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Original article

Maintenance of asthma control by once-daily inhaled ciclesonide in adults with persistent asthma

Background: Inhaled corticosteroids (ICS) are recommended therapy for persistent asthma, although side effects can limit appropriate use. Ciclesonide, a novel ICS, is activated in the lung, thereby reducing systemic activity and side effects. This 12-week, double-blind, randomized, parallel-group, placebo-controlled study evaluated the efficacy and safety of ciclesonide in adults with persistent asthma.
Methods: After a 2-week baseline period in which current ICS treatment was continued, 329 patients were randomized to receive ciclesonide 160 μg ($n = 107$) or 640 μg ($n = 112$) (ex-actuator doses, equivalent to 200 and 800 μg ex-valve, respectively), or placebo ($n = 110$) once daily in the morning. Efficacy was monitored by asthma symptom scores, rescue medication use, morning and evening peak expiratory flow (PEF) measurements, spirometry, and probability of study completion without experiencing lack of efficacy.
Results: Morning PEF remained stable with either ciclesonide dose but decreased with placebo; the differences were significant ($P < 0.0001$) for both ciclesonide doses *vs* placebo. The forced expiratory volume in 1 s and forced vital capacity decreased significantly with placebo ($P < 0.005$), but were unchanged with ciclesonide. Lack of efficacy was significantly greater for patients switched to placebo (63%) than it was for those treated with ciclesonide 160 μg (30%) ($P < 0.0001$ *vs* placebo) or ciclesonide 640 μg (31%) ($P < 0.0001$ *vs* placebo). There were no significant differences between the two tested doses of ciclesonide with respect to efficacy and safety. Serum and 24-h urine cortisol were unaffected by ciclesonide treatment. Both doses of ciclesonide were well tolerated with no cases of oral candidiasis.
Conclusion: Ciclesonide (160 or 640 μg) once daily in the morning effectively maintains asthma control, does not affect cortisol levels, and has an adverse event profile comparable with placebo in adults with primarily mild to moderate asthma.

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Key words: asthma; ciclesonide; cortisol; inhaled corticosteroids; safety.

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Inhaled corticosteroids (ICS) are regarded as the maintenance therapy of choice for patients with persistent asthma of all severities (1–4). These agents reduce airway inflammation characteristic of asthma and thereby reduce the day-to-day symptoms, progression, and long-term sequelae of uncontrolled asthma. Unfortunately, current surveys of asthma management show that ICS are underused and that asthma is often uncontrolled as a consequence (5, 6).

Among factors that account for the underuse of ICS are concerns about systemic side effects at high doses (6). Inhaled corticosteroids have been shown to suppress serum and urinary cortisol levels (7, 8), to reduce bone density in a dose-related fashion (9, 10), and, in one retrospective database study, to be associated with an increased risk of hip fracture in the elderly (11). Although the benefits of appropriately dosed ICS therapy are widely regarded as outweighing the associated risks, there is a medical need for an ICS with better safety and tolerability.

Ciclesonide is a novel, nonhalogenated glucocorticosteroid that is converted in the airways by esterases to the active metabolite, desisobutyryl-ciclesonide, which has a high binding affinity to glucocorticoid receptors (12). Ciclesonide has a low oral bioavailability (1%), is highly protein bound (99%) in the systemic circulation, and is rapidly metabolized by the liver, resulting in low systemic exposure and low potential for systemic side effects (13). In addition, in a double-blind, randomized, parallel-group study, treatment of asthmatics with ciclesonide once daily (ex-actuator dose 160 μg, equivalent to 200 μg ex-valve) in the morning or evening significantly improved asthma control (14).

The aim of the present study was to evaluate the clinical efficacy, tolerability, and safety of ciclesonide 160 and 640 μg (ex-actuator doses, equivalent to 200 and 800 μg ex-valve, respectively) inhaled once daily in the morning for 12 weeks compared with placebo in patients with persistent asthma.

Patients and methods

Patients

Inclusion criteria. Outpatients of either sex, ages 18–70 years, with a history of persistent asthma as defined by the American Thoracic Society (ATS) were eligible for entry into the study (15). Additionally, patients must have been previously treated with ICS for at least 4 weeks at a stable dose equivalent to 400–800 μg/day beclomethasone dipropionate, triamcinolone acetonide, budesonide, or flunisolide, or 200–500 μg/day fluticasone propionate. To be randomized to study medication, patients were required to have a forced expiratory volume in 1 s (FEV_1) between 60 and 90% of predicted normal before the use of an inhaled bronchodilator and to demonstrate at least one of the following: (i) an improvement in $FEV_1 \geq 12\%$ and ≥ 200 ml within 15–30 min after inhalation of salbutamol 200–400 μg; (ii) airway hyperresponsiveness to methacholine causing a 20% decline in FEV_1 (PC_{20} FEV_1) at a concentration of ≤ 8 mg/ml; or (iii) diurnal peak expiratory flow (PEF) variability of $\geq 15\%$ during at least 3 of 7 days before randomization.

Exclusion criteria. Patients with either an exacerbation of asthma or respiratory tract infection within 6 weeks or admission to a hospital for asthma within 6 months before the study were excluded. Patients with chronic obstructive pulmonary disease and current or former smokers of >10 pack-years were also excluded, as were pregnant or lactating women and premenopausal women not using an effective method of contraception. Further exclusion criteria were symptoms or a condition fulfilling the lack of efficacy (LOE) criteria prior to randomization, use of concomitant medication that was not allowed (e.g. oral corticosteroids), and use of more than eight puffs per day of salbutamol on two successive days during baseline.

Ethics

The study was conducted in accordance with the International Conference on Harmonisation guidelines of Good Clinical Practice and the ethical principles stated in the revised Declaration of Helsinki (Somerset West, October 1996). The protocol was reviewed and approved by the corresponding regional Independent Ethics Committees or Institutional Review Boards. Before enrollment in the study, patients were asked to provide documented informed consent.

Study design

This randomized, placebo-controlled, double-blind, parallel-group study was performed in 25 centers throughout Canada. During the 2-week baseline period, eligible patients continued their usual prescribed ICS at a constant dose while all other anti-asthma medications (with the exception of salbutamol and theophylline) were withdrawn. Morning and evening PEF, use of rescue medication, and asthma-related symptoms were recorded twice daily in a diary. On completion of the baseline period, eligible patients were randomized and had their usual inhaled ICS therapy replaced by either ciclesonide 160 μg (ex-actuator dose, equivalent to 200 μg ex-valve), ciclesonide 640 μg (ex-actuator dose, equivalent to 800 μg ex-valve), or placebo once daily in the morning for 12 weeks. Study medication was administered using four puffs from a metered dose inhaler with hydrofluoroalkane 134a as a propellant and either 40 or 160 μg (ex-actuator dose, equivalent to 50 or 200 μg ex-valve) of ciclesonide or placebo per puff. Salbutamol (100 μg/puff) was provided for as-needed rescue medication. The primary efficacy endpoints in this study were change in morning PEF from patient diary at the end of treatment compared with baseline and evaluation of LOE defined as the occurrence of at least one of the following: clinical exacerbation (increasing asthma symptoms requiring a change in treatment other than increased use of rescue medication); decrease in FEV_1 of at least 20% of the baseline value or to $< 50\%$ of predicted; decrease in diary PEF value by $\geq 20\%$ *vs* the average baseline PEF value (on two successive mornings or evenings during the 7 days directly preceding a clinic visit); nighttime asthma score of ≥ 2 or ≥ 3 for at least four or two nights, respectively, during the seven nights directly preceding a clinic visit; or daytime asthma score of ≥ 3 on at least 4 of 7 days directly preceding a clinic visit. Patients experiencing LOE were withdrawn from the trial. Secondary efficacy endpoints were evening PEF from patient diary, FEV_1, forced vital capacity (FVC), PEF derived from spirometry, and diurnal PEF variability from patient diary, as well as asthma symptom scores and use of rescue medication.

During the 12-week treatment period, patients measured their morning and evening PEF using a peak flow meter (Mini-Wright; Clement Clarke International, Harlow, Essex, UK) and recorded daytime and nighttime symptoms of asthma and use of rescue medication. At baseline, 2, 4, 8, and 12 weeks of treatment, patients underwent spirometry according to the ATS recommendations at clinic visits (16). The measurements were scheduled to be carried out between 6:00 and 10:00 am, thereby ensuring that the tests were performed within ± 90 min of the time of the initial measurements at treatment start. Patients were instructed to withhold their rescue medication for at least 4 h before lung function testing.

For FEV_1 and FVC, the highest value from at least three technically satisfactory attempts was used for analysis. Percentages of predicted values for FEV_1 and FVC were calculated using reference values (17, 18). For PEF, the largest value from three technically satisfactory efforts was recorded.

Asthma symptom scores were recorded as the sum of patient diary assessments of nighttime and daytime symptoms. Nighttime symptoms were classified by the patient every morning on a 5-point scale ranging from 0 (no symptoms) to 4 (awake most of the night because of asthma). Daytime symptoms were scored every evening on a 5-point scale ranging from 0 (no symptoms) to 4 (unable to carry out daily activities as usual). The efficacy of the treatment was assessed by both the investigator and the patient on a 4-point scale ranging from 1 (very effective, good control of asthma) to 4 (ineffective, poor control of asthma).

Adverse events were assessed by the investigator as 'mild,' 'moderate,' or 'severe,' and with 'no relation,' 'unlikely relation,' 'likely relation,' or 'definite relation' to the study medication (19). Possible effects of ciclesonide on the hypothalamic–pituitary–adrenal (HPA) axis were evaluated by measuring cortisol levels in serum (morning sample) and 24-h urinary cortisol analysis just before the start of treatment and again after 12 weeks of treatment. Routine laboratory investigations of hematologic and biochemical parameters as well as urinalysis were performed at a central laboratory at clinic visits just prior to the start of treatment and after 4 and 12 weeks of treatment. In addition, safety was assessed by physical examination including electrocardiogram and vital signs.

Statistical analysis

Sample size was based on the primary variable, morning PEF from the patient diary. It ensured 80% power in correctly concluding that 640 μg ciclesonide administered daily for 12 weeks could increase morning PEF by at least 12.75% above baseline when compared with placebo. A sample size of 72 valid cases per group [i.e. 90 patients in the intention-to-treat (ITT) population] was calculated to be sufficient. Data from the ITT population were used for statistical analyses.

For lung function variables, the last available value of the treatment period was compared with the baseline value. Weekly time averages were compared for parameters from patient diaries. An analysis of covariance was performed using treatment, sex, and center as factors, and age and baseline values as covariates. The dose response was performed using pairwise contrasts. The type I error was set to $\alpha = 0.025$ for one-sided tests between treatments (corresponding to $\alpha = 0.05$, two-sided). A Bonferroni adjustment to $\alpha = 0.0125$, one-sided (corresponding to $\alpha = 0.025$, two-sided) was performed for confirmatory testing of two variables: morning PEF and LOE. For evaluation of LOE, dose dependency was established using the log-rank test for trend. Subsequently, pairwise log-rank tests were used to differentiate between doses.

Asthma symptom scores, daily use of rescue medication, and PEF variability [(highest PEF − lowest PEF)/highest PEF × 100%] were analyzed by nonparametric tests: for between-treatment comparisons, the pairwise Mann–Whitney *U*-test was performed; for within-group comparisons, the Pratt's modification of the Wilcoxon's signed-rank test was used.

Urine and serum cortisol were analyzed using paired *t*-tests (within-group differences) and pairwise independent *t*-tests (between-group differences).

Results

Patient population

Of 440 patients recruited at 25 centers, 329 were randomized and received at least one dose of study medication (ITT population: placebo, $n = 110$; ciclesonide 160 μg, $n = 107$; ciclesonide 640 μg, $n = 112$). All patients had a history of chronic asthma and were on current treatment with 400–800 μg/day of either beclomethasone dipropionate, triamcinolone, budesonide, or 200–500 μg/day fluticasone propionate. The majority of patients had mild to moderate asthma as defined by ATS based on FEV_1 percent predicted. The majority of the patients (64%) were nonsmokers (Table 1). Patients in all treatment groups received similar doses of ICS, and all patients received inhaled short-acting β_2-agonists before the baseline period. Patients in both ciclesonide treatment groups were slightly more likely to have been given inhaled long-acting β_2-agonists in addition before the baseline period. However, there were no significant between group differences with respect to demographic and baseline characteristics.

Among the randomized patients, 65 (59%), 36 (34%), and 43 (38%) patients in the placebo, ciclesonide 160 μg, and ciclesonide 640 μg groups, respectively, withdrew prematurely from the study (44% overall). Most withdrawals were attributed to LOE criteria [114 (35%)], and the incidence of LOE was substantially higher in the placebo group. Other reasons for withdrawal were major protocol violation [17 (5%)], adverse events [5 (2%)], nonmedical reasons [6 (2%)], or other medical reasons [2 (< 1%)].

Table 1. Demographic and baseline characteristics (intention-to-treat population)

Parameter	Placebo	Ciclesonide 160 μg QD	Ciclesonide 640 μg QD
Patients (*n*)	110	107	112
Sex, male/female (%)	54/46	52/48	46/54
Median age, years (range)	41 (19–69)	41 (18–68)	39 (18–69)
Nonsmokers/(ex-)smokers (%)	63/37	64/36	65/35
Daily ICS dosage in baseline period (BDP equivalents; μg/day)			
Mean ± SD	733 ± 245	775 ± 253	756 ± 254
Median	750	1000	1000
Prebaseline use of inhaled long-acting β_2-agonist, *n* (%)	1 (1)	8 (8)	6 (5)
Mean FEV_1 (l) ± SD	2.61 ± 0.70	2.70 ± 0.64	2.66 ± 0.72
Mean FEV_1 (% of predicted) ± SD	77 ± 9	78 ± 9	78 ± 11
Mean reversibility with β_2-agonist (% change in FEV_1), ± SD	21.2 ± 9.7	17.9 ± 8.5	18.8 ± 9.8
Median asthma symptom score sum	0.57	1.00	0.86

Lung function and asthma symptom score baseline data are before randomization. Ciclesonide 160 and 640 μg are ex-actuator doses, equivalent to 200 and 800 μg ex-valve, respectively.

QD, once daily; ICS, inhaled corticosteroids; BDP, beclomethasone dipropionate; SD, standard deviation; FEV_1, forced expiratory volume in 1 s.

Efficacy

Morning PEF. Morning PEF values from patient diaries decreased significantly in patients switched from their usual ICS therapy to placebo (−28 l/min; $P < 0.0001$ *vs* baseline), but remained stable in patients switched to either dose of ciclesonide (Fig. 1). Both doses of ciclesonide were superior to placebo with regard to maintenance of morning PEF from baseline ($P < 0.0001$ *vs* placebo). Differences between the two ciclesonide groups were small and not clinically or statistically significant.

Spirometry. The spirometric variables FEV_1, FVC, and PEF remained unchanged or increased slightly in patients switched to either dose of ciclesonide. Both ciclesonide doses were superior to placebo with respect to improvement from baseline ($P < 0.05$ *vs* placebo), but differences between the two doses were not statistically significant. The change in FEV_1 is shown in Fig. 2. Similarly, increases in FVC [increased from baseline by 0.059 l ($P = 0.2673$) and by 0.009 l ($P = 0.8627$) for ciclesonide 160 and 640 μg, respectively] and PEF [increased from baseline by 4.753 l/min ($P = 0.5296$) and by 5.228 l/min ($P = 0.4895$) for ciclesonide 160 and 640 μg, respectively] were not statistically significant during the 12-week treatment period for either dose of ciclesonide. However,

statistically significant reductions were observed in patients switched to placebo: FEV_1 decreased by 0.144 l (5.4%, $P = 0.0011$ *vs* baseline), FVC by 0.161 l (4.5%, $P = 0.0030$ *vs* baseline), and PEF by 21.613 l/min (5.1%, $P = 0.0055$ *vs* baseline) in patients receiving placebo.

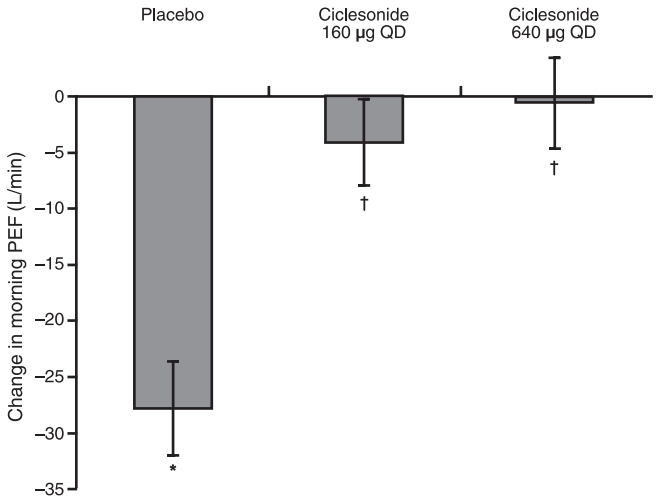

Figure 1. Change in morning PEF from patient diaries following a switch to ciclesonide or placebo therapy (LOCF). Morning PEF significantly decreased with placebo treatment (*$P < 0.0001$ *vs* baseline) but remained stable with treatment in either dose of ciclesonide (†$P < 0.0001$ *vs* placebo for both ciclesonide doses). Intention-to-treat patient population reported here. Data are based on least-squares mean (±SEM). Ciclesonide 160 and 640 µg are ex-actuator doses, equivalent to 200 and 800 µg ex-valve, respectively. PEF, peak expiratory flow; QD, once daily; LOCF, last observation carried forward.

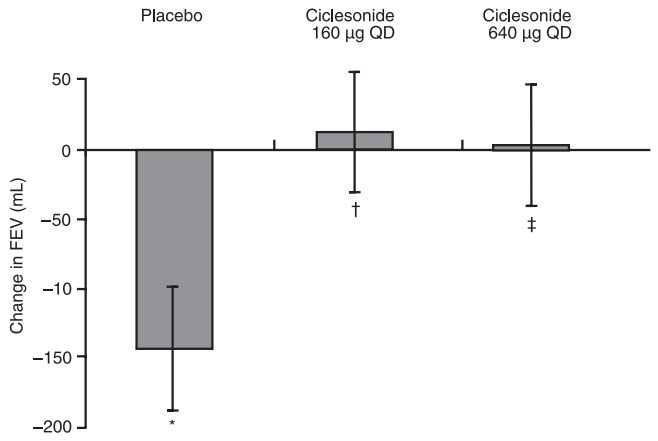

Figure 2. Change in FEV_1 in stable asthmatics after switch to ciclesonide or placebo treatment (LOCF). FEV_1 significantly declined (*$P = 0.0011$) with placebo and was maintained for both doses of ciclesonide. Significant between-group differences were observed (†$P = 0.0070$, ciclesonide 160 µg *vs* placebo; and ‡$P = 0.0108$, ciclesonide 640 µg *vs* placebo). Intention-to-treat population reported here. Data are based on least-squares mean (±SEM). Ciclesonide 160 and 640 µg are ex-actuator doses, equivalent to 200 and 800 µg ex-valve, respectively. FEV_1, forced expiratory volume in 1 s; QD, once daily; LOCF, last observation carried forward.

Asthma symptom scores and use of rescue medication. In patients switched to placebo, significant increases in daily asthma symptoms (score sum of daytime and nighttime scores; $P < 0.0001$ *vs* baseline) and use of rescue medication ($P < 0.0001$ *vs* baseline) were observed. There were no significant changes from baseline in patients switched to either dose of ciclesonide (Fig. 3). Both ciclesonide doses were superior to placebo with regard to the change from baseline in daily asthma symptoms and use of rescue medication ($P \leq 0.0006$ and $P < 0.0001$ *vs* placebo, respectively).

Symptom- and rescue medication-free days. Compared with placebo, patients treated with ciclesonide 640 µg experienced significantly more symptom-free and rescue medication-free days ($P = 0.0429$ and $P = 0.0251$, respectively). A significant difference was also noted for rescue medication-free days between the ciclesonide 160 µg and placebo groups ($P = 0.0372$). There were no significant differences between the two ciclesonide groups.

Evening PEF and diurnal PEF variability. Evening PEF from patient diary decreased by 17 l/min ($P < 0.0001$ *vs* baseline) in patients switched to placebo but remained stable in patients switched to ciclesonide (decreases of 3.5 and 0.7 l/min in the ciclesonide 160 and 640 µg groups,

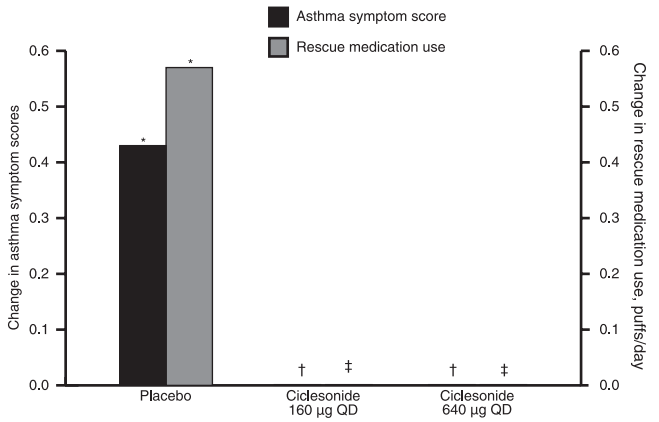

Figure 3. Change in daily asthma symptom scores (sum of daytime and nighttime symptom scores) and use of rescue medication in stable asthmatics switched to ciclesonide or placebo treatment. Asthma symptoms and use of rescue medication significantly increased with placebo (both measures, *$P < 0.0001$) but remained stable with either dose of ciclesonide. Both ciclesonide doses were superior to placebo with regard to the change from baseline in both measures (†$P \leq 0.0006$ and ‡$P < 0.0001$ *vs* placebo, respectively). Intention-to-treat population reported here. Data are presented as medians. Ciclesonide 160 µg and 640 µg are ex-actuator doses, equivalent to 200 and 800 µg ex-valve, respectively. QD, once daily.

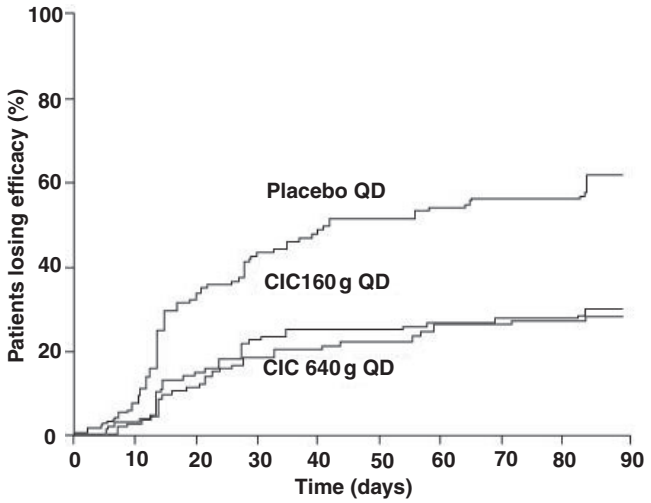

Figure 4. Percentage of patients fulfilling criteria for lack of efficacy after being switched to ciclesonide or placebo. Both ciclesonide doses were superior to placebo ($P < 0.0001$ *vs* placebo). Intent-to-treat population reported here. Ciclesonide 160 and 640 μg are ex-actuator doses, equivalent to 200 and 800 μg ex-valve, respectively. CIC, ciclesonide; QD, once daily.

respectively). Diurnal PEF variability decreased in both ciclesonide groups [from a mean of 6.5% before randomization to a mean of 5.7% at the end of treatment for ciclesonide 160 μg ($P = 0.0135$ *vs* baseline); and from 6.1 to 5.7% for ciclesonide 640 μg], whereas diurnal PEF variability increased in the placebo group (from 7.3 to 8.0%). Both ciclesonide doses were superior to placebo with respect to evening PEF ($P = 0.0066$ and $P = 0.0011$ *vs* placebo) and PEF variability ($P = 0.0088$ and $P = 0.0298$ *vs* placebo, for ciclesonide 160 and 640 μg, respectively), whereas the differences between the two ciclesonide doses were minimal.

Lack of efficacy. The probability of experiencing LOE (i.e. fulfilling at least one of the predefined LOE criteria) increased markedly beginning on days 8 and 9 of the 12-week treatment period and was approximately two times more likely in patients switched to placebo *vs* ciclesonide. The percentage of patients experiencing LOE was significantly greater among those switched to placebo (63%) than it was for those treated with ciclesonide 160 μg (30%) ($P < 0.0001$ *vs* placebo) or ciclesonide 640 μg (31%) ($P < 0.0001$ *vs* placebo, for the log-rank test for trend) (Fig. 4). The pairwise log-rank tests demonstrated the superiority of both doses of ciclesonide over placebo. However, there were no significant differences between the two doses of ciclesonide with regard to LOE.

Effectiveness rating. Both the investigators and patients provided subjective effectiveness rating scores. At the end of treatment, investigators considered the treatment as 'very effective/effective' for 43, 64, and 70% of the patients in the placebo, ciclesonide 160 μg, and ciclesonide 640 μg groups, respectively. The corresponding values for the patients' subjective self-ratings at the end of treatment were 42, 68, and 74%, respectively.

Table 2. Mean serum cortisol and 24-h urine cortisol levels in patients switched to ciclesonide or placebo treatment (intention-to-treat population)

Parameter	Placebo	Ciclesonide 160 μg QD	Ciclesonide 640 μg QD
Serum cortisol (nmol/l)			
n	51	66	61
Baseline	459	468	471
Week 12	463	453	475
P-value *vs* baseline	0.8684	0.3763	0.8370
Urine cortisol (nmol/24 h)			
n	35	63	58
Baseline	96	99	97
Week 12	124	87	106
P-value *vs* baseline	0.2253	0.0975	0.5158

Data are presented as mean values.
Ciclesonide 160 μg and 640 μg are ex-actuator doses equivalent to 200 and 800 μg ex-valve, respectively.
n, Number of patients; QD, once daily.

Safety

Cortisol levels. Mean changes from baseline in serum and urinary cortisol levels were not statistically significant in any of the treatment groups (Table 2). Furthermore, there were no statistically significant differences between treatment groups (serum cortisol differences: 160 μg *vs* placebo, $P = 0.5347$; 640 μg *vs* placebo, $P = 0.9910$; 640 μg *vs* 160 μg, $P = 0.4579$; corresponding urine cortisol differences: $P = 0.0972$, $P = 0.4599$, $P = 0.1766$, respectively). It should be noted, however, that variability for cortisol values was high (data not shown) and only a limited number of patients were available for the paired value analysis.

Adverse events. Adverse events were reported by 222 of 329 (67%) patients during the study. Most of the adverse events were mild or moderate in intensity; severe adverse events accounted for 5, 7, and 6% of the adverse events in the placebo, ciclesonide 160 μg, and ciclesonide 640 μg groups, respectively. The most frequently reported adverse events included asthma (29, 14, and 13% in the placebo, ciclesonide 160 μg, and ciclesonide 640 μg groups, respectively), headache (16, 13, and 17%), upper respiratory tract infection (6, 8, and 13%), and rhinitis (15, 9, and 13%). Asthma-related events, which included asthma exacerbations, wheezing, asthma worsening, or increased asthma symptoms, were reported twofold more frequently with placebo than with ciclesonide. The majority of adverse events (73, 79, and 68% in the placebo, 160, and 640 μg ciclesonide groups, respectively) were assessed by the investigator as 'not related' to study

medication. Few adverse events were assessed as 'likely related' to study medication and included mainly adverse events related to the respiratory system, such as wheezing, dyspnea, or increased cough (incidences of 6, 4, and 8% in the placebo, ciclesonide 160 μg, and ciclesonide 640 μg groups, respectively). A total of seven local adverse events, commonly associated with ICS, were assessed as 'likely' or 'definitely' related to study medication. These events were sore throat ($n = 1$ for placebo, $n = 2$ for ciclesonide 160 μg), voice alteration ($n = 1$ for placebo, $n = 2$ for ciclesonide 640 μg), and dry mouth ($n = 1$ for ciclesonide 640 μg). There were no cases of oral candidiasis. Adverse events leading to premature discontinuation from the study represented mainly a worsening of asthma or events associated with asthma.

Laboratory tests and physical examination. Changes in clinical chemistry and hematology parameters during the treatment period were, in most cases, small and not clinically relevant. Individual clinically significant abnormalities (one each in the placebo and ciclesonide 640 μg groups; two in the ciclesonide 160 μg group) were assessed as 'not related' to the study medication. Vital signs and electrocardiogram did not reveal any clinically relevant changes due to study drug. Overall, both doses of ciclesonide were safe and well tolerated, and there were no differences in safety aspects compared with placebo.

Discussion

The present study demonstrates that ciclesonide (160 or 640 μg) inhaled once daily is superior to placebo in maintaining lung function and asthma control in adults with persistent asthma previously managed with moderate doses of ICS. These results are further supported by a previous study that showed that 160 μg of ciclesonide given once daily is equally effective in the morning or evening in the treatment of mild to moderate asthma (14). Disease control with ciclesonide treatment was also evident from a reduction in asthma symptoms and use of rescue medication. Ciclesonide therapy was well tolerated, showing no evidence of systemic activity with either dosage as measured by serum or urinary cortisol levels. There were no cases of self-reported oral candidiasis.

The present study was designed to challenge the performance of ciclesonide or placebo in clinically stable asthma patients who are currently managed on available ICS. The patients were closely monitored for LOE and, if this occurred, were withdrawn from the trial and treated as necessary. Inhaled corticosteroid withdrawal in a closely monitored study population has been advocated and used as a means to evaluate novel anti-asthma compounds (20, 21). Among patients switched to ciclesonide, lung function variables, asthma symptoms, and use of rescue medication remained stable or showed a slight improvement. In patients switched to placebo, asthma control deteriorated with respect to all variables tested. Morning PEF remained stable in patients treated with either dose of ciclesonide. Moreover, improvement or maintenance of morning PEF 24 h after the administration of ciclesonide demonstrates the robust effect of ciclesonide therapy. Furthermore, patients were withdrawn from the study as soon as deterioration or LOE was detected, a procedure that attempts to ensure patient safety but reduces the difference in the magnitude of outcome measures.

The present study did not show a clear difference in efficacy between the two tested doses of ciclesonide. Despite subtle differences between the two doses of ciclesonide, no clinically relevant dose response was demonstrated. This outcome might be due to several reasons. Patients were withdrawn for reasons of safety at the first sign of LOE (meeting at least one of several predefined LOE criteria). Therefore, withdrawal due to LOE interfered with the assessment of lung function, symptoms, and other variables of asthma control. Furthermore, the asthma severity of the enrolled patient population might have been too mild and the duration of the study might have been too short to detect any significant differences in exacerbation rates. It has been suggested that increasing the maintenance dose of ICS might be of benefit in patients with repeated severe exacerbations. However, the OPTIMA randomized trial demonstrated that doubling the dose of budesonide from 200 to 400 μg/day had only a marginal increase in benefit (22), whereas the FACET study concluded that patients treated with higher dose of budesonide (800 μg/day) had a reduced exacerbation rate compared with patients receiving 200 μg/day (23).

The dose–response curve differs for the various measurable effects of ICS (24). Some variables may not be sensitive enough to distinguish between the two doses and may not detect clinical improvements in the study population. It has been reported previously that a fourfold or greater difference in dose (as was used in this study) is required to show a statistically significant difference in effect with commonly measured outcomes, but even such large differences are not always associated with a significant difference in response (24). In contrast, tightly controlled laboratory-based outcome measures consistently demonstrate dose responsiveness to ICS such as ciclesonide. Taylor et al. (25) have shown a dose-dependent reduction in adenosine-5′-monophosphate responsiveness (a sensitive marker of airway inflammation) among patients with asthma treated with ciclesonide in daily doses of 100, 400, or 1600 μg (ex-valve dose; equivalent to 80, 320, or 1280 μg ex-actuator dose, respectively) compared with placebo.

Ciclesonide at both 160 and 640 μg did not cause a significant reduction in cortisol secretion, and cortisol levels in these treatment groups were comparable with placebo. These data suggest that ciclesonide has little

systemic activity even at high doses (640 μg/day). Both ciclesonide doses were well tolerated. Most of the commonly reported adverse events were related to underlying or concomitant disease, and thus were assessed as 'not related' or 'unlikely related' to the study medication. Other adverse events for which a 'likely relation' could not be excluded were mostly those frequently seen with ICS treatment. Adverse events resulting in a patient's withdrawal from the study were mainly from deterioration of asthma, and the incidence of those events was approximately twofold higher with placebo *vs* ciclesonide treatment.

In conclusion, once-daily ciclesonide (160 or 640 μg) was superior to placebo in maintenance of asthma control in adult patients previously treated with moderate doses of ICS. The effect of ciclesonide on cortisol levels was comparable with that of placebo. Ciclesonide was well tolerated, there were no cases of oral candidiasis, and ciclesonide demonstrated an adverse events profile similar to that of placebo.

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