An open-label pilot study of apremilast for the treatment of moderate to severe lichen planus: A case series

Joan Paul, MD, MPH, Clare E. Foss, MD, Stefanie A. Hirano, MD, Tina D. Cunningham, PhD, and David M. Pariser, MD
Norfolk, Virginia

**Background:** Current treatments for chronic lichen planus (LP) are often ineffective and may have significant adverse side effects. An alternative safe and effective treatment for recalcitrant LP is needed.

**Objectives:** We sought to study the safety and efficacy of apremilast in the treatment of moderate to severe LP.

**Methods:** Ten patients with biopsy-proven LP received 20 mg of apremilast orally twice daily for 12 weeks with 4 weeks of treatment-free follow-up. The primary efficacy end point was the proportion of patients achieving a 2-grade or more improvement in the Physician Global Assessment (PGA) after 12 weeks of treatment.

**Results:** Three (30%) of the 10 patients achieved a 2-grade or more improvement in the PGA after 12 weeks of treatment; however, all patients demonstrated statistically significant clinical improvement with respect to secondary parameters between baseline and the end of treatment.

**Limitations:** It may be difficult to generalize the results of this study to a larger patient population with LP because of our small sample size and lack of a control group. In addition, a longer treatment period or higher dose may have been needed for therapeutic efficacy. The safety and efficacy of long-term apremilast therapy is currently unknown.

**Conclusion:** Apremilast may be efficacious in the treatment of LP, but double-blinded, controlled trials are necessary to thoroughly evaluate its safety and efficacy. (J Am Acad Dermatol 10.1016/j.jaad.2012.07.014.)

**Key words:** apremilast; interferon-γ; interleukin; leukotriene B4; lichen planus; treatment; tumor necrosis factor-α.

Lichen planus (LP) is a chronic inflammatory disease that typically affects the skin, mucous membranes, and nails. It frequently causes significant morbidity, including severe pruritus and pain. LP lesions can resolve spontaneously within a year; however, 15% to 20% of cases have a relapsing and remitting clinical course that is very difficult to treat. Patients in the latter category have very few efficacious therapeutic options available to them, such as topical and oral corticosteroids, retinoids, cyclosporine, griseofulvin, dapsone, and phototherapy, and often with less than optimal results and...
significant adverse side effects. Considering the paucity of available efficacious agents and the severity of clinical symptoms, the investigation of other medications in the treatment of LP is well merited.

The cause of LP is multifactorial, but predominantly involves skin and mucosal damage by T-cell-mediated inflammatory agents, such as tumor necrosis factor-α and interferon-γ. Apremilast is a novel phosphodiesterase type IV inhibitor, which promotes the accumulation of intracellular cyclic adenosine monophosphate. Increased levels of cyclic adenosine monophosphate activate protein kinase A and effectively inhibit proinflammatory cytokine transcription and neutrophil degranulation, chemotaxis, and adhesion to endothelial cells. Ultimately, apremilast inhibits the production of various inflammatory mediators, such as tumor necrosis factor-α, interferon-γ, leukotriene B4, and interleukin (IL)-2, IL-5, IL-8, and IL-12. Thus, it is plausible that apremilast may be an effective treatment for LP.

The primary objective of this study was to evaluate the overall efficacy of oral apremilast in patients with moderate to severe LP after 12 weeks of treatment. Secondary objectives included assessing the safety and toxicity of apremilast therapy, its efficacy for mucosal disease if present, and its effect on quality of life.

METHODS

Study patients

This was an investigator-initiated clinical trial approved by the institutional review board at Chesapeake Research Review Review Inc (Columbia, MD). Patients 18 years and older were recruited from the clinical practice of Pariser Dermatology Specialists (Norfolk, VA); the World Wide Web site of Virginia Clinical Research Inc, Norfolk (www.vcrinc.org); and referrals from community dermatologists. Written informed consent was obtained before study entry. In all, 28 adult patients were screened, and 10 were enrolled into the study (Fig 1). Patients were included if they had more than 20 distinct LP lesions and were appropriate candidates for systemic therapy (patients with a Physician Global Assessment [PGA] score >3 [moderate or severe], symptomatic [severe itching and/or pain that significantly interfered with activities of daily living], or refractory to treatment with topical corticosteroids [no improvement after at least 4 weeks of therapy]); patient exclusion criteria are available upon request.

Study design

This was a case series of an investigator-initiated, single-center, nonrandomized, open-label, pilot study of the safety and efficacy of apremilast in the treatment of moderate to severe LP (registered as NCT 01041625 on www.clinicaltrials.gov). The study was designed to have a 28-day screening period, 12-week open-label treatment phase, and 1 follow-up visit 28 days after the discontinuation of study medication. A total of 10 clinic visits were conducted over the course of 113 days.

Treatments and assessments

Study patients were treated with 20 mg of apremilast orally twice a day for 12 weeks. The PGA, PGA of Mucosal Disease (PGAMD), target area lesion count, Target Area Lesion Severity Score (TALSS), Subject Global Assessment (SGA), Subject Visual Analog Scale for Itch (SVAS), and Dermatology Life Quality Index (DLQI) questionnaires were performed at baseline (day 1; visit 2). The PGA was used to estimate the global burden of disease with respect to erythema, elevation, and pruritus at the time of evaluation, and the PGAMD assessed the extent of the patient’s oral disease. “Target area” was defined as the part of the body with the greatest disease severity; its boundaries were clearly defined and documented at baseline to facilitate future assessments. The PGA, PGAMD, target lesion count, TALSS, SGA, SVAS, and DLQI questionnaires were also performed at 2-week intervals from baseline to the end of treatment (day 85; visit 9), and a final set of assessments were done at the end of the study (day 113; visit 10). A skin biopsy within the target area was performed at screening (day −34 to 0; visit 1) and the end of treatment.

Safety

Vital signs and physical examinations were performed at every office visit. Blood chemistry and hematology were assessed at every visit, except for visits 3 and 10. Serum antinuclear antibody (ANA) titers were assessed at screening (visit 1), and visits 6
and 10. Twelve-lead electrocardiograms were obtained at visits 1, 4, 5, 6, 7, 8, and 9. Chest radiographs, tuberculosis testing, hepatitis B and C panels, and cytoplasmic antineutrophil cytoplasmic antibodies and antiphospholipid antibody levels were assessed at visit 1. Adverse events (AEs) were recorded from initial apremilast administration to the end of the study.

**Study end points**

The primary end point was the proportion of patients who achieved a significant clinical response in cutaneous disease, defined as a 2-grade or more improvement in the PGA score after 12 weeks of treatment. Secondary end points included the proportion of patients achieving a significant clinical response in mucosal disease (PGAMD of “complete resolution” or “marked resolution”), a SGA of “complete resolution” or “marked improvement,” and a change in their target area lesion count, TALSS, DLQI score, and SVAS after 12 weeks of treatment.

**Statistical analysis**

Descriptive statistics were computed for demographic characteristics, including patients’ age, sex, and race. The proportion of patients who achieved a 2-grade or more improvement in the PGA score after 12 weeks of treatment was calculated. Wilcoxon signed rank tests were used to evaluate the pre-post difference among SGA, SVAS, PGA, TALSS, DLQI, and lesion count assessments. Test results were interpreted with \( P \) values of less than or equal to .05 defined as statistically significant. Statistical analyses were performed using a Statistical Analysis Software package (SAS for Windows, Version 9.2, SAS Institute, Cary, NC).

**RESULTS**

Compliance throughout the study was excellent and all 10 study patients had biopsy-proven LP at screening. Only 1 patient missed an appointment (patient 20; visit 4), which did not aberrantly affect the results of our study analysis. Patient demographics at study onset are listed in Table I. Patients were given the diagnosis of LP on average for 7.8 years (range: 1 month to 26 years) before study entry. Three (30%) patients achieved a 2-grade or more improvement in the PGA score after 12 weeks of treatment (95% confidence interval 0.108-0.603), but all 10 patients experienced clinical improvement regarding secondary end points, including median lesion count, PGA, TALSS, SGA, SVAS, and DLQI between baseline (day 1; visit 2) and the end of treatment (day 85; visit 9) (Table II).

In addition, the number of LP lesions within the target area progressively decreased throughout the 12-week treatment period. After the discontinuation of study drug, many patients continued to improve or their LP lesion count stabilized; however, a number of study patients had a subsequent increase in their lesion counts (Fig 2). Two study patients achieved significant clearance of their feet and hands at the end of treatment (Figs 3 and 4, respectively). Of note, no significant difference in median lesion count, PGA, TALSS, SGA, SVAS, and DLQI was observed between the end of treatment and the end of study (day 113; visit 10) (Table II).

Seven patients who progressed from a PGA score of 3 or 4 at study onset to a PGA score of 2 or 3 at the end of treatment had evidence of LP, lichenoid tissue reaction, or lichenoid infiltrate on biopsy specimen. Two patients achieved complete clearance at the end of treatment and had histopathologic evidence of postinflammatory pigment changes or resolving lichenoid dermatitis. One patient with a PGA score of 3 at screening improved to a PGA score of 1 at the end of treatment and had evidence of spongiotic dermatitis on histopathology.

Only patient 09 had mucosal involvement, and after treatment initiation, her oral lesions improved from 40% involvement of her bilateral buccal mucosa at baseline to 12% involvement at the end of the study. At visit 4 (day 15), her PGAMD had improved to “marked resolution.” At the end of the study, her PGAMD had stabilized to “moderate improvement.”

**Adverse events**

Patients 15, 17, 26, and 28 experienced headaches and nausea that were classified as “likely related” to the study drug, as these are known side effects of apremilast, and no change to the dose was made. Patient 09 developed electrocardiographic evidence of an incomplete right bundle branch block at the end of treatment (day 85; visit 9), which was not present at baseline, but was reported as “not clinically significant” by the study cardiologist. Of note,
this patient had a personal history of congestive heart failure and coronary artery bypass graft surgery; all of her previous electrocardiograms had evidence of an old inferior wall myocardial infarction, which was also reported as “not clinically significant.” The manifestation of an incomplete right bundle branch block at visit 9 was not thought to be related to the study drug, and no change in dosage was made.

Patient 28 experienced increased itching in the target area that was deemed unrelated to the study drug, and no changes were made.

Patient 17 became ANA+ during the 28-day follow-up period between visits 9 and 10, which was thought to be related to the study drug, as she had no other signs or symptoms of another autoimmune disease process. No study patients experienced a serious AE throughout the duration of the study.

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**Table I.** Patient demographics and baseline characteristics (n = 10)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Female</td>
<td>7 (70)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Black</td>
<td>7 (70)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>48.8 ± 12.8</td>
</tr>
<tr>
<td>Median</td>
<td>51.0</td>
</tr>
<tr>
<td>Minimum-maximum</td>
<td>27.0-74.0</td>
</tr>
<tr>
<td>PGA rating, n (%)</td>
<td></td>
</tr>
<tr>
<td>(3) Moderate</td>
<td>8 (80)</td>
</tr>
<tr>
<td>(4) Severe</td>
<td>2 (20)</td>
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PGA, Physician Global Assessment.
DISCUSSION

Apremilast has been used successfully in the treatment of chronic inflammatory conditions, such as psoriasis, psoriatic arthritis, rheumatoid arthritis, cutaneous sarcoidosis, and atopic dermatitis. It has been studied at daily oral doses between 10 and 100 mg in phase I clinical studies, and between 20 and 30 mg twice a day in phase II and III clinical trials. In CC-10004-PSOR-001 and CC-10004-PSOR-003, a statistically greater proportion of patients with moderate to severe plaque psoriasis achieved a reduction in their Psoriasis Area and Severity Index score with the use of apremilast. Apremilast effectively inhibits the production of tumor necrosis factor-α, interferon-γ, leukotriene B4, and IL-2, IL-5, IL-8, and IL-12, all of which contribute to the pathogenesis of LP, psoriasis, and other chronic inflammatory conditions.

Although only 3 patients achieved the primary end point of a 2-grade or more improvement in the PGA score, considering the lack of established and validated clinical assessment scales for LP in the current literature, our parameters may have been too stringent. Because there is no consensus regarding the best method to assess response to therapy for LP, we modeled our assessments after those routinely used in psoriasis clinical trials. PGA has been shown to have low interrater variability and high correlation.

**Table II. Lichen planus results summary**

<table>
<thead>
<tr>
<th></th>
<th>Median (range)</th>
<th>EOT(^1)</th>
<th>EOS(^1)</th>
<th>EOT(^1) P value</th>
<th>EOS(^1) P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lesion count</strong></td>
<td>35 (20-73)</td>
<td>20.5 (0-28)</td>
<td>13.5 (0-28)</td>
<td>(.002)</td>
<td>.938</td>
</tr>
<tr>
<td><strong>PGA</strong></td>
<td>3 (3-4)</td>
<td>2 (0-3)</td>
<td>2 (0-3)</td>
<td>.0078</td>
<td>.250</td>
</tr>
<tr>
<td><strong>TALSS</strong></td>
<td>8.5 (7-11)</td>
<td>3.5 (0-8)</td>
<td>3.5 (0-7)</td>
<td>.0078</td>
<td>.477</td>
</tr>
<tr>
<td><strong>SGA</strong></td>
<td>0 (0-2)</td>
<td>1.5 (1-4)</td>
<td>2 (1-4)</td>
<td>.0117</td>
<td>.625</td>
</tr>
<tr>
<td><strong>SVAS</strong></td>
<td>67 (28-100)</td>
<td>18.5 (2-57)</td>
<td>28.5 (7-92)</td>
<td>.0059</td>
<td>.355</td>
</tr>
<tr>
<td><strong>DLQI</strong></td>
<td>15.5 (8-26)</td>
<td>4 (0-11)</td>
<td>4 (0-9)</td>
<td>.002</td>
<td>.254</td>
</tr>
</tbody>
</table>

\(^{*}\)Visit 2; day 1.

\(^{\dagger}\)Visit 9; day 85.

\(^{\ddagger}\)Visit 10; 28 days after end of treatment.

**Fig 2.** Number of lichen planus (LP) lesions progressively decreased from baseline (day 1; visit 2) to end of treatment (day 85; visit 9). Between end of treatment and end of study (28 days of follow-up with no further treatment; visit 10), many patients continued to improve or their LP lesion count stabilized; however, a number of patients had a subsequent increase in their lesion counts.

**Fig 3.** Lichen planus. Patient 17 at baseline (day 1; visit 2; A) compared with end of treatment (day 85; visit 9; B).
between inexperienced and experienced clinicians with respect to psoriasis, which is why this particular assessment was chosen to measure our primary end point. However, because all 10 study patients in this pilot study demonstrated therapeutic improvement with regard to our secondary end points, but only 3 achieved the primary end point, our primary study objective may not have been realistic. Further research is therefore needed to determine appropriate assessment tools and clinically relevant primary and secondary end points with respect to LP.

There was no statistically significant difference in lesion count, PGA, TALSS, SGA, SVAS, and DLQI scores between the end of treatment and the end of study. One possible explanation is the therapeutic effect of apremilast may continue for longer than 28 days after its discontinuation. Although the mean half-life of apremilast is 8.2 hours, its therapeutic effects may be much longer.

In patients exposed to apremilast (20 mg twice a day), headache and nausea were the most commonly reported AEs, which is similar to what we found in this pilot study. Although 1 patient became ANA+ (ANA: 150 AU/mL) during the 28-day follow-up period, the significance of this conversion is unknown, as no cases of apremilast-induced autoimmune disease or ANA positivity have been reported in the literature. To date, no serious AEs have been reported with the use of apremilast; therefore, it may be a safe alternative to current treatment modalities for LP and other chronic, immune-mediated inflammatory diseases.

Limitations

Considering our small sample size and lack of a control group, the generalizability of our results is limited. In addition, a longer treatment period or a higher dose may have been needed as only 3 (30%) of our patients achieved a 2-grade reduction in the PGA score after 12 weeks of therapy. The safety and efficacy of long-term apremilast therapy is currently unknown, as there are a limited number of studies regarding its use in the current literature. Apremilast may be an important alternative treatment for recalcitrant LP, and further investigation of its effectiveness and safety through randomized controlled trials is recommended.

Conclusions

In this pilot study, it appears that apremilast may be efficacious in the treatment of LP. It was well tolerated, and patients who experienced adverse side effects, namely nausea and headache, did not require treatment discontinuation or alteration. Apremilast may be a safe and effective alternative to current treatment modalities for LP; however, double-blinded, randomized, controlled trials are necessary to thoroughly evaluate the safety and efficacy of apremilast.

The authors would like to sincerely thank study coordinator Celina Davis whose help in compiling patient data and photographs was invaluable.

REFERENCES


Fig 4. Lichen planus. Patient 18 at baseline (day 1; visit 2; A) compared with end of treatment (day 85; visit 9; B).


