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A Comparative Study of Inhaled Ciclesonide 160 μg/day and Fluticasone Propionate 176 μg/day in Children With Asthma

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Summary. Ciclesonide (CIC) is an inhaled corticosteroid (ICS) with high anti-inflammatory activity and low incidence of local and systemic adverse effects. The objective of this study was to compare the efficacy and safety of CIC with fluticasone propionate (FP) in children and adolescents with persistent asthma. This was a 12-week, randomized, double blind, parallel-group study. After a 2-to 4-week baseline period, a total of 556 children (ages 6–15 years) with asthma (forced expiratory volume in 1 sec [FEV_1], 50% to 90% predicted) were treated twice daily with CIC 80 μg (ex-actuator, equivalent to 100 μg ex-valve) or FP 88 μg (ex-actuator, equivalent to 100 μg ex-valve) administered via a hydrofluoroalkane-propelled metered-dose inhaler. A statistically significant increase from baseline was observed in FEV_1 for both CIC (285 ± 16 ml) and FP (285 ± 15 ml) ($P < 0.0001$ for both) and in morning and evening peak expiratory flow ($P < 0.0001$ for both). Significant improvements were seen in asthma symptoms, use of rescue medication, and asthma symptom-free days in both treatment groups, without any differences between the treatment groups in changes from baseline. Two FP-treated patients experienced oral candidiasis and one patient experienced voice alteration. Creatinine-adjusted 24-hr urine cortisol levels increased from baseline levels by 10% in the CIC group ($P < 0.05$) and by 6% in the FP group (not significant). The efficacy and safety of CIC 160 μg/day were comparable to those of FP 176 μg/day in children with asthma. **Pediatr Pulmonol. 2006; 41:954–961.**

Key words: inhaled corticosteroid; ciclesonide; fluticasone propionate; clinical effect; oral candidiasis; cortisol; children; adolescents.

INTRODUCTION

Because of their marked clinical effects and good safety profiles, inhaled corticosteroids (ICS) are now recommended by all international guidelines as the preferred first-line therapy for all patients with persistent asthma. Currently available ICS have a high anti-inflammatory activity and it may be difficult to improve the clinical effectiveness of ICS. However, as all ICS have some systemic activity, improving the systemic availability may

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be an area where there is room for improvement with newer substances.

Ciclesonide (CIC) is a high-potency, highly lipophilic, nonhalogenated ICS with pharmacodynamic (PD) and pharmacokinetic (PK) properties that are consistent with effective therapy with a low risk of side effects.[1] Fluticasone propionate (FP) is currently the most potent commercially available ICS and, with respect to PK/PD properties, shares some characteristics of CIC.[2,3] CIC is activated on-site by airway epithelium to the active metabolite, desisobutyryl-ciclesonide (des-CIC), by esterase-mediated hydrolysis.[4] CIC is dispensed via metered-dose inhaler in an inactive form in solution. Therefore, low oropharyngeal deposition of inactive drug occurs after oral inhalation.[2,5] In contrast, FP is administered in an active form in suspension.[6]

In adults and children, CIC has been shown to be effective in patients with persistent asthma.[7–9] It also seems to have fewer side effects on the hypothalamic-pituitary-adrenal (HPA) axis compared with other ICS.[10,11] The limited safety data available for children treated with CIC are generally in agreement with the findings in adults.[12] However, more comparisons with other ICS are needed before firm conclusions can be made. Therefore, the aim of the present study was to compare the efficacy and safety of CIC 80 μg twice daily (BID) with FP 88 μg BID in children and adolescents with persistent asthma.

MATERIALS AND METHODS

Patients

Patients between the ages of 6–15 year with persistent asthma (as defined by the American Thoracic Society) for at least 6 months were eligible.[13] Each patient had to be clinically stable for 4 weeks before screening, without any need for treatment adjustment. At the beginning of the baseline period, forced expiratory volume in 1 sec (FEV_1) percent predicted had to be between 50% and 90% predicted for patients currently on rescue medication only; between 80% and 100% predicted for patients treated with ICS for at least 30 days before screening; and between 50% and 100% predicted for patients taking other controller asthma medication, but no ICS. The study was conducted from September 2001 to October 2002.

Patients with a history of life-threatening asthma, two or more inpatient hospitalizations in the past year, >60 days of systemic steroids within the previous 2 years, use of >400 μg beclomethasone or equivalent 30 days before baseline, current history of smoking, >8 puffs/day of salbutamol for 3 consecutive days before randomization, or suspected noncompliance were to be excluded.

Written consent was obtained before any study-specific procedures were performed. The patient as well as the patient's legal representative/parent had to sign and date the consent form after being informed about the details of the study. The study was approved by the local Ethics Committees of the various centers.

Study Design

The study followed a randomized, multicenter, double-blind, double-dummy, 2-arm, parallel-group design. A baseline period of 2–4 weeks during which the patients used only β_2-agonist as needed was followed by a treatment period of 12 weeks. Randomization criteria included an FEV_1 of 50% to 90% predicted 4 hr after administration of salbutamol, reversibility of $FEV_1 \geq 12\%$ predicted after inhalation of 200 to 400 μg salbutamol, asthma symptom scores ≥1 on 6 of 10 consecutive days before randomization, or ≥8 puffs of rescue medication during the 10 days preceding randomization. Only patients with an adequate inhalation technique using a metered-dose inhaler without a spacer were included. Patients were randomized to either CIC 80 μg BID (ex-actuator dose; i.e., drug that leaves the inhaler), equivalent to 100 μg BID ex-valve (i.e., drug that leaves the metering-chamber valve [the 20 μg difference is because some drug is retained in the mouthpiece of the inhaler]), or FP 88 μg BID (ex-actuator dose, equivalent to 100 μg BID ex-valve) administered via a hydrofluoroalkane-propelled metered-dose inhaler. Randomization was based on a computer-generated list (Program RANDOM[14]) provided to the study center by ALTANA Pharma AG (Konstanz, Germany). The randomization list was generated for a total of 1,600 patients at a ratio of 1:1, and every eligible patient was assigned a random number in sequential order, starting with the lowest number available at a given study center. Blinding was performed using the code labeling and was maintained throughout the study. Neither the investigator nor anyone at the study center knew whether CIC or FP was administered. A premature breaking of the code was allowed in emergency cases only when knowledge of the administered medication was necessary, and those patients were withdrawn from further participation in the study.

Patient Assessments

Efficacy

Lung function was recorded at screening, at weekly intervals during baseline, and at treatment weeks 2, 4, 8, and 12. Measurements were performed as recommended by the American Thoracic Society.[15] Percent-predicted values were calculated as described by Polgar and Promadhat.[16] Morning and evening peak expiratory flow (PEF), use of salbutamol, and asthma symptoms (daytime, nighttime, each scored from 0 to 4) were recorded in dairies throughout the study. A score of 0 was defined as no

asthma symptoms, and a score of 4 represented being awake most of the night because of asthma or being unable to carry out daytime activities because of asthma. The primary efficacy variable was change in FEV_1 from randomization to the end of treatment, and the co-primary variables were the change in morning and evening PEF at the end of treatment. Secondary variables included changes in FEV_1 between the various post-randomization visits; PEF fluctuation; PEF from spirometry; asthma symptom scores; use of rescue medication; number of symptom-free, rescue medication-free, and nocturnal awakening-free days; and dropout rate due to asthma exacerbations. Asthma exacerbations were defined as worsening of asthma symptoms requiring change in the patient's medication other than rescue medication. Patients fulfilling these stipulations met lack-of-efficacy (LOE) criteria.

Safety

Adverse events (AEs) were recorded at each study visit. The nature, incidence rate, intensity, and investigator's causality assessment were documented for each AE. Physical exams with vital signs, laboratory tests (hematology, biochemistry, urinalysis, and serum pregnancy for females of childbearing potential) were performed at screening and at treatment week 12. Collection of 24-hr urine samples for analysis of free urine cortisol and creatinine was performed during week 2 of the baseline period and at the end of treatment.

Statistical Analysis

In this noninferiority study, a per-protocol (PP) analysis based on the valid cases set (i.e., the set of patients without any major protocol violation) was performed. Additionally, to check the robustness of the results, an intention-to-treat (ITT) analysis based on the full analysis set (i.e., the set of all patients who received at least one dose of the respective treatment) was also performed. The statistical analysis focused on noninferiority of CIC compared with FP. Noninferiority acceptance limits for this analysis were: for the primary endpoint, change in FEV_1 (-0.100 L), and for the coprimary endpoints, morning and evening PEF (-12.5 L/min for both). Lung function (FEV_1, morning and evening PEF) was assessed by analysis of covariance (ANCOVA) with age and randomization values as covariates and with sex, treatment, and region/country as fixed factors.

Based on previous studies with CIC, where approximately 80% of all randomized patients completed the study without a major protocol violation, 250 patients per group were to be randomized to achieve 198 patients per group in the PP analysis, thereby providing a 90% power to demonstrate noninferiority of CIC to FP under the assumption of a between-treatment difference of at most 0.015 L and a standard deviation of 0.260 L for the FEV_1 changes.

Change in asthma symptom scores and use of rescue medication were analyzed within treatments using Pratt's modification of the Wilcoxon signed-rank test and the Mann–Whitney *U*-test for differences between treatment groups. Mann–Whitney *U*-tests were also used for the between treatment comparison of the proportions of days without asthma symptoms or the use of rescue medication and nights without awakenings because of asthma and rescue medication-free days. The between-treatment differences in time to LOE were analyzed by the log-rank test.

Twenty-four hour urine cortisol measurements adjusted for creatinine were analyzed by ANCOVA using: (A) the ITT analysis, which included all valid measurements; and (B) the restricted ITT analysis, which included only those urine cortisol measurements with a corresponding urine creatinine value within the normal laboratory range. The robustness of the results was checked using a nonparametric van Elteren test.

RESULTS

Patient Demographics and Baseline Characteristics

Among 728 patients enrolled at 51 investigational centers in 8 countries, 172 patients did not meet randomization criteria and were withdrawn. The remaining 556 patients were randomized and treated (full analysis set), and 511 patients, excluding 23 patients in the CIC group and 22 in the FP group, composed the valid cases set. The demographic and baseline characteristic profiles were similar between the two treatment groups (Table 1). Seventy percent of the patients were Caucasian of European descent, 7% were Caucasian of nonEuropean descent, 4% were black, and 19% were of other ethnic origin. Based on percent predicted FEV_1 values at randomization, 54% of patients in the CIC group and 58% in the FP group had mild persistent asthma, 39% and 38% had moderate persistent asthma, and 7% and 4% had severe asthma, respectively. Sixteen CIC patients and 11 FP patients terminated the study prematurely. The reasons for study discontinuation were LOE (2.4% for CIC, 1.2% for FP), not fulfilling the inclusion criteria, wrong randomization, or refusal to participate (4% for CIC, 3% for FP), and AEs (none for CIC, <1% for FP).

Pulmonary Function

Both CIC and FP treatments were associated with significant and progressive improvements in lung function. FEV_1 improved by 0.298 L for CIC and 0.297 L for FP ($P < 0.0001$ for both vs. baseline, PP analysis) and the mean FEV_1 percent predicted value increased from 79%

TABLE 1— Demographics and Baseline Characteristics

Characteristics	CIC 80 μg BID (n = 254)	FP 88 μg BID (n = 257)
Median age, years (range)	10 (6–15)	10 (6–15)
Sex (male), n (%)	170 (67)	161 (63)
Add-on therapy before baseline, n (%)	80 (31)	67 (26)
Patients with ICS therapy before baseline, n (%)	162 (64)	170 (66)
Dose of ICS before baseline, μg (mean + range)	393 (125–500)	389 (100–500)
Patients without ICS therapy, n (%)	92 (36)	87 (34)
Mean FEV_1, L ± SD*	1.68 ± 0.53	1.67 ± 0.50
Mean FEV_1,% predicted ± SD*	79 ± 10	80 ± 9
FEV_1 % predicted*, n (%)		
≥ 80%	137 (54)	150 (58)
<80% to >60%	98 (39)	98 (38)
≤60%	19 (7)	9 (4)
Mean reversibility: change in FEV_1, %*	20	20
Mean morning PEF (diary), L/min ± SD	257 ± 85	256 ± 86
Mean PEF fluctuation, %*	10	9

CIC, ciclesonide; BID, twice daily; FP, fluticasone propionate; FEV_1, forced expiratory volume in 1 sec; SD, standard deviation; PEF, peak expiratory flow.
Five hundred eleven patients, valid cases set.
*At baseline before randomization.

to 94% for CIC and from 80% to 84% for FP. Noninferiority of CIC versus FP was shown, as the lower limit of the 95% confidence interval for the between-treatment differences (−44 ml, PP analysis) was above the stipulated noninferiority acceptance limit of −100 ml (Table 2). These improvements in lung function were confirmed by ITT analysis (Fig. 1). Statistically significant increases ($P < 0.0001$ for both, PP analysis) in morning PEF (31 L/min for CIC, 34 L/min for FP) were observed in both treatment groups. Comparable results were demonstrated for evening PEF and PEF from spirometry ($P < 0.0001$ for each). For all outcomes, changes over 12 weeks were similar between the two treatment groups (Table 2).

TABLE 2— Differences Between Treatment Groups in Lung Function Variables

	CIC (80 μg BID) − FP (88 μg BID)		
Variable	LS Mean ± SEM	95% CI	Two-sided *P* value
FEV_1, L			
PP	0.001 ± 0.023	−0.044, 0.046	0.961
ITT	0.000 ± 0.021	−0.042, 0.042	0.986
PEF spirometry, L/min			
PP	−5.0 ± 4.2	−13.1, 3.2	0.235
ITT	−2.5 ± 4.0	−10.4, 5.3	0.530
Morning PEF, L/min			
PP	−3.3 ± 4.4	−12.0, 5.4	0.454
ITT	−2.9 ± 4.3	−11.3, 5.5	0.500
Evening PEF, L/min			
PP	0.2 ± 4.3	−8.3, 8.6	0.972
ITT	−0.2 ± 4.1	−8.3, 7.9	0.960

CIC, ciclesonide; BID, twice daily; FP, fluticasone propionate; LS, least squares; SEM, standard error of the mean; CI, confidence interval; FEV_1, forced expiratory volume in 1 sec; PEF, peak expiratory flow; PP, per-protocol analysis; ITT, intention-to-treat analysis.

Subgroup analysis in populations of adequate sample size supported that CIC was comparable with FP across all ages and disease severities. Furthermore, the change in FEV_1 was similar for CIC and FP both in patients pretreated with ICS and in those not pretreated with ICS.

Asthma Symptom Scores and Rescue Medication Use

Median total asthma symptom scores improved from 1.43 to 0.00 in both the CIC and FP groups by PP analysis ($P < 0.0001$ for both). Median change from baseline in daytime asthma symptom score was −0.64 with CIC and −0.58 with FP. Median change from baseline in nighttime

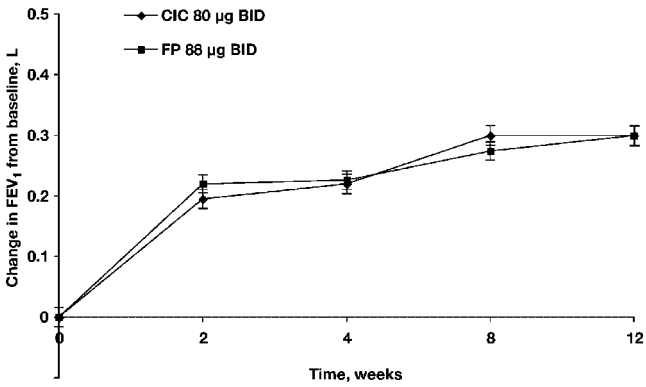

Fig. 1. Ciclesonide (CIC) 80 μg BID and fluticasone propionate (FP) 88 μg BID improve FEV_1 over 12 weeks of treatment. Data are least-squares mean ± standard error of the mean for the intention-to-treat analysis. BID, twice daily; FEV_1, forced expiratory volume in 1 sec.

asthma symptom score was −0.50 with CIC and −0.44 with FP ($P < 0.0001$ for all variables) by PP analysis. Likewise, the median change from baseline in use of rescue medications was −1.14 with CIC and −1.07 with FP ($P < 0.0001$ for both) by PP analysis. These improvements in asthma symptom scores and rescue medication use were confirmed by ITT analysis. Over 12 weeks of therapy, reduction in asthma symptom score and rescue medication use were similar between the two treatment groups (Table 3). Similar results in asthma symptom score and rescue medication use were seen for younger and older children and were independent of disease severity at study entry. Finally, the percentage of asthma symptom-free days, rescue medication-free days, and nocturnal awakening-free days were similar in the two treatment groups (Fig. 2).

Onset of Efficacy

The onset of treatment effect was rapid, for both treatment arms. Asthma symptoms and use of rescue medications improved by day 1 for both treatment arms ($P < 0.0001$ for both groups). The onset of treatment effect for morning PEF was significant by day 1 for FP ($P = 0.002$, PP analysis) and by day 2 for CIC ($P = 0.042$, PP analysis).

TABLE 3— Differences Between Treatment Groups in Asthma Symptoms and Rescue Medication Use

	CIC (80 μg BID) − FP (88 μg BID)		
Variable	Point estimate	95% CI	Two-sided *P* value
Asthma symptom score sum			
PP	0.00*	−0.29, 0.14	0.618
ITT	0.00*	−0.29, 0.14	0.546
Use of rescue medication			
PP	0.00*	−0.29, 0.14	0.606
ITT	0.00*	−0.14, 0.14	0.874
Asthma symptom-free days			
PP	−1.01	−4.82, 2.51	0.580
ITT	−1.01	−4.60, 2.46	0.600
Rescue medication-free days			
PP	0.00	−1.44, 2.13	0.922
ITT	0.00	−1.23, 2.12	0.844
Nocturnal awakening-free days			
PP	0.00	0.00, 0.00	0.632
ITT	0.00	0.00, 0.00	0.812

CIC, ciclesonide; BID, twice daily; FP, fluticasone propionate; C/o, confidence interval; PP, per-protocol analysis; ITT, intention-to-treat analysis.
*Data presented are Hodges–Lehmann point estimates.

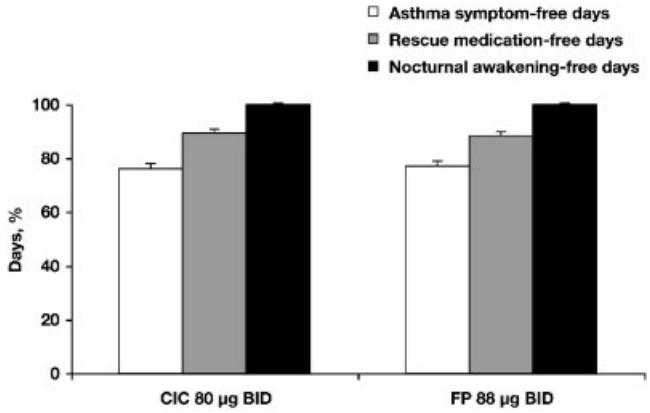

Fig. 2. Improvement in control of asthma symptoms over C/o 12 weeks of CIC 80 μg BID and FP 88 μg BID treatment. The values represent the percentages of asthma symptom-free days, rescue medication-free days, and nocturnal awakening-free days. Data are median values ± standard error for the intention-to-treat analysis. BID, twice daily.

Lack of Efficacy

A total of nine (1.6%) patients (five in the CIC group and four in the FP group) experienced an asthma exacerbation according to predefined criteria for LOE. The time to exacerbation was similar in the two treatment groups and was evenly distributed along the study period. No statistically significant difference was observed in survival analysis of time to LOE between the treatment arms (log-rank $P = 0.689$, PP analysis).

Safety

A similar percentage of patients from both the CIC and FP groups reported AEs (Table 4). In the CIC group, 96% of the AEs were assessed by the investigator as

TABLE 4— Adverse Events Frequently Reported During Treatment Period

	Patients, n (%)	
Adverse event	CIC 80 μg BID (n = 277)	FP 88 μg BID (n = 279)
Rhinitis	22 (7.9)	23 (8.2)
Upper respiratory tract infection	19 (6.9)	18 (6.5)
Pharyngitis	12 (4.3)	11 (3.9)
Asthma	10 (3.6)	8 (2.9)
Headache	10 (3.6)	7 (2.5)
Infection	7 (2.5)	7 (2.5)
Sinusitis	5 (1.8)	9 (3.2)
Bronchitis	5 (1.8)	7 (2.5)
Conjunctivitis	7 (2.5)	4 (1.4)
Flu syndrome	5 (1.8)	1 (0.4)
Gastroenteritis	5 (1.8)	1 (0.4)

CIC, ciclesonide; BID, twice daily; FP, fluticasone propionate.
Percentages are calculated from the total number of patients in the safety set.

"unrelated" or "unlikely related" to study drug, and 98% of the AEs from the FP group were assessed as "unrelated" or "unlikely related" to study drug. Most of the AEs were mild to moderate in intensity and the incidence of local AEs (defined as sore throat, pharyngitis, voice alteration, and oral candidiasis) was low in both treatment arms. No clinically meaningful changes in vital signs or clinical laboratory variables were observed during this study.

Twenty-four hours free urine cortisol levels (adjusted for creatinine) increased in patients treated with both study medications, but the increase was statistically significant only in patients treated with CIC ($P = 0.040$) by ITT analysis. The difference between the two groups was not statistically significant. Based on the nonparametric van Elteren test, 24-hr free urine cortisol levels (median values) increased in the CIC group, whereas the cortisol levels in the FP group were reduced (Fig. 3) in both the ITT analysis and the restricted ITT analysis (which included only those urine cortisol measurements with a corresponding urine creatinine value within the normal range). A statistically significant difference in favor of CIC was seen in the restricted ITT analysis ($P = 0.006$). The findings were similar for patients who were ICS naive and patients who had received ICS prior to study entry—although the differences were numerically greater in previously ICS-naive patients.

DISCUSSION

In this pediatric clinical trial comparing the efficacy and safety of CIC and FP in children with persistent asthma, it was found that, microgram for microgram, CIC was noninferior to FP and that both treatments were well tolerated at clinically effective doses. A PP analysis based on the valid cases set was performed because we wanted the study to be as powerful as possible and it is potentially easier to show noninferiority in the ITT population. Therefore, ITT analysis was performed to check the robustness of the PP results. Results of both analyses support the consistent finding that CIC provides efficacy that is comparable with FP in pediatric patients with asthma.

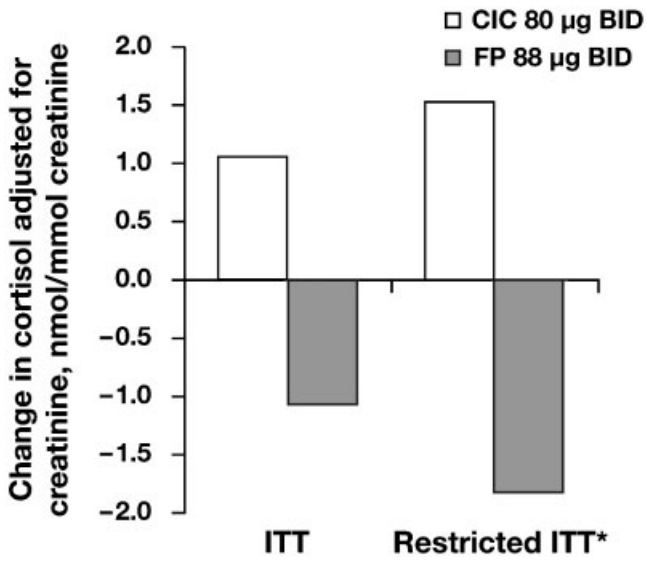

Fig. 3. Analyses of the median change from baseline in 24-hr free urine cortisol levels adjusted for creatinine. The restricted ITT analysis is based on data with 24-hr creatinine values in the normal range. *Significant difference between treatment groups ($P = 0.0062$). ITT, intention to treat; CIC, ciclesonide; FP, fluticasone propionate; BID, twice daily.

Dose–response curves show that low-dose ICS cause a marked clinical improvement in measures of lung function.[17] Subsequent dose increases are associated with much smaller improvements in clinical outcomes.[17–19] Therefore, this study evaluated low doses of both drugs to increase the likelihood of detecting potential differences in clinical effect between the two drugs. A placebo arm was not included for two reasons. First, low-dose CIC and FP were previously demonstrated to be clinically more effective than placebo in controlling asthma and improving lung function in adult and pediatric patients with persistent asthma.[7,9,20–22] Second, 12 weeks of treatment with placebo in patients with moderate and severe asthma would have been deemed unacceptable by many ethics committees[23] and could have caused excessive dropouts that would have markedly reduced the value of a placebo arm. FP was used as the active comparator in the present study because it is the most potent commercially available ICS and is a well-established treatment in pediatric and adolescent patients at the tested dose level.[3,24,25] The marked improvements in lung functions and clinical effects observed in the present study corroborate the clinical effectiveness of low doses of the two drugs found in placebo-controlled trials.

The present results seem comparable with those of other pediatric studies performed with currently available ICS.[20,22,26–29] Ideally, comparisons of two ICS should use two doses of each drug to establish accurate clinical effect ratios.[30] However, despite the use of single doses in the present study, the almost identical clinical effects observed in all three disease severity groups together with the magnitude and speed of onset of the clinical effects strongly suggest that CIC and FP have comparable efficacy.

Local and systemic AEs associated with ICS remain a point of concern for long-term management of asthma. Both CIC and FP were well tolerated in the present study and had similar AE profiles. The incidence of local AEs was low in both groups. CIC has been shown to have low oropharyngeal deposition of active drug. Theoretically, this should reduce the occurrence of unwanted local side effects, such as oral candidiasis and hoarseness. The occurrence of these AEs was so low in the present study that this potential advantage could not be assessed or demonstrated.

In the present study, creatinine-adjusted 24-hr urine cortisol levels were used as a surrogate marker for systemic effects. Because of the duration of the study, we did not investigate effects on growth or bone mineral density.[31–34] Generally, both drugs were found to be safe and without clinically important effects on 24-hr urine cortisol levels. Accurate 24-hr urine cortisol levels are highly dependent on correct sampling of urine. Therefore, because a urine creatinine value within the normal range is considered a good indicator of reliable 24-hr urine sampling, a separate restricted ITT analysis was performed, which included only urine cortisol measurements with a corresponding urine creatinine value within the normal range. This analysis demonstrated a significant difference between the two study medications, with an increase in cortisol for CIC-treated patients but a decrease in cortisol for FP-treated patients. This trend was seen in other analyses as well, but the difference failed to reach statistical significance.

These cortisol results for CIC are consistent with earlier clinical trials in which low and high doses had no detectable adverse effect on the HPA axis.[35,36] The difference in the effects of these two drugs on 24-hr urine cortisol levels in the restricted ITT analysis is in agreement with the findings of Szefler et al.,[11] who found no significant change from baseline in 24-hr serum cortisol area under the curve at CIC doses up to 1,280 μg/day compared with placebo (−4.5%, $P = 0.785$), whereas FP 880 μg BID caused significant cortisol suppression compared with placebo (−39.8%, $P = 0.001$). The small reduction in urine cortisol levels in the restricted ITT analysis during fluticasone treatment is in agreement with the findings of Eid et al.,[37] where 17% of patients treated with FP 176 μg/day developed abnormal, low morning cortisol.

In conclusion, at comparable doses, CIC is as effective as FP in the treatment of children and adolescents with persistent asthma. CIC treatment may be associated with less systemic effect on the HPA axis than FP. Further studies are required to substantiate this.

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