Long-term safety and efficacy of intranasal ciclesonide in adult and adolescent patients with perennial allergic rhinitis

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Background: Ciclesonide is a corticosteroid in development for allergic rhinitis that has been shown to be safe and effective in seasonal allergic rhinitis and perennial allergic rhinitis (PAR) trials of up to 6 weeks in duration. However, the long-term safety and efficacy of ciclesonide are unknown.

Objective: To demonstrate the long-term safety of intranasal ciclesonide, 200 μg once daily, in patients with PAR.

Methods: Patients (≥12 years old) with a 2-year or longer history of PAR were randomized in a double-blind fashion to receive ciclesonide, 200 μg, or placebo once daily in the morning for up to 52 weeks. Spontaneous and elicited adverse events were monitored throughout the study. Ear, nose, and throat examinations were performed to evaluate local tolerability. Additionally, 24-hour urinary free cortisol level, morning plasma cortisol level, intraocular pressure, and lens opacification were monitored to evaluate the systemic safety of intranasal ciclesonide. Ciclesonide efficacy was determined by measuring 24-hour reflective total nasal symptom scores.

Results: No clinically relevant differences were observed between the ciclesonide and placebo groups in adverse events, ear, nose, and throat examinations, or 24-hour urinary free or morning plasma cortisol levels. Similarly, no clinically relevant differences were found between treatment groups in intraocular pressure, visual acuity, or lens opacification. With regard to efficacy, ciclesonide achieved a significantly greater reduction in 24-hour reflective total nasal symptom score compared with placebo over more than 52 weeks ($P < .001$).

Conclusion: In this study, intranasal ciclesonide, 200 μg once daily, was safe and effective for the long-term treatment of PAR, with no evidence of tachyphylaxis.

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INTRODUCTION

Allergic rhinitis (AR) is characterized by nasal itching, sneezing, rhinorrhea, and nasal obstruction.[1] Approximately 20 million to 40 million people in the United States have AR; approximately 20% of patients have seasonal AR (SAR), 40% of patients have perennial AR (PAR), and 40% of patients have PAR with seasonal exacerbations. Allergic rhinitis increases absenteeism from work, decreases productivity, impairs health-related quality of life (QOL), and imposes a considerable economic burden on the health care system.[2–4]

Although intranasal corticosteroids (INCSs) are the mainstay treatment for patients with moderate to severe AR,[5] a recent study has shown that the major reasons patients are dissatisfied with their current AR medications are related to their long-term effectiveness and the adverse effects associated with nasal allergy medications (eg, a drying feeling, dripping down the throat, drowsiness, bad taste, and burning).[3,6] Approximately 60% of current or previous users of INCSs stated that the effectiveness of these agents wore off within 1 year of use, and of those patients, half reported that the medication began losing effectiveness within 3 months. However, a number of other studies have reported that treatment of AR with INCSs for periods ranging from 3 months to 2 years did not result in tachyphylaxis.[7–10]

Ciclesonide, an investigational INCS in development for the treatment of AR, is converted to the pharmacologically active metabolite desisobutyryl-ciclesonide by esterases in the upper and lower airways, and desisobutyryl-ciclesonide is subsequently esterified with fatty acids.[11–14] In recent studies, ciclesonide, administered intranasally as a hypotonic suspension, was effective and displayed a favorable side effect profile in the treatment of AR. Ciclesonide, 200 μg once daily, resulted in significantly greater improvements in reflective total nasal symptom scores (TNSSs) compared with placebo in patients with SAR after 14 days and in patients with PAR after 42 days.[15,16] Furthermore, ciclesonide was well tolerated and did not cause suppression of 24-hour urinary free cortisol or serum cortisol levels, thereby suggest-

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ing that ciclesonide may not suppress the hypothalamic-pituitary-adrenal axis.[17]

Although ciclesonide has been shown to have a favorable side effect profile and to be efficacious in the treatment of SAR and PAR, these studies were relatively short; thus, the long-term safety, tolerability, and efficacy of this compound have not been established. Therefore, the primary objective of this study was to demonstrate the long-term safety and tolerability of intranasal ciclesonide, 200 μg once daily, in patients with PAR. Additionally, the long-term efficacy of ciclesonide and the QOL of patients receiving ciclesonide therapy were evaluated to evaluate the effectiveness of ciclesonide with long-term therapy.

METHODS

Patients

Patients (age ≥12 years) with a history of PAR (≥2 years) that was anticipated to require treatment for the duration of the study and with a demonstrated sensitivity through a standard skin prick test to at least 1 allergen known to induce PAR were eligible to participate in this study. Patients were excluded from the study if they had any history or physical findings of nasal pathology, including nasal polyps or other clinically significant respiratory tract malformations, recent nasal biopsy, nasal trauma, nasal surgery, atrophic rhinitis, or rhinitis medicamentosa. Additional exclusion criteria included active asthma that required treatment with inhaled or systemic corticosteroids and/or routine use of β-agonists, a known hypersensitivity to corticosteroids, a history of respiratory infection within 14 days of the screening visit or development of a respiratory infection during baseline, or use of antibiotics for acute conditions within 14 days of the screening visit. Patients with evidence of cortical opacity or a history of chronic cataracts or glaucoma were excluded.

Allergy Testing

Allergy testing was conducted at the screening or baseline visit using standard skin prick or intradermal tests. Patients were tested for responses to a range of perennial allergens, including dust mite, cat dander, dog dander, mixed cockroach, and mixed mold. Histamine was used as positive control.

Study Design and Treatment

This was a randomized, double-blind, parallel-group, placebo-controlled, multicenter clinical trial (Fig 1). After a 7- to 14-day baseline period, patients were randomized in a 2:1 ratio to receive ciclesonide, 200 μg, or placebo administered intranasally (2 actuations per nostril) once daily in the morning for up to 52 weeks. All patients were asked to participate in the study for a 48-week treatment period. Patients who enrolled early were asked to remain in the study for an additional 4 weeks to obtain approximately 100 patients exposed to ciclesonide for 52 weeks. This study was approved by an institutional review board (Schulman Associates IRB Inc, Cincinnati, OH) and conducted in accordance with the principles of the revised Declaration of Helsinki.[18] Written informed consent was obtained from each patient before study participation.

Safety Assessments

Treatment-emergent adverse events (TEAEs) were recorded throughout the study. Ear, nose, and throat examinations were recorded at every study visit. Physical examinations, vital signs, clinical chemistry, and hematologic assessments were performed at baseline and at weeks 24, 48, and 52. Ocular examinations, 24-hour urine and plasma cortisol measurement (in a subset of 250 patients at preselected sites), and electrocardiogram evaluations were recorded at baseline and at weeks 24 and 48.

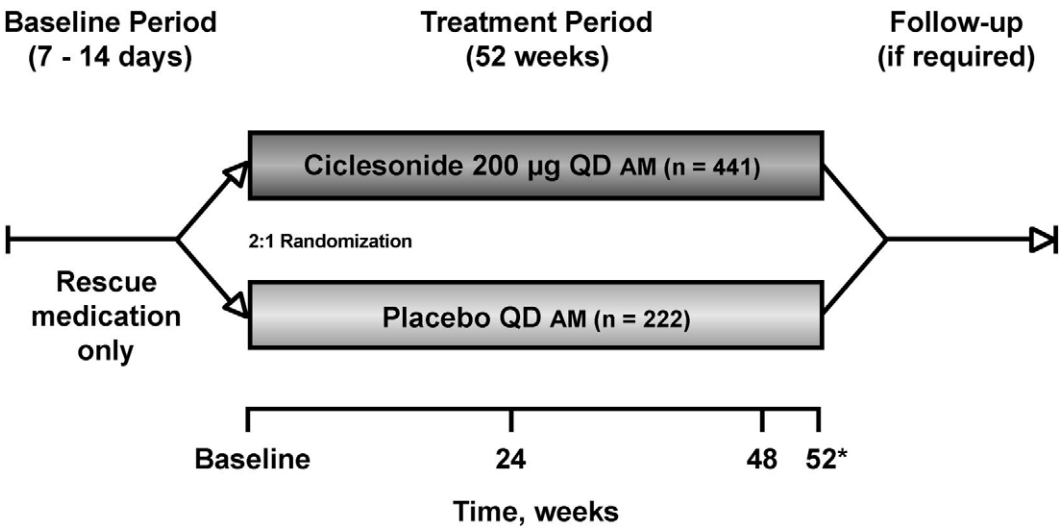

Figure 1. Study design. QD indicates once daily. *Approximately 150 patients were extended during weeks 48 to 52.