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ORIGINAL ARTICLE

Intranasal Ciclesonide Coadministration with Inhaled Fluticasone Propionate-Salmeterol does not Suppress Cortisol in Allergic Rhinitis Patients

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Intranasal and inhaled corticosteroid administration concurrently in comorbid allergic rhinitis (AR) and asthma may potentially enhance cortisol suppression. This study determined whether intranasal ciclesonide 200 μ g once daily has an additional effect on cortisol suppression when coadministered with inhaled fluticasone propionate-salmeterol (FP-SAL) 500 to 50 μ g twice daily. Adults ($N = 150$) with perennial AR received FP-SAL and placebo nasal spray during the run-in period. Patients were randomized to ciclesonide or placebo and FP-SAL (43 days). A single 2-mg dose of dexamethasone was administered on the last treatment day. Plasma cortisol decreased during run-in period ($p < 0.001$), indicating cortisol suppression by FP-SAL. After ciclesonide was added to FP-SAL, plasma cortisol was similar in both groups. Dexamethasone decreased mean plasma cortisol ($p < 0.001$), demonstrating that further suppression was possible. Ciclesonide coadministered with FP-SAL did not have an additive effect on cortisol suppression compared with FP-SAL.

Keywords safety, intranasal corticosteroids, cortisol suppression, allergic rhinitis, asthma

INTRODUCTION

Allergic rhinitis (AR) is a chronic inflammatory disease characterized by nasal itching, sneezing, rhinorrhea, nasal obstruction, and often by allergic conjunctivitis in many patients (1). The incidence of AR increases from infancy, peaks in childhood and adolescence, and decreases in the elderly (2). Of the estimated 20 to 40 million Americans with AR, approximately 20% have seasonal AR (SAR), 40% have perennial AR (PAR), and 40% have PAR with seasonal exacerbation, depending on the allergen sensitivity (3, 4). The continued increase in the incidence of AR has become a major cause of morbidity, absenteeism, restricted activity in children and adults, and decreased quality of life for patients (4). Furthermore, AR is associated with a considerable burden on the healthcare system and also appears to be correlated with the development of asthma in later life (5). In contrast to the original belief that AR and asthma are distinct entities of the upper and lower airways, respectively, recent evidence suggests that these two disease states may be linked. A recent report by the American Academy of Allergy, Asthma, and Immunology estimates that 38% of patients with AR have asthma, and other studies estimate that 60% to 78% of patients diagnosed with asthma have coexisting AR (6, 7). Notably, patients with asthma and concomitant AR have more severe asthma than patients without AR (6).

Intranasal corticosteroids (INS) provide greater relief from most of the nasal symptoms of AR compared with other

agents and are more cost-effective than other therapies (8). Moreover, patients with asthma and AR are often prescribed inhaled corticosteroids (ICS), concurrently with an INS. A recent retrospective cohort study demonstrated that the treatment of nasal symptoms with INS in patients with asthma and concomitant AR reduced emergency room visits because of asthma exacerbations (1). However, despite the demonstrated efficacy of ICS and INS in asthma and AR, there are concerns about their systemic safety, particularly the suppression of the hypothalamic-pituitary-adrenal (HPA) axis. Moreover, treatment of patients with AR and comorbid asthma with ICS and concomitant INS may cause additional suppression of the HPA axis beyond that observed with ICS therapy alone and may lead to risk for further systemic side effects. However, the data that are currently available on the concurrent use of ICS and INS have been inconclusive, particularly regarding the possible effects on HPA-axis function (9, 10).

Several clinical studies on ciclesonide, an ICS for the treatment of asthma, have demonstrated systemic safety, including the lack of HPA-axis suppression (11–15). Moreover, the intranasal formulation of ciclesonide nasal spray under development for AR has been shown to be effective in the treatment of AR (16, 17). In a previous study, the effect of administration of once-daily intranasal ciclesonide in combination with orally inhaled hydrofluoroalkane-beclomethasone dipropionate (HFA-BDP), which has a high degree of systemic bioavailability and, therefore, a high potential to cause systemic side effects, was investigated (18). The results demonstrated that there were no additive inhibitory effects of coadministration of intranasal ciclesonide with HFA-BDP on the HPA axis compared with a placebo plus HFA-BDP regimen. The present study was carried out as an additional

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study to determine the effect of coadministration of intranasal ciclesonide with inhaled fluticasone propionate (ADVAIR DISKUS; GlaxoSmithKline, Research Triangle Park, North Carolina), which is one of the most widely prescribed agents and includes an ICS for the treatment of asthma.

The primary objective of this study was to confirm that there was no clinically relevant additive suppression of the HPA axis when ciclesonide nasal spray was concomitantly administered with orally inhaled fluticasone propionate-salmeterol (FP-SAL). The secondary objectives of this study were to evaluate the safety and tolerability of the combined dosing regimen of orally inhaled FP-SAL and ciclesonide nasal spray.

METHODS

Patients

Patients 18 to 60 years of age in good health with a ≥ 1 -year history of PAR of sufficient severity to have required continuous or intermittent treatment in the past and would require treatment throughout the study period were included in the study. Patients must have demonstrated sensitivity through a standard prick test to at least 1 allergen known to induce PAR. Moreover, patients were required to complete a nasal assessment test at screening and must have achieved a total nasal symptom score (TNSS) of at least 6 (of a possible

12), with an individual score of 2 or greater for rhinorrhea or congestion.

Patients with a history or physical findings of nasal pathology, including nasal polyps or other clinically significant respiratory tract malformations; recent nasal biopsy; nasal trauma or surgery; or atrophic rhinitis or rhinitis medicamentosa (all within the last 60 days) were excluded from the study. Patients with a history of respiratory infection or disorder other than AR or asthma within the 14 days before the Screening Period or who had been exposed to corticosteroids over the past 2 months were also excluded from the study. To qualify for randomization, patients must have achieved a 24-hour patient-assessed reflective TNSS of ≥ 4 (out of a possible 12) on at least 5 of the last 7 days of the 10-day Run-in Period.

Study Design and Treatment

This was a randomized, double-blind, parallel-group, placebo- and active-controlled non-inferiority study. Blood and urine samples were collected to establish baseline cortisol levels on the day before the initiation of treatment during the 10-day Run-in Period (day -1). During the 10-day Run-in Period (days 1 to 10), patients received FP-SAL 500-50 μg twice daily ([BID] in the morning and evening) and placebo nasal spray (Figure 1). All patients continued to receive

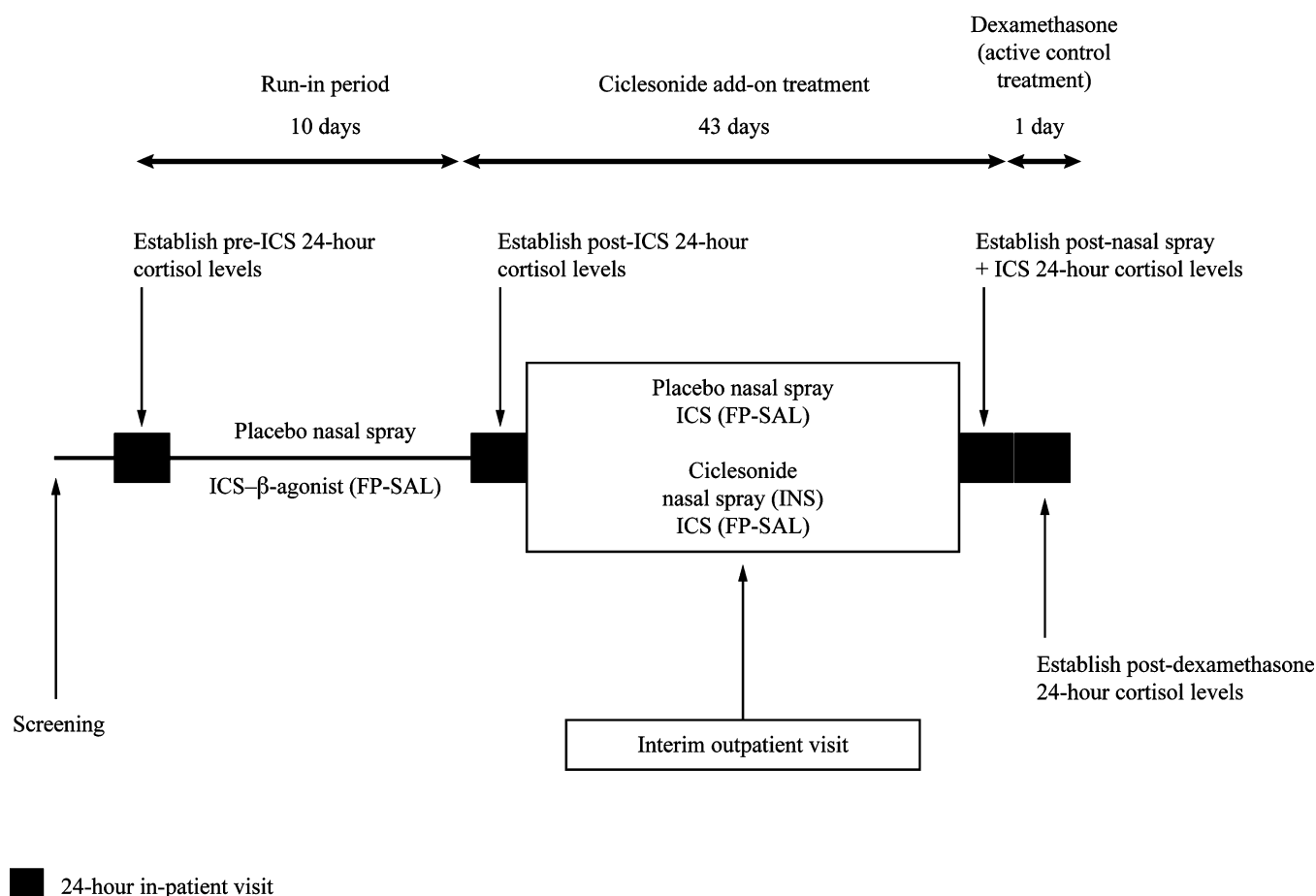


FIGURE 1.—Study design. Abbreviations: ICS, inhaled corticosteroid; FP-SAL, fluticasone propionate-salmeterol; INS, intranasal corticosteroid.

FP-SAL 500–50 μg BID during the 43-day Treatment Period (days 11 to 53). At the initiation of the treatment period, patients were randomized to receive ciclesonide 200 μg or placebo nasal spray (2 actuations per nostril) once daily (QD) in the morning. At the end of the 43-day Treatment Period (day 53), all patients received a single dose of dexamethasone 2 mg in addition to their daily dose of FP-SAL and the randomized nasal spray. The study was completed with a final examination on day 54. This study was approved by an Institutional Review Board and conducted in accordance with the principles of the revised version of the Declaration of Helsinki (19). All patients provided written informed consent.

Safety Measurements

Safety was assessed by estimation of 24-hour plasma cortisol area under the concentration-time curve ($\text{AUC}_{0-24\text{h}}$) and the 24-hour urinary free cortisol at Screening (day –1), the end of the Run-in Period (day 10), the last day of study treatment (day 52), and the day of active control treatment (day 53). Other assessments included a full physical examination, vital signs, and ear, nose, and throat (ENT) examinations that were performed at Screening (day –1), the end of the Run-in Period (day 10), the last day of study treatment (day 52), and at the posttreatment assessment (day 54). An additional ENT examination was done on day 31. Laboratory evaluations were performed during the Screening Period before Treatment Period (days –11 to day –1) and at the posttreatment assessment (day 54). Vital signs and treatment-emergent adverse events (AEs) were monitored throughout the study.

Compliance with Treatment

Treatment compliance was assessed from diary recordings of randomized study medication use as well as bottle weights during patient visits. Compliance with FP-SAL use during the Run-in and Treatment Periods was assessed by diary as well as by recording the dose identified on the DISKUS dose counter during the visits on days 10, 31, and 53. Compliance with the placebo nasal spray during the Run-in Period was also assessed using the diary recordings.

Statistical Methods

The full analysis set included all randomized patients who received at least 1 dose of study medication. The per-protocol (PP) analyses were based on the valid-cases set (all data obtained before a major protocol violation). Because of the non-inferiority design, the primary analyses for the assessments of the effect of ciclesonide were based on the PP population.

The primary comparison was the non-inferiority of ciclesonide treatment versus placebo in changes from days 10 to 52 in plasma cortisol $\text{AUC}_{0-24\text{h}}$ using the PP analysis. The non-inferiority margin of 27.2 $\mu\text{g}\cdot\text{h}/\text{dL}$ was chosen based on a previous study to reflect 20% of the expected means after 10 days of FP-SAL 500–50 μg BID treatment (20).

Additional supporting analyses for the non-inferiority aspect of the study included the PP analysis of plasma cortisol $\text{AUC}_{0-12\text{h}}$, plasma cortisol $\text{AUC}_{0-24\text{h}}$, and all ITT analyses of plasma and urinary cortisol. Results were summarized with 95% confidence intervals (CIs) using an analysis of covariance (ANCOVA) model, incorporating factors of age, sex, treatment group, and baseline cortisol value. Differences

were calculated as the change in the placebo group minus the change in the ciclesonide group. Changes within treatment groups over the study periods were assessed using paired *t* tests.

RESULTS

Patient Disposition and Baseline Demographics

Two hundred eleven patients were screened, and 150 were randomized to receive ciclesonide ($n = 75$) or placebo ($n = 75$). Eighteen patients withdrew from the study: 6 (8.0%) patients treated with ciclesonide and 12 (16.0%) patients treated with placebo. The primary reasons for discontinuation were patient request or unwillingness to continue (2 patients treated with ciclesonide and 5 patients treated with placebo) and lack of compliance (1 patient treated with ciclesonide and 3 patients treated with placebo). Patient demographics and baseline characteristics were generally similar between treatment groups (Table 1). More than half (52.0% and 54.7% in the ciclesonide and placebo groups, respectively) of the patients were male. Baseline averages of AM reflective TNSS values were 7.61 and 7.76 for the ciclesonide and placebo groups, respectively, indicating a patient population with moderately severe PAR.

Treatment Compliance

Assessment of diary recordings regarding study drug use indicated that the mean treatment compliance was comparable between groups (95.6% and 93.3% for ciclesonide and placebo, respectively). The majority of patients were 100% compliant; 2 patients in the ciclesonide group and 5 patients in the placebo group were not at least 80% compliant over the Treatment Period. Compliance as determined by comparing the actual weight of the study drug bottle to the predicted change in bottle weight showed a mean compliance of 94.2% for the ciclesonide group and 94.9% for the placebo group. Compliance for FP-SAL use over the Run-in and Treatment Periods was 96.6% by diary records and 99.2% by dose-counter data.

Safety

Plasma Cortisol. During the 10-day Run-in Period, administration of FP-SAL 500–50 μg BID and placebo

TABLE 1.—Patient demographics and baseline characteristics.

Characteristic	Ciclesonide 200 μg QD ($n = 75$)	Placebo ($n = 75$)
Age, years		
Mean (SD)	30.81 (10.51)	30.72 (9.78)
Range	18–57	18–57
Sex, n (%)		
Male	39 (52.0)	41 (54.7)
Female	36 (48.0)	34 (45.3)
Smoking history, %		
Never smoked	70.7	74.7
Former smokers	17.3	6.7
Current smokers	12.0	18.7
Skin prick test results		
Allergen challenge results, median mm (range)	6 (3–38)	7 (3–35)
Control results, median mm	0 (0–4)	0 (0–0)
Mean 24-hour baseline AM reflective TNSS	7.61	7.76

Data are from the intent-to-treat population.
Abbreviations: QD, once daily; SD, standard deviation; TNSS, total nasal symptom score.

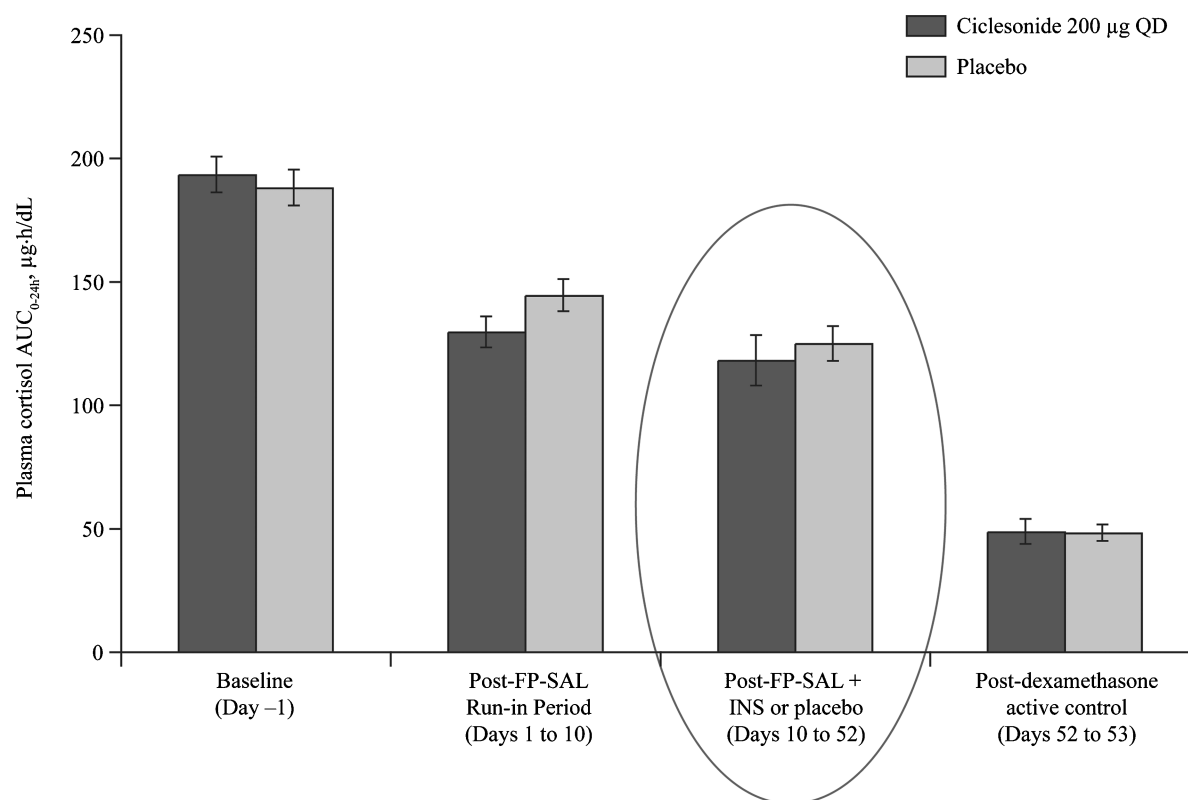


FIGURE 2.—Ciclesonide did not suppress mean plasma cortisol AUC_{0-24h} in patients with perennial allergic rhinitis. Mean values for the per-protocol population. Abbreviations: AUC_{0-24h}, area under the concentration-time curve from 0 to 24 hours; QD, once daily; FP-SAL, fluticasone propionate-salmeterol; INS, intranasal corticosteroid.

nasal spray decreased mean plasma cortisol AUC_{0-24h} from 193.3 µg·h/dL to 129.5 µg·h/dL (33%) and from 188.0 µg·h/dL to 144.4 µg·h/dL (23.2%) in the ciclesonide 200 µg QD and placebo groups, respectively ($p < 0.001$) (Figure 2). Addition of ciclesonide treatment to the FP-SAL 500–50 µg BID regimen (after day 10) did not result in an additional decrease in mean plasma cortisol AUC_{0-24h}. The treatment difference (placebo minus ciclesonide) in the change in AUC_{0-24h} from days 10 to 52 between ciclesonide and placebo was -2.9 µg·h/dL (95% CI for the difference between treatments = $-22.6, 16.8$; Table 2). Thus, the upper limit of this 95% CI of the treatment difference in the change in AUC_{0-24h} from days 10 to 52 between ciclesonide and placebo (16.8 µg·h/dL) was less than the prespecified non-inferiority margin of 27.2 µg·h/dL. Similar results were observed for plasma cortisol AUC_{0-12h} and AUC_{0-24h}. There-

fore, treatment with ciclesonide was non-inferior to placebo and resulted in no relevant additive inhibitory effects on the HPA axis when administered concomitantly with orally inhaled FP-SAL. After a single oral 2 mg dose of dexamethasone on day 53, the mean plasma cortisol AUC_{0-24h} decreased by an additional 71.7 µg·h/dL ($p < 0.001$) in the ciclesonide group and 74.8 µg·h/dL ($p < 0.001$) in the placebo group and confirmed that additional HPA-axis suppression was possible. Similar results were obtained in the intent-to treat (ITT) analysis.

Urinary Free Cortisol. Similar to the results observed for plasma cortisol, there was a measurable decrease in both creatinine-corrected and creatinine-uncorrected urine cortisol levels over the Run-in Period in response to FP-SAL administration ($p \leq 0.001$ and $p \leq 0.002$, for both corrected and uncorrected, respectively; Table 3). Further decreases in both creatinine-corrected and creatinine-uncorrected urine cortisol levels were observed during the Treatment Period (days 10 to 52) when ciclesonide or placebo was administered with FP-SAL, although there were no appreciable differences between the treatment groups. Moreover, further decreases in urine cortisol were observed from days 52 to 53 in both treatment groups in response to dexamethasone administration ($p < 0.001$). Similar results were obtained in the ITT analysis.

Adverse Events. Ciclesonide 200 µg QD was well tolerated, and there were no serious AEs. The frequency of AEs was similar in the two treatment groups (26.7% in the

TABLE 2.—Change in plasma cortisol (µg·h/dL) AUC_{0-24h}.

	Ciclesonide 200 µg QD (n = 69)	Placebo (n = 70)	Treatment difference (95% CI)
Days -1 to 10 (FP-SAL run-in)	-63.0 (5.0)	-44.4 (5.0)	18.6 (4.6, 32.6)
Days 10 to 52 (ciclesonide/placebo)	-12.7 (6.9)	-15.7 (7.1)	-2.9 (-22.6, 16.8)
Days 52 to 53 (dexamethasone)	-71.7 (2.8)	-74.8 (3.0)	-3.1 (-11.2, 5.0)

Data are least-squares means (standard error) for the per-protocol population. Abbreviations: AUC_{0-24h}, area under the concentration-time curve from 0 to 24 hours; QD, once daily; CI, confidence interval; FP-SAL, fluticasone propionate-salmeterol.

TABLE 3.—Change in 24-hour urinary free cortisol.

Urinary cortisol	Ciclesonide 200 µg QD (n = 69)	Placebo (n = 70)	Treatment difference (95% CI)
Corrected for creatinine (µg/g)			
Days -1 to 10 (FP-SAL Run-in)	-15.12 (2.2)	-19.29 (2.2)	-4.17 (-10.37, 2.04)
Days 10 to 52 (ciclesonide/placebo)	-5.59 (1.9)	-8.99 (2.1)	-3.41 (-9.05, 2.23)
Days 52 to 53 (dexamethasone)	-7.11 (1.2)	-10.63 (1.2)	-3.53 (-6.94, -0.12)
Uncorrected for creatinine (µg/g)			
Days -1 to 10 (FP-SAL Run-in)	-12.46 (2.2)	-12.84 (2.2)	-0.39 (-6.42, 5.65)
Days 10 to 52 (ciclesonide/placebo)	-4.28 (2.2)	-5.9 (2.3)	-1.62 (-7.93, 4.68)
Days 52 to 53 (dexamethasone)	-8.07 (0.9)	-10.69 (0.9)	-2.62 (-5.26, 0.03)

Data are least-squares means (standard error) for the per-protocol population.
Abbreviations: QD, once daily; CI, confidence interval; FP-SAL, fluticasone propionate-salmeterol.

ciclesonide group versus 22.7% in the placebo group; Table 4). The majority of AEs were judged as unlikely related to study medication. Almost all of the treatment-related AEs were mild to moderate in intensity. Only one treatment-related AE of severe intensity was reported in each treatment group. The most frequently occurring AE was headache, which occurred with a lower frequency in the ciclesonide group compared with placebo (5.3% in the ciclesonide group versus 8.0% in the placebo group). Epistaxis and pharyngolaryngeal pain each were reported by 2.7% of patients in the placebo group and were not reported in the ciclesonide group.

DISCUSSION

Allergic rhinitis frequently precedes asthma and is a risk factor for the development of asthma (7). Because ICS are considered the gold standard therapy for asthma, coadministration of ICS and INS is an attractive option for optimal symptom control in patients with comorbid AR and asthma. However, coadministration of ICS and INS may increase the corticosteroid burden on the HPA axis than monotherapy with either agent.

The data that are currently available regarding the effects of concurrent use of ICS and INS have been inconclusive (9, 10). In an ad hoc analysis of two studies in patients with asthma and rhinitis who were treated concomitantly with ICS and INS, the results from cosyntropin stimulation suggested that concurrent use of inhaled and intranasal FP did not increase the risk of HPA-axis suppression (21). In contrast, another study using 24-hour plasma and urine cortisol measurements demonstrated that although there was no statistically significant additional cortisol suppression with concurrent treatment of INS in patients receiving ICS therapy, there was a trend toward a greater reduction in cortisol levels when patients received both ICS and INS (22).

TABLE 4.—Adverse events reported by ≥2% of patients in each treatment group.*

Adverse event	Patients, (n%)	
	Ciclesonide 200 µg (n = 75)	Placebo (n = 75)
Total patients experiencing ≥1 adverse event	20 (26.7)	17 (22.7)
Headache	4 (5.3)	6 (8.0)
White blood cell count increase	3 (4.0)	0
Blood glucose increase	2 (2.7)	0
Epistaxis	0	2 (2.7)
Pharyngolaryngeal pain	0	2 (2.7)

Abbreviation: QD, once daily.
*Safety analysis set.

The study described here was conducted as a randomized, placebo- and active-controlled, double-blind, parallel-group trial designed to analyze the effects of intranasal ciclesonide 200 µg QD on plasma cortisol when administered concomitantly with orally inhaled FP-SAL in adults with PAR. One hundred fifty patients were randomized: 75 to the intranasal ciclesonide group and 75 to the placebo group. Ciclesonide 200 µg administered intranasally QD did not demonstrate additive inhibitory effects on the HPA axis compared with placebo when concomitantly administered with orally inhaled FP-SAL.

The present study consisted of a 10-day Run-in Period during which patients received FP-SAL 500–50 µg BID by inhalation and placebo nasal spray followed by a 43-day treatment period during which patients were randomly assigned to either ciclesonide 200 µg nasal spray QD or placebo nasal spray while continuing to receive FP-SAL. Treatment with inhaled FP has been reported to cause HPA-axis suppression in patients with asthma (14, 23). The dose of FP-SAL was chosen to demonstrate observable suppression of the HPA axis after the Run-in Period while preserving the possibility to observe additional cortisol suppression with ciclesonide nasal spray during the Treatment Period. Furthermore, on the last treatment day, patients received oral dexamethasone, which served as an active control to validate the study results by establishing that additional reductions in serum and urine cortisol levels were possible even after treatment with FP-SAL.

As expected, administration of FP-SAL at the approved dose resulted in measurable reductions in mean plasma cortisol AUC_{0–24h} after the 10-day Run-in Period. However, the addition of ciclesonide did not result in further suppression of the HPA axis, as determined by the plasma cortisol AUC_{0–24h}. These findings were further supported by assessment of the 24-hour urine cortisol levels. Furthermore, the decrease in cortisol after the administration of dexamethasone on the last treatment day demonstrated that the HPA axis that was partially suppressed by FP-SAL was further suppressed by dexamethasone. Notably, the lack of additional suppression observed over the Treatment Period with ciclesonide compared with placebo indicates the absence of a meaningful effect of ciclesonide nasal spray on the HPA axis when coadministered with FP-SAL.

The aim of this non-inferiority study was to demonstrate that HPA-axis suppression that may result from the addition of intranasal ciclesonide to an ongoing FP-SAL regimen is not worse than that resulting from the addition of placebo. Accordingly, a non-inferiority test was implemented by comparing the upper end of the 95% CI for the treatment difference,

16.8 $\mu\text{g}\cdot\text{h}/\text{dL}$, with the *a priori*-defined non-inferiority margin of 27.2 $\mu\text{g}\cdot\text{h}/\text{dL}$, a margin that was set with the intention of establishing a level of HPA-axis suppression that was not clinically relevant. This margin was in fact validated by the results of the trial where 20% of the actual mean after the Run-in Period was 27.4 $\mu\text{g}\cdot\text{h}/\text{dL}$.

The results of this study also demonstrated that intranasal administration of ciclesonide 200 μg QD for 6 weeks in combination with orally inhaled FP-SAL in patients with PAR was well tolerated and showed no clinically meaningful differences from placebo in the incidence of AEs.

To further justify the safety of ciclesonide observed in this study, compliance with medication use was also measured using three different methods. The assessment of data from diary cards, bottle weights, and dose-counter data available with the FP-SAL dispenser demonstrated a favorable rate of compliance with the study treatment, indicating that compliance was adequately and reliably assessed during this study. Therefore, the absence of HPA-axis suppression after ciclesonide administration was not as a result of a lack of adherence in the two treatment groups.

In conclusion, in this study, ciclesonide 200 μg QD nasal spray did not have additive inhibitory effects on the HPA axis compared with placebo when administered concomitantly with orally inhaled FP-SAL. Moreover, administration of ciclesonide 200 μg QD nasal spray concurrently with inhaled FP-SAL BID was well tolerated.

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