score for the physical component of SF-36 (4.72 vs. –1.70, P=0.001). There were no significant differences between the placebo group and the apremilast group in the mean change from baseline to week 12 in the summary score for the mental component of SF-36.

ADVERSE EVENTS

Placebo-Controlled Phase

During the placebo-controlled phase of the study, the number of patients who had at least one adverse event was similar in the apremilast group and the placebo group (47 patients [85%] and 45 patients [80%], respectively) (Table 3). Serious adverse events occurred in 2 patients who were receiving apremilast (4%) and in 1 who was receiving placebo. In the apremilast group, 1 patient had worsening of a preexisting anal fissure and hemorrhoids resulting from diarrhea and another patient had transient paralysis of both legs, which an investigator determined to be caused by conversion disorder; the patient in the placebo group had fever. Adverse events leading to discontinuation of treatment occurred in 4 patients receiving apremilast (7%) and none receiving placebo. The events in the apremilast group were nausea in 1 patient, diarrhea in 1 patient, nausea, anal fissure, and hemorrhoids in 1 patient, and dysfunctional uterine bleeding in 1 patient. The most frequent adverse event was headache, which occurred with similar frequency in the two study groups. Nausea, vomiting, and diarrhea occurred more frequently among the patients treated with apremilast than among those receiving placebo (nausea, 22 patients vs. 10 patients; vomiting, 9 vs. 1; and diarrhea, 12 vs. 2).

Apremilast-Exposure Phase

Among the 45 patients who had received placebo in the placebo-controlled phase and were switched to apremilast at week 12, a total of 32 (71%) had

Table 2. Disease Activity and Quality of Life at Baseline, Week 12, and Week 24.*

Measure	Placebo-Controlled Phase				Active Treatment Phase	
	Baseline		Week 12		Week 24	
	Placebo (N=56)	Apremilast (N=55)	Placebo (N=56)	Apremilast (N=55)	Placebo (N=56)	Apremilast (N=55)
Behçet's Disease Current Activity Form†						
Mean	2.5±1.1	3.4±1.6	2.5±1.4	2.0±1.7	1.4±1.2	1.4±1.2
Mean change from baseline			−0.1	−1.5‡	−1.2	−2.0
Behçet's Syndrome Activity Score§						
Mean	35.6±12.2	37.8±16.6	29.6±16.7	16.6±14.2	13.81±14.8	15.97±14.7
Mean change from baseline			−6.0	−21.2‡	−22.0	−22.3
Behçet's Disease Quality of Life Measure¶						
Mean	10.5±8.5	12.6±8.3	8.9±9.0	8.1±9.6	7.8±8.2	7.1±8.7
Mean change from baseline			−1.6	−4.5‖	−3.9	−5.5
SF-36**						
Physical component						
Mean	43.8±8.2	40.4±9.7	42.1±9.9	45.2±9.9	44.2±9.6	45.1±10.2
Mean change from baseline			−1.7	4.7††	1.3	4.94
Mental component						
Mean	39.9±10.3	38.7±10.9	41.5±11.3	40.6±12.9	42.1±11.0	42.5±12.8
Mean change from baseline			1.6	2.0	3.0	3.7

* Plus–minus values are means ±SD. P values are two-sided and were calculated for the comparison of apremilast versus placebo with 95% confidence intervals.
† Scores on Behçet's Disease Current Activity Form range from 0 to 12, with higher scores indicating more active disease.
‡ P≤0.001.
§ The Behçet's Syndrome Activity Score ranges from 0 to 100, with higher scores indicating more active disease.
¶ Scores on the Behçet's Disease Quality of Life Measure range from 0 to 30, with higher scores indicating greater impairment in quality of life.
‖ P=0.04.
** Scores on version 2 of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) range from 0 to 100 for each component, with lower scores indicating greater impairment in quality of life.
†† P=0.001.

at least one adverse event during the apremilast-exposure phase. Among the patients who received apremilast throughout the study, 33 of 50 patients (66%) had at least one adverse event between week 12 and week 24, and 50 of 55 patients (91%) had at least one adverse event between baseline and week 24. One patient who received placebo until week 12 and was then switched to apremilast had a serious adverse event (influenza A infection) between week 12 and week 24. Apremilast was discontinued permanently, and the infection was treated. One other patient who had received apremilast throughout the study had an adverse event (diarrhea) that led to discontinuation of apremilast in week 13.

DISCUSSION

This study suggests that apremilast is an effective agent for the management of oral ulcers in Behçet's syndrome. Its onset of action occurred within 2 weeks after treatment was started, and within 2 weeks after the discontinuation of apremilast, the number of and pain from oral ulcers increased to levels close to baseline values. In addition, disease activity decreased significantly and quality-of-life measures improved significantly from baseline to week 12 in the apremilast group as compared with the placebo group.

Adverse events, including nausea, vomiting, and diarrhea, occurred more frequently with apre-

Table 3. Adverse Events.*

Event	Placebo-Controlled Phase		Active Treatment Phase	
	Weeks 0–12		Weeks 13–24	Weeks 0–24
	Placebo (N=56)	Apremilast (N=55)	Placebo (N=45)	Apremilast (N=55)
	number (percent)			
Type and number				
≥1 Event	45 (80)	47 (85)	32 (71)	50 (91)
≥1 Severe event	2 (4)	3 (6)	0	4 (7)
≥1 Serious event	1 (2)	2 (4)	0	3 (5)
≥1 Event leading to drug discontinuation†	0	4 (7)	0	6 (11)
≥1 Event leading to death	0	0	0	0
Reported by ≥10% of patients in any treatment group‡				
Headache	25 (45)	26 (47)	11 (24)	30 (55)
Nausea	10 (18)	22 (40)	13 (29)	23 (42)
Diarrhea	2 (4)	12 (22)	3 (7)	17 (31)
Vomiting	1 (2)	9 (16)	2 (4)	10 (18)
Abdominal pain	7 (13)	8 (15)	1 (2)	10 (18)
Pain in arm or leg	5 (9)	6 (11)	5 (11)	8 (15)
Influenza	1 (2)	3 (6)	4 (9)	9 (16)
Arthralgia	3 (5)	3 (6)	4 (9)	7 (13)
Asthenia	2 (4)	5 (9)	1 (2)	6 (11)
Upper respiratory tract infection	4 (7)	2 (4)	0	6 (11)

* Safety analyses for the active-treatment phase included all patients who underwent randomization to apremilast at the randomization visit or who switched from placebo to apremilast at the week 12 visit and received at least 1 dose of apremilast.

† Behçet's flares were not included in events leading to discontinuation of the study drug. During the placebo-controlled phase, 5 patients in the placebo group (9%) and 4 in the apremilast group (7%) had flares that caused them to discontinue placebo or apremilast.

‡ During the placebo-controlled phase, manifestations of Behçet's syndrome that were not present at baseline were observed in 27 of 56 participants in the placebo group (48%) and in 12 of 55 participants in the apremilast group (22%).

milast than with placebo. With the exception of transient paralysis in both legs in one patient, the type and severity of adverse events were similar to those listed in the known safety profile for apremilast, as was observed in previous studies of apremilast for the treatment of psoriasis and psoriatic arthritis.[7-9] A total of 91% of the patients in the apremilast group completed the 12-week placebo-controlled phase, and 85% completed all 24 weeks of the study. Two patients required dose reduction owing to gastrointestinal adverse events.

It is difficult to compare the efficacy of apremilast for oral ulcers with that of other, previously studied drugs because of differences in outcomes assessed, study durations, and patient populations. In order to make indirect comparisons, we calculated Cohen's effect size for the number of oral ulcers after treatment with apremilast and after treatment with colchicine. Cohen's effect size for colchicine is estimated to be approximately 0.27 after 4 months of treatment on the basis of results reported by Davatchi et al.[4] In our study, the effect size was estimated to be 1.62 after 3 months of treatment (an effect size of ≥0.8 is considered to

be large). When we compared the odds ratio for freedom from oral ulcers with apremilast versus placebo at the end of the placebo-controlled phase of our study with the odds ratio for freedom from oral ulcers with etanercept versus placebo at the end of the placebo-controlled phase of an earlier study, the ratios were 6.1 (95% confidence interval [CI], 2.7 to 13.9) and 15.6 (95% CI, 1.7 to 139.7), respectively.[17]

This study had some limitations. First, there were few patients with genital ulcers, other skin lesions, or arthritis. Second, randomization was stratified according to sex because previous data indicated that women with Behçet's syndrome had milder disease than did men.[3,11,12] However, the number of men in the study was relatively small. Third, our study was not large enough or long enough to allow for the assessment of uncommon adverse events or serious adverse events that might occur after 24 weeks of treatment.

Finally, this study was conducted mainly in Turkey, with a small number of patients from the United States. Behçet's syndrome shows a specific geographic distribution, with a higher frequency along the ancient Silk Road, and regional differences in disease characteristics have been reported.[18] Thus, to improve external validity, it would be valuable to have data on apremilast from a wider geographic range and from patients with a wider spectrum of clinical manifestations.

In conclusion, this preliminary study showed the efficacy of apremilast in reducing oral ulcers associated with Behçet's syndrome. However, this was a preliminary study that was neither large enough nor long enough to assess long-term efficacy, the effect on other manifestations of Behçet's syndrome, or the risk of uncommon serious adverse events.

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