An Oral Phosphodiesterase Inhibitor (Apremilast) for Inflammatory Rosacea in Adults: A Pilot Study

Rosacea is a chronic skin disorder characterized by facial flushing, persistent erythema, telangiectasias, and inflammatory papules and pustules. In addition to the physical manifestations, rosacea may contribute to lower self-esteem, thereby having significant psychosocial implications. Some patients do not respond to conventional treatments for rosacea or are unable to tolerate the adverse effects; therefore, effective new therapies are needed. We sought to investigate the safety and efficacy of apremilast, an oral phosphodiesterase 4 inhibitor, for the treatment of moderate to severe inflammatory rosacea. Apremilast modulates multiple proinflammatory and anti-inflammatory pathways through targeted phosphodiesterase type 4 inhibition, including augmenting interleukin 10 production, which in turn suppresses other proinflammatory cytokines. Inhibitors of phosphodiesterase type 4 have been tested for treatment of many inflammatory dermatologic diseases but not for rosacea.

Methods | In this investigator-initiated, open-label pilot study, 10 patients with moderate to severe inflammatory rosacea were administered apremilast, 20 mg orally twice daily, for 12 weeks. The inclusion criteria for enrollment were age of 18 to 75 years and moderate to severe erythematotelangiectatic and papulopustular rosacea defined as a minimum of 10 papules and pustules, the presence of moderate to severe erythema, and the presence of telangiectasias. Patients avoided known triggers of rosacea or treatments that might affect rosacea severity. Extensive exclusion criteria were also used in screening. The study population included 3 men and 7 women (age range, 39 to 74 years). Patients were seen between May 5, 2010, and November 20, 2012. This study was approved by the institutional review board of Columbia University, and written informed consent was obtained from all patients.

All patients received active drug. Visits occurred at baseline, every 2 weeks during treatment (weeks 2, 4, 6, 8, 10, and 12), and 1 month after discontinuation of treatment (week 16). Safety factors were assessed at each visit. Patients acclimated for at least 15 minutes before being examined.

Table. Physician’s Rating of Nontransient Erythema in 10 Patients

<table>
<thead>
<tr>
<th>Visit</th>
<th>Rating, No. (%) of Patients</th>
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<tbody>
<tr>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td>Baseline</td>
<td>2 (20)</td>
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<tr>
<td>End of treatment</td>
<td>6 (60)</td>
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<tr>
<td>1 mo After discontinuation of treatment</td>
<td>6 (60)</td>
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* The physician used a 4-point rating system to grade nontransient erythema: 0 indicates absent; 1, mild; 2, moderate; and 3, severe. No patient received a rating of 0 or 3 at any visit.

Results | The primary end point was the total number of papulopustular lesions at baseline compared with the end of treatment and with follow-up 1 month after treatment. Secondary outcomes assessed drug toxicity as well as efficacy as defined by changes in the telangiectasia counts, chromometer readings, and ratings on the Physician Global 7-Point Assessment, Patient Global Assessment, Physician Overall Erythema Severity, and physician-rated variable scales. When baseline scores were compared with those at the end of treatment, there was a statistically significant improvement in ratings on the Physician Global 7-Point Assessment (t statistic = −2.86, P = 0.02), Physician Overall Erythema Severity (t statistic = −4.85, P = 0.001), erythematotelangiectatic rating (t statistic = −4.67, P = 0.005), and nontransient erythema (t statistic = −2.45, P = 0.04) (Table and Figure). When baseline ratings were compared with those at follow-up 1 month after discontinuation of treatment, measures that reached statistical significance were Physician Overall Erythema Severity (t statistic = −3.0, P = 0.02) and nontransient erythema (t statistic = −2.45, P = 0.04) (Table and Figure). None of the remaining comparisons reached statistical significance, including the primary end point of papule and pustule count, which was additionally analyzed by the Wilcoxon signed rank test to compare median values (Figure and the eTable and eFigure in the Supplement). Comparisons of chromometer readings also were not significant (data not shown).

Apremilast was well tolerated. Few patients experienced adverse effects; the most common event was minor infection, including urinary tract infections and upper respiratory tract infections (2 patients each). No adverse effects required treatment alteration or discontinuation.

Discussion | These results support further investigation of treatment with apremilast in rosacea, in particular, to perhaps fill a gap for the treatment of the erythematous component of rosacea, which has historically been refractory to other therapies. Although brimonidine tartrate is used topically for this indication, adverse effects are common and alternative therapies are still needed. An overall trend toward improvement was observed, and 3 of 4 measures of erythema showed significant improvement, two of which were durable 1 month after
Figure. Rosacea Severity Over Time in 10 Patients

A, Physician Global 7-Point Assessment. Possible ratings were 0, clear; 1, minimal; 2, mild; 3, mild to moderate; 4, moderate; 5, moderate to severe; and 6, severe rosacea. B, Patient Global Assessment. Possible ratings were 0, absent; 1, mild; 2, moderate; and 3, severe rosacea. This assessment uses the standard grading system from the Report of the National Rosacea Society Expert Committee on the classification and staging of rosacea. C, Physician Overall Erythema Severity ratings illustrate the shift from mostly moderate erythema to mostly mild erythema. This scale is somewhat restrictive because mild is defined as “slight erythema” and moderate as “pronounced erythema” without a choice in between. At baseline, 1 patient was rated as having mild erythema on the Physician Overall Erythema Severity measure but as having moderate erythema on other measures.

Apremilast may represent a novel alternative treatment for rosacea and rosacea-associated erythema. Larger randomized clinical studies are needed to more adequately evaluate the drug’s efficacy and safety.

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