

Effectiveness of ciclesonide nasal spray in the treatment of seasonal allergic rhinitis

Paul H. Ratner, MD*; Mark A. Wingertzahn, PhD†; Julius H. van Bavel, MD‡; Frank Hampel, MD§; Patrick F. Darken, PhD¶; Stefan Hellbardt, PhD¶; Sheldon Brookman, PhD||; and Tushar Shah, MD†

Background: Ciclesonide is an investigational corticosteroid under development for treatment of allergic rhinitis. Ciclesonide is converted to active metabolite, desisobutyl-ciclesonide (des-CIC), by upper and lower airway esterases. In vitro studies in human nasal epithelial cells and bronchial epithelial cells have demonstrated a long duration of anti-inflammatory activity of des-CIC.

Objective: To evaluate the dose-dependent efficacy and safety of a hypotonic intranasal formulation of ciclesonide in patients with seasonal allergic rhinitis (SAR).

Methods: This was a phase 2, randomized, parallel-group, double-blind, placebo-controlled study. Adults (n = approximately 145 per treatment group) with a minimum 2-year history of SAR received placebo or ciclesonide (25, 50, 100, or 200 $\mu\text{g}/\text{d}$) for 14 days. The primary end point was change in the sum of morning and evening reflective total nasal symptom scores (TNSSs) over 2 weeks. Safety was monitored throughout the study.

Results: Ciclesonide, 100 $\mu\text{g}/\text{d}$ ($P = .04$) and 200 $\mu\text{g}/\text{d}$ ($P = .003$), significantly improved the sum of morning and evening reflective TNSS vs placebo at more than 2 weeks of treatment. Baseline values for morning and evening reflective TNSS ranged from 17.80 to 18.82 across treatment groups. The average change from baseline in reflective TNSS was -4.2 for placebo and -4.8 , -4.8 , -5.3 , and -5.8 for ciclesonide, 25, 50, 100, and 200 $\mu\text{g}/\text{d}$, respectively. There were no dose-related differences in the incidence of adverse events among treatment groups.

Conclusions: Results from this study indicate that 100- μg and 200- μg daily doses of ciclesonide are effective in the treatment of SAR. Ciclesonide, 200 $\mu\text{g}/\text{d}$, appears to be the optimal dose studied for reducing the symptoms of SAR while maintaining an acceptable safety profile.

Ann Allergy Asthma Immunol. 2006;97:657–663.

INTRODUCTION

Of the 20 million to 40 million Americans who are affected by allergic rhinitis (AR), 20% have seasonal allergic rhinitis (SAR), 40% have perennial allergic rhinitis, and 40% have a combination of perennial AR with seasonal exacerbation.^{1,2} Allergic rhinitis is an inflammatory disease characterized by sneezing, nasal itch, nasal congestion, and rhinorrhea that affects quality of life, performance, and productivity.^{3–5} Current pharmacologic treatments for AR include antihistamines, decongestants, and intranasal corticosteroids (INCs).⁶ INCs exhibit potent anti-inflammatory activity and are currently the most effective pharmacotherapeutic treatment for patients with persistent AR.^{7,8}

Ciclesonide is a new-generation corticosteroid that is currently in development for the treatment of asthma and is also being investigated for use in the treatment of AR.^{9–11} Ciclesonide is administered as an inactive parent compound that is converted to the pharmacologically active metabolite,

desisobutyl-ciclesonide (des-CIC), in the upper and lower airways.^{12,13} In vitro studies in rat lung have shown that esterification of des-CIC generates reversible lipid conjugates of des-CIC that serve as a pool of active drug that may lead to a long duration of anti-inflammatory activity.¹⁴ Ciclesonide shows high nasal tissue uptake and greater lipid conjugation compared with other commonly used INCs, including beclomethasone, budesonide, and fluticasone propionate.^{14–17}

Ciclesonide is formulated in a hypotonic suspension that preclinical in vivo studies have shown enhances the delivery of ciclesonide to the nasal mucosa.¹⁵ The formulation of ciclesonide does not contain benzalkonium chloride or phenyl ethyl alcohol, excipients that have been associated with reduced mucociliary transport and rhinitis medicamentosa and unpleasant sensory perceptions.^{18,19} These beneficial properties could potentially lead to enhanced ciclesonide uptake in nasal mucosal tissue and higher local tissue concentrations of des-CIC, leading to a sustained anti-inflammatory effect. In this phase 2 study, we evaluated the efficacy and safety of 4 doses of ciclesonide nasal spray compared with placebo administered once daily for 14 days in patients with SAR.

METHODS

Patients

Patients between 18 and 65 years of age in good health with at least a 2-year history of SAR and experiencing nasal allergy symptoms with a minimum score of 8 of a maximum

* Sylvana Research, San Antonio, Texas.

† ALTANA Pharma US Inc, Florham Park, New Jersey.

‡ Allergy and Asthma Associates, PLLC, Austin, Texas.

§ Central Texas Health Research, New Braunfels, Texas.

¶ ALTANA Pharma AG, Konstanz, Germany.

|| TEIJIN America Inc, Princeton, New Jersey.

This research was supported by a grant from ALTANA Pharma US Inc.

Received for publication March 30, 2006.

Accepted for publication in revised form June 26, 2006.

of 12 in either the morning or evening reflective total nasal symptom score (TNSS) for at least 3 days during the baseline period were randomized. All patients demonstrated sensitivity to mountain cedar pollen by either positive skin test results or an in vitro test specific for IgE, had no concurrent disease that could worsen by participating in the study, and were not receiving concomitant therapy that could interfere with the study. All patients provided written informed consent.

Patients were excluded from participating in the trial if they had clinically significant abnormal laboratory test results or physical findings including but not limited to nasal polyps or nasal tract malformations; evidence of ocular herpes simplex or cataracts or a history of glaucoma; evidence of a bronchial, pulmonary, or respiratory tract infection or disorder other than AR or asthma within 14 days before the screening visit; or positive test results for hepatitis B, hepatitis C, or human immunodeficiency viruses. Additionally, patients with active asthma who required daily treatment with β -agonists were excluded, as were patients who received prohibited medications during various washout periods (in days before the screening visit) or any inhaled, intranasal, or ocular corticosteroids (30 days); oral corticosteroids other than oral contraceptives or hormone replacement therapy or topical corticosteroids (42 days); oral antihistamines (3 to 10 days) and intranasal antihistamines (3 days); or inhaled or oral anticholinergics (12 hours to 7 days). Patients receiving immunotherapy in a regimen or dose that changed in 30 days before the first study visit were not eligible for participation in the study. However, immunotherapy was permitted if the maintenance regimen was stable for at least 30 days before first study visit and it was not planned to change the dose during the study.

Study Design and Treatment

This was a phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study (Fig 1) conducted during the 2002 to 2003 mountain cedar pollen season. After a 1-week baseline period, patients were randomized to placebo or ciclesonide (25, 50, 100, or 200 μ g/d) in a 1:1:1:1 ratio at each study center. Patients self-administered the daily

dose in both nostrils each morning for 14 days. Patients were provided with 4-mg chlorpheniramine maleate tablets as rescue medication and were permitted 1 tablet every 4 to 6 hours as needed, not exceeding 24 mg in a 24-hour period. Rescue medication use was evaluated based on the number of tablets of rescue medication that were used by patients in each of the 5 treatment groups. This study was approved by Sterling Institutional Review Board (Atlanta, GA) and conducted in accordance with the principles of the revised version of the Declaration of Helsinki (Edinburgh, Scotland; October 2000).

Efficacy Evaluation

The primary efficacy variable was a patient-rated, 12-hour reflective TNSS, defined as the sum of the scores for 4 nasal symptoms (runny nose, itchy nose, sneezing, and nasal congestion). Nasal symptoms were evaluated twice daily beginning after the screening visit (day -7) and continuing to day 14. Each symptom was rated on a severity scale ranging from 0 (no evident signs or symptoms) to 3 (severe signs or symptoms). Nasal symptoms were evaluated in the morning before administration of ciclesonide or placebo and in the evening. The primary efficacy measure was the change in the sum of the morning and evening patient-rated reflective TNSS from baseline to more than 2 weeks. Secondary efficacy end points included the change from baseline in the sum of morning and evening instantaneous TNSSs and the use of rescue medication. Patients' and physicians' global evaluations of the treatment effect were also conducted on a 5-point scale, ranging from complete relief (score of 1) to no relief (score of 5) on day 7 and day 14.

Safety Evaluation

Safety was monitored throughout the study and evaluated by incidence of adverse events, vital signs, physical examination, electrocardiogram, and routine clinical laboratory tests. Eye examinations and intraocular pressure measurements were performed at baseline and study end. Tonometry was used to evaluate intraocular pressure, and intraocular pressure greater than 20 mm Hg was considered an adverse event.

Statistical Analysis

The intent-to-treat (ITT) population (ie, all randomized patients) was used for all analyses. Data are presented as least squares mean changes adjusted for study day, treatment, and treatment by study day. Analyses were performed using a repeated-measures analysis of variance model. Using a 2-sided α level of .05, a sample size of 125 patients in each treatment group was planned to provide 80% power to demonstrate a difference of 1.8 units for the change from baseline in the sum of morning and evening reflective TNSSs between ciclesonide dose and placebo. Baseline was calculated as the average over the screening period of the sum of morning and evening reflective TNSSs. Post hoc, a Jonckheere-Terpstra nonparametric test for trend was used to determine whether there was a dose-related trend for the primary efficacy measure.

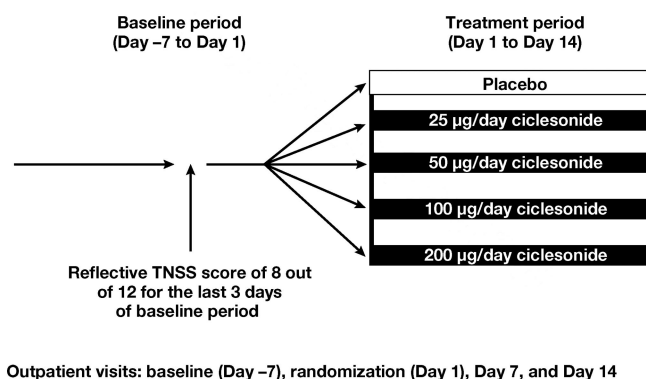


Figure 1. Study design. TNSS indicates total nasal symptom score.

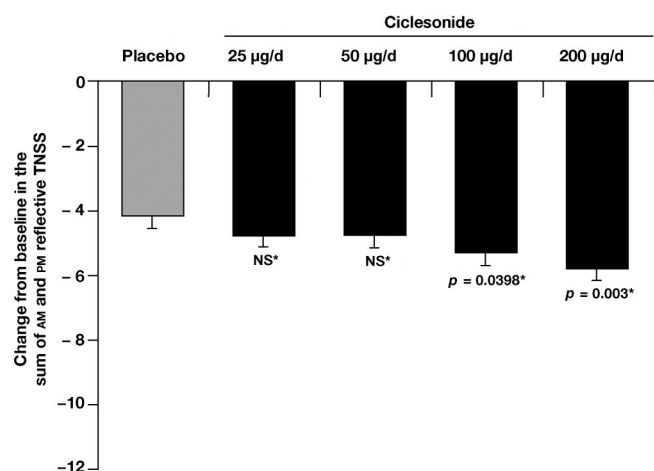


Figure 2. Change in the patient-evaluated sum of the morning and evening reflective total nasal symptom scores (TNSSs) from baseline over 14 days of treatment. The baseline sums of the morning and evening reflective TNSSs were as follows: 25 µg/d of ciclesonide, 18.72; 50 µg/d of ciclesonide, 18.35; 100 µg/d of ciclesonide, 18.71; 200 µg/d of ciclesonide, 18.82; and placebo, 17.80. Data are presented as least squares means and SEM. NS indicates not significant; asterisk, vs placebo.

RESULTS

Patient Disposition and Demographics

A total of 726 patients were randomized, and 703 patients (97%) completed the study. All randomized patients received at least 1 dose of study medication and were included in the

ITT population. Twenty-three patients withdrew from the study: 6 (4.1%) from the 25-µg ciclesonide group, 4 (2.8%) from the 50-µg ciclesonide group, 6 (4.1%) from the 100-µg ciclesonide group, 1 (0.7%) from the 200-µg ciclesonide group, and 6 (4.1%) from the placebo group. The primary reasons for discontinuation were adverse events (7 patients [1%]) and lack of efficacy (5 patients [0.7%]). Patient demographics and baseline characteristics were comparable among treatment groups (Table 1). Most patients (65.5% to 73.4%) were female. Approximately half of the patients (46.2% to 52.4%) in all treatment groups had previously used intranasal corticosteroids. Baseline mean sum of morning and evening reflective TNSS values ranged from 17.8 to 18.8 for the ciclesonide and placebo groups, indicating a patient population with moderate to severe SAR.

Efficacy

Ciclesonide, 200 µg/d ($P = .003$), treatment resulted in a significant improvement in the sum of morning and evening reflective TNSS from baseline vs placebo (Fig 2). This improvement was also observed for ciclesonide, 100 µg/d, compared with placebo ($P = .04$), although to a lesser extent. The estimated differences from placebo in the changes in the various components of the summed morning and evening TNSSs are given in Tables 2 and 3. The data show that the greatest magnitude of benefit over vehicle alone was achieved by the 200-µg ciclesonide group for all of the components of the primary efficacy measure. This finding was supported by a post hoc test for a dose-related trend in the sum of morning and evening reflective TNSSs that dem-

Table 1. Patient Demographics and Baseline Characteristics

Variable	Placebo (n = 148)	Ciclesonide			
		25 µg/d (n = 146)	50 µg/d (n = 143)	100 µg/d (n = 145)	200 µg/d (n = 144)
Age, y					
Median	38	41	41	36	43
Range	16–65	18–65	20–65	18–65	18–66
Sex, No. (%)					
Male	44 (30)	42 (29)	38 (27)	50 (34)	40 (28)
Female	104 (70)	104 (71)	105 (73)	95 (66)	104 (72)
Race, No. (%)					
White	142 (96)	138 (95)	137 (96)	142 (98)	129 (90)
Black	3 (2)	5 (3.4)	5 (4)	3 (2)	12 (8.3)
Asian	3 (2)	2 (1.4)	1 (0.7)	0	2 (1.4)
Other	0	1 (0.7)	0	0	1 (0.7)
Skin prick testing results, mean (SD), mm*	8.5 (4.01)	9 (4)	8.5 (4)	8.2 (3.63)	8.8 (4)
Control results, mean (SD), mm*	0.4 (0.95)	0.3 (1.03)	0.4 (1.2)	0.3 (0.92)	0.3 (0.88)
Sum of the morning and evening reflective TNSSs†	17.8	18.7	18.4	18.7	18.8
Sum of the morning and evening instantaneous TNSSs†	16.8	18.0	17.6	17.6	18.0
Corticosteroid use, No. (%)					
No	76 (51)	77 (53)	77 (54)	69 (48)	72 (50)
Yes	72 (49)	69 (47)	66 (46)	76 (52)	72 (50)

Abbreviations: TNSS, total nasal symptom score.

* Performed with a skin prick test.

† Data presented as least squares means.

Table 2. Improvement in Morning and Evening Reflective and Instantaneous TNSSs vs Placebo Over 14 Days of Treatment*

Comparisons	Reflective TNSS		Instantaneous TNSS	
	Morning	Evening	Morning	Evening
Ciclesonide, 200 $\mu\text{g}/\text{d}$, vs placebo	-0.76 ($P = .006$)	-0.91 ($P = .002$)	-0.76 ($P = .004$)	-0.98 ($P < .001$)
Ciclesonide, 100 $\mu\text{g}/\text{d}$, vs placebo	-0.48 ($P = .08$)	-0.70 ($P = .19$)	-0.43 ($P = .11$)	-0.62 ($P = .03$)
Ciclesonide, 50 $\mu\text{g}/\text{d}$, vs placebo	-0.19 ($P = .49$)	-0.42 ($P = .16$)	-0.15 ($P = .57$)	-0.31 ($P = .28$)
Ciclesonide, 25 $\mu\text{g}/\text{d}$, vs placebo	-0.20 ($P = .47$)	-0.40 ($P = .17$)	-0.20 ($P = .46$)	-0.40 ($P = .16$)

Abbreviation: TNSS, total nasal symptom score.

* Data presented as least squares means.

Table 3. Improvement in Individual Components of Reflective TNSSs vs Placebo Over 14 Days of Treatment

Symptom	Morning reflective TNSS (95% CI)	Evening reflective TNSS (95% CI)	Morning and evening reflective TNSS (95% CI)
Nasal congestion*			
Ciclesonide, 200 $\mu\text{g}/\text{d}$	-0.040 (-0.192 to 0.112)	-0.088 (-0.252 to 0.074)	-0.115 (-0.420 to 0.191)
Ciclesonide, 100 $\mu\text{g}/\text{d}$	-0.040 (-0.192 to 0.112)	-0.054 (-0.217 to 0.108)	-0.072 (-0.377 to 0.232)
Ciclesonide, 50 $\mu\text{g}/\text{d}$	-0.026 (-0.126 to 0.180)	-0.014 (-0.177 to 0.150)	-0.022 (-0.284 to 0.330)
Ciclesonide, 25 $\mu\text{g}/\text{d}$	0.017 (-0.135 to 0.170)	0.006 (-0.157 to 0.170)	-0.014 (-0.290 to 0.320)
Itchy nose*			
Ciclesonide, 200 $\mu\text{g}/\text{d}$	-0.193 (-0.350 to 0.036)	-0.254 (-0.423 to -0.085)	-0.425 (-0.740 to -0.111)
Ciclesonide, 100 $\mu\text{g}/\text{d}$	-0.133 (-0.290 to 0.024)	-0.233 (-0.401 to -0.064)	-0.345 (-0.660 to -0.032)
Ciclesonide, 50 $\mu\text{g}/\text{d}$	-0.058 (-0.216 to 0.010)	-0.102 (-0.271 to 0.068)	-0.148 (-0.464 to 0.170)
Ciclesonide, 25 $\mu\text{g}/\text{d}$	-0.044 (-0.202 to 0.112)	-0.114 (-0.282 to 0.055)	-0.149 (-0.462 to 0.165)
Runny nose*			
Ciclesonide, 200 $\mu\text{g}/\text{d}$	-0.226 (-0.386 to -0.066)	-0.206 (-0.372 to -0.041)	-0.440 (-0.754 to -0.127)
Ciclesonide, 100 $\mu\text{g}/\text{d}$	-0.108 (-0.267 to 0.052)	-0.155 (-0.320 to 0.010)	-0.266 (-0.579 to 0.047)
Ciclesonide, 50 $\mu\text{g}/\text{d}$	-0.017 (-0.177 to 0.143)	-0.080 (-0.244 to 0.089)	-0.092 (-0.407 to 0.222)
Ciclesonide, 25 $\mu\text{g}/\text{d}$	-0.064 (-0.223 to 0.095)	-0.140 (-0.305 to 0.026)	-0.215 (-0.528 to 0.097)
Sneezing*			
Ciclesonide, 200 $\mu\text{g}/\text{d}$	-0.301 (-0.460 to -0.142)	-0.360 (-0.520 to -0.200)	-0.666 (-0.971 to -0.361)
Ciclesonide, 100 $\mu\text{g}/\text{d}$	-0.197 (-0.356 to -0.040)	-0.257 (-0.417 to -0.097)	-0.460 (-0.764 to -0.155)
Ciclesonide, 50 $\mu\text{g}/\text{d}$	-0.144 (-0.304 to 0.015)	-0.226 (-0.386 to -0.065)	-0.384 (-0.690 to -0.078)
Ciclesonide, 25 $\mu\text{g}/\text{d}$	-0.103 (-0.262 to 0.056)	-0.156 (-0.316 to 0.004)	-0.272 (-0.576 to 0.032)

Abbreviations: TNSS, total nasal symptom score; CI, confidence interval.

* Values are estimates.

onstrated a dose-dependent increase in the efficacy of ciclesonide ($P = .003$). When the daily sum of morning and evening reflective TNSSs was examined over time (Fig 3), the benefit of ciclesonide, 200 μg , compared with placebo was sustained throughout the trial and appeared to be greatest on day 5. Differences in the sum of morning and evening reflective TNSSs between the ciclesonide (100 $\mu\text{g}/\text{d}$ and 200 $\mu\text{g}/\text{d}$) and placebo groups were already apparent on day 2, the first day after randomization. The difference in reflective TNSS between the ciclesonide, 200 $\mu\text{g}/\text{d}$, and placebo groups was significant on day 3 ($P = .03$). Furthermore, the difference in reflective TNSS between the ciclesonide, 100 $\mu\text{g}/\text{d}$, and placebo groups was significant on day 4 ($P = .02$).

Ciclesonide also demonstrated improvements in instantaneous TNSS. The sum of morning and evening instantaneous TNSSs decreased in a manner comparable with the reflective TNSS (Fig 4). Both ciclesonide, 100 $\mu\text{g}/\text{d}$, and ciclesonide, 200 $\mu\text{g}/\text{d}$, demonstrated greater improvements in instanta-

neous TNSS compared with placebo. Additionally, the physicians' global evaluation of the treatment effect revealed a moderate (score of 3) to slight (score of 4) relief of SAR signs and symptoms at day 7 and moderate (score of 3) to marked relief (score of 2) of SAR signs and symptoms at day 14 that were somewhat better in the 100- $\mu\text{g}/\text{d}$ and 200- $\mu\text{g}/\text{d}$ ciclesonide groups compared with placebo (data not shown). No appreciable differences were seen in the use of rescue medication. Across the treatment groups, 38% to 47% of the patients in the ciclesonide groups and 41% of patients in the placebo group used rescue medication at least once during the study. The average number of tablets of daily rescue medication used ranged from 0.14 tablet to 0.23 tablet in the ciclesonide groups and 0.19 tablet in the placebo group.

Safety

All ciclesonide doses were well tolerated, and only 176 patients (24%) experienced at least 1 adverse event. The 2

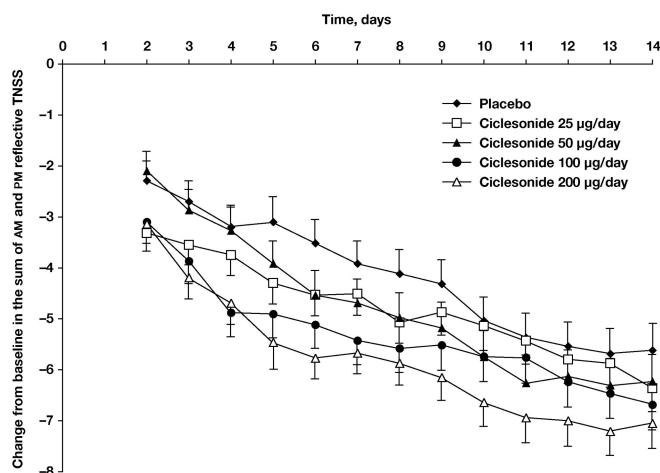


Figure 3. Change from baseline over time in the daily patient-evaluated sum of the morning and evening reflective total nasal symptom scores (TNSSs) over 14 days of treatment. Data are presented as least squares means and SEM.

most common adverse events reported were headache and pharyngitis (Table 4). The incidence of adverse events between patients receiving ciclesonide or placebo was similar, and no dose-dependent effects on adverse events were observed. Eleven patients had intraocular pressures above the 20 mm Hg upper limit, but pressure increases were evenly distributed among the ciclesonide and placebo treatment groups, and none of the increases was considered clinically meaningful. Severe adverse events were reported by 29 patients (3.9%): 4 (2.7%) in the 25- μ g ciclesonide group, 5 (3.5%) in the 50- μ g ciclesonide group, 8 (5.5%) in the 100- μ g ciclesonide group, 7 (4.9%) in the 200- μ g ciclesonide group, and 5 (3.4%) in the placebo group. Serious adverse events were reported by 2 patients (1.4%) in the 100- μ g ciclesonide group and were not related to the study drug. Seven patients discontinued participation in the study because of adverse events: 3 (2.1%) in the 100- μ g ciclesonide group, 1 (0.7%) each in the 25- μ g and 50- μ g ciclesonide groups, and 2 (1.4%) in the placebo group. Only 1 patient in the 100- μ g ciclesonide group discontinued the study because of

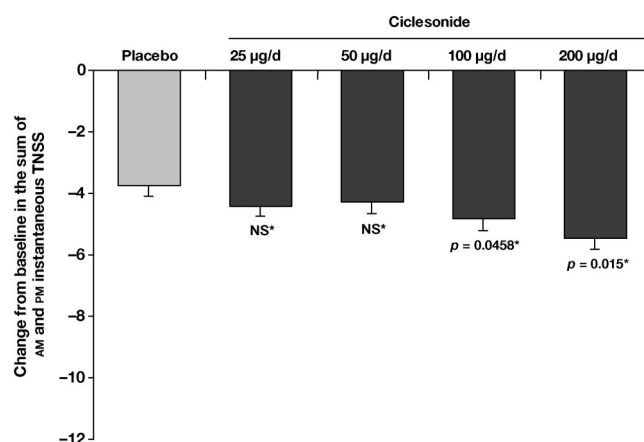


Figure 4. Change from baseline in the patient-evaluated sum of morning and evening instantaneous total nasal symptom scores (TNSSs) over 14 days of treatment. The baseline sums of the morning and evening instantaneous TNSSs were as follows: 25 μ g/d of ciclesonide, 18.01; 50 μ g/d of ciclesonide, 17.56; 100 μ g/d of ciclesonide, 17.56; 200 μ g/d of ciclesonide, 18.00; and placebo, 16.75. Data are presented as least squares means and SEM. NS indicates not significant; asterisk, vs placebo.

a moderately severe case of urticaria considered by the investigator as possibly related to study drug. Most of the remaining patients who discontinued study participation had moderate to severe upper respiratory tract infections that were considered not related to study drug.

DISCUSSION

This study was a multicenter, double-blind, randomized, placebo-controlled, 2-week safety and efficacy dose-ranging study. Ciclesonide nasal spray (25, 50, 100, or 200 μ g/d) was administered once daily for 14 days. The ITT analysis set consisted of 726 men and women at least 18 years of age with a minimum of a 2-year documented history of SAR. This study was conducted in Texas during the mountain cedar pollen season.

Ciclesonide was shown to be safe and effective in the treatment of SAR. Doses of intranasal ciclesonide at 25 μ g/d and 50 μ g/d did not achieve statistically significant differ-

Table 4. Adverse Events Reported in 2% or More of Patients in Any Treatment Group*

Adverse event	Placebo (n = 148)	Ciclesonide			
		25 μ g/d (n = 146)	50 μ g/d (n = 143)	100 μ g/d (n = 145)	200 μ g/d (n = 144)
Patients with at least 1 adverse event	31 (21.0)	36 (24.7)	39 (27.3)	38 (26.2)	32 (22.2)
Headache	4 (2.7)	3 (2.1)	6 (4.2)	2 (1.4)	3 (2.1)
Pharyngitis	4 (2.7)	4 (2.7)	1 (0.7)	5 (3.4)	2 (1.4)
Epistaxis	0	1 (0.7)	3 (2.1)	3 (2.1)	2 (1.4)
Nasal passage irritation	2 (1.4)	0	2 (1.4)	1 (0.7)	3 (2.1)
Dizziness	1 (0.7)	3 (2.1)	0	1 (0.7)	0
Intraocular pressure >20 mm Hg	3 (2.0)	2 (1.4)	2 (1.4)	2 (1.4)	2 (1.4)

* Data are number (percentage) of patients.

ences from placebo for the primary or any secondary efficacy measures. However, intranasal ciclesonide administration at doses of 100 $\mu\text{g}/\text{d}$ and 200 $\mu\text{g}/\text{d}$ was associated with dose-related improvements in nasal symptom relief compared with placebo when measured by the change from baseline in summed morning and evening reflective TNSSs. Although statistically significant differences were not observed between the 2 highest doses of intranasal ciclesonide, the 200- $\mu\text{g}/\text{d}$ dose of intranasal ciclesonide was numerically superior to the 100- $\mu\text{g}/\text{d}$ dose on the primary and most secondary measures. Also, for the primary analysis, baseline was not included in the statistical model as is customary for analyses of change from baseline. For the comparison of the 100- $\mu\text{g}/\text{d}$ dose of ciclesonide to placebo, the inclusion of baseline in the model would have resulted in the lack of statistical significance, whereas the 200- $\mu\text{g}/\text{d}$ dose of ciclesonide would have still achieved a statistical difference from placebo (data not shown).

Evidence supporting the 200- $\mu\text{g}/\text{d}$ dose of ciclesonide nasal spray as the starting and maximum doses in adult patients was obtained from a post hoc test for trend that was performed on the change from baseline in the sum of morning and evening reflective TNSSs. These data demonstrated that there was a dose-dependent increase in the efficacy of ciclesonide nasal spray ($P = .003$), further supporting the finding that the 200- $\mu\text{g}/\text{d}$ dose of ciclesonide is the most effective dose studied in ameliorating the symptoms associated with SAR.

Although no direct head-to-head trials between ciclesonide and other AR products have been performed to date, indirect comparisons across studies (corrected on a 12-point scale) suggest that the treatment-effect size of 0.90 observed between ciclesonide, 200 $\mu\text{g}/\text{d}$, and placebo in this study is larger than generally observed with the leukotriene inhibitor montelukast, as well as with nonsedating oral antihistamines such as desloratadine, in the treatment of SAR.^{20,21} Additionally, the magnitude of effect observed in this study appears comparable to what has been demonstrated previously with mometasone.²²

Another noteworthy observation in this trial is the magnitude of the benefit observed in the placebo group as measured by the change from baseline in the primary efficacy measure, the summed morning and evening reflective TNSSs. The placebo effect increased throughout the trial. The magnitude of this change was already more than 2 on the day after the initiation of treatment and averaged 4.18 throughout the 2 weeks of treatment. Although a placebo effect is not unexpected in AR trials because of the benefits of an aqueous nasal spray and use of subjective efficacy measures, the placebo effect observed in this trial appeared larger than typically observed in SAR clinical trials with INCs.^{23–27} Although the limited use of rescue medication may have partially contributed to the improvement in the sum of morning and evening reflective TNSSs in the placebo group, it is more likely that the use of a hypotonic formulation is the major contributor to the improved TNSSs observed in this group.

No clinically meaningful differences were found among the treatment groups in incidence of adverse events or other safety assessments during the study. Ciclesonide at doses of 25, 50, 100, and 200 μg was safe and well tolerated by patients with SAR. The percentage of patients experiencing adverse events was similar across all treatment groups. The most frequently reported adverse events (2% or more of patients) were dizziness, epistaxis, nasal passage irritation, pharyngitis, and headache and occurred at similar rates in the ciclesonide and placebo groups without any dose-related trends. Epistaxis only occurred in the ciclesonide treatment groups but without any evidence of a dose-related increase in frequency or severity.

Although these results have shown that the 100- $\mu\text{g}/\text{d}$ and 200- $\mu\text{g}/\text{d}$ doses of ciclesonide were effective in the treatment of SAR, the magnitude of response indicates that the 100- $\mu\text{g}/\text{d}$ dose would be at best marginally effective in the treatment of AR. Therefore, the 200- μg dose is indicated as appropriate for further study in the treatment of AR. The characteristics of ciclesonide, which include onsite activation, low systemic bioavailability, and lipid conjugation for durable activity, position ciclesonide nasal spray as a favorable treatment option for patients with SAR.

REFERENCES

1. Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol*. 2001;108(suppl):S2–S8.
2. Berger WE. Overview of allergic rhinitis. *Ann Allergy Asthma Immunol*. 2003;90(suppl 3):7–12.
3. Bousquet J, Jacquot W, Vignola AM, et al. Allergic rhinitis: a disease remodeling the upper airways? *J Allergy Clin Immunol*. 2004;113:43–49.
4. Gelfand EW. Inflammatory mediators in allergic rhinitis. *J Allergy Clin Immunol*. 2004;114:S135–S138.
5. Thompson AK, Juniper E, Meltzer EO. Quality of life in patients with allergic rhinitis. *Ann Allergy Asthma Immunol*. 2000;85:338–347.
6. Bloebaum R. Managing allergic rhinitis: the role of pharmacotherapy; sound treatment can improve your patient's quality of life. *J Respir Dis*. 2002;23:370–376.
7. Storms WW. Pharmacologic approaches to daytime and nighttime symptoms of allergic rhinitis. *J Allergy Clin Immunol*. 2004;114:S146–S153.
8. Nielsen LP, Dahl R. Comparison of intranasal corticosteroids and antihistamines in allergic rhinitis: a review of randomized, controlled trials. *Am J Respir Med*. 2003;2:55–65.
9. Stoeck M, Riedel R, Hochhaus G, et al. In vitro and in vivo anti-inflammatory activity of the new glucocorticoid ciclesonide. *J Pharmacol Exp Ther*. 2004;309:249–258.
10. Mealy NE, Bayés M, Castañer J. Ciclesonide: treatment of allergic rhinitis antiallergy/asthmatic. *Drugs Future*. 2001;26:1033–1039.
11. Schmidt B, Timmer W, Georgens AC, et al. The new topical steroid ciclesonide is effective in the treatment of allergic rhinitis. *J Clin Pharmacol*. 1999;39:1062–1069.
12. Dietzel K, Engelstätter R, Keller A. Ciclesonide: an on-site-activated steroid. In: Hansel TT, Barnes PJ, eds. *New Drugs for Asthma, Allergy and COPD*. Progress in Respiratory Research,

-
- vol 31. Basel, Switzerland: Karger; 2001:91–93.
13. Wingertzahn M, Sato H, Nave R, et al. Uptake and activation of ciclesonide (CIC) in hypotonic and isotonic suspensions and the formation of fatty acid conjugates of desisobutyryl-ciclesonide (des-CIC) in vivo in rabbit nasal mucosa. Paper presented at: 23rd Annual Aspen Allergy Conference; July 26–30, 2005; Aspen, Colorado.
 14. Nave R, Meyer W, Fuhst R, et al. Formation of fatty acid conjugates of ciclesonide active metabolite in the rat lung after 4-week inhalation of ciclesonide. *Pulm Pharmacol Ther*. 2005; 18:390–396.
 15. Wingertzahn MA, Sato H, Nave R, et al. Comparison of nasal tissue concentrations in rabbits following administration of hypotonic and isotonic ciclesonide suspensions [abstract]. *J Allergy Clin Immunol*. 2005;115(suppl):S126. Abstract 503.
 16. Allen DB, Bielory L, Derendorf H, et al. Inhaled corticosteroids: past lessons and future issues. *Allergy Clin Immunol*. 2003;112:S1–S40.
 17. Nave R, Hummel R-P, Wohlsen A, et al. The active metabolite of ciclesonide, des-isobutyryl ciclesonide, forms highly lipophilic fatty acid conjugates in precision-cut rat lung slices [abstract]. *Am J Respir Crit Care Med*. 2004;169(suppl):A91.
 18. Bernstein IL. Is the use of benzalkonium chloride as a preservative for nasal formulations a safety concern? a cautionary note based on compromised mucociliary transport. *J Allergy Clin Immunol*. 2000;105:39–44.
 19. Bachert C, El-Akkad T. Patient preferences and sensory comparisons of three intranasal corticosteroids for the treatment of allergic rhinitis. *Ann Allergy Asthma Immunol*. 2002;89: 292–297.
 20. van Adelsberg J, Philip G, Pedinoff AJ, et al. Montelukast improves symptoms of seasonal allergic rhinitis over a 4-week treatment period. *Allergy*. 2003;58:1268–1276.
 21. Salmun LM, Lorber R. 24-hour efficacy of once-daily desloratadine therapy in patients with seasonal allergic rhinitis. *BMC Fam Pract*. 2002;3:14.
 22. Nasonex (mometasone furoate monohydrate) [product information]. Kenilworth, NJ: Schering Corp; 2003.
 23. Dykewicz MS, Kaiser HB, Nathan RA, et al. Fluticasone propionate aqueous nasal spray improves nasal symptoms of seasonal allergic rhinitis when used as needed (prn). *Ann Allergy Asthma Immunol*. 2003;91:44–48.
 24. Weiler JM, Meltzer EO, Benson PM, et al. A dose-ranging study of the efficacy and safety of azelastine nasal spray in the treatment of seasonal allergic rhinitis with an acute model. *J Allergy Clin Immunol*. 1994;94:972–980.
 25. Weiler JM, Gellhaus M, Donnelly A, et al. Randomized, double-blind, parallel groups, placebo-controlled study of efficacy and safety of Rynatan in the treatment of allergic rhinitis using an acute model. *Ann Allergy*. 1990;64:63–67.
 26. Weiler JM, Meltzer EO. Azelastine nasal spray as adjunctive therapy to azelastine tablets in the management of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 1997;79: 327–332.
 27. Meltzer EO, Weiler JM, Dockhorn RJ, et al. Azelastine nasal spray in the management of seasonal allergic rhinitis. *Ann Allergy*. 1994;72:354–359.
- Requests for reprints should be addressed to:*
Paul H. Ratner, MD
Sylvana Research Associates
7711 Louis Pasteur Dr
Suite 406
San Antonio, TX 78229
E-mail: phratner@swbell.net
-