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ORIGINAL ARTICLE

Efficacy and safety of once-daily inhaled ciclesonide in adults with mild to moderate asthma: A double-blind, placebo-controlled study*

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Efficacy and safety of once-daily inhaled ciclesonide in Japanese adults with mild to moderate asthma: A double-blind, placebo-controlled study
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Background and objective: Inhaled corticosteroids are recommended as first-line therapy for the management of asthma, although side-effects may limit their use. Ciclesonide, a novel pro-drug inhaled corticosteroid, exerts potent and prolonged local anti-inflammatory effects in the lungs, and is considered to have an improved safety and tolerability profile. The aim of this study was to evaluate the efficacy and safety of ciclesonide in adult patients with mild to moderate asthma.

Methods: A placebo-controlled, multicentre, randomized, double-blind, parallel-group study was conducted. During the 4-week baseline period, patients were given 400 μg/day of beclomethasone dipropionate in a chlorofluorocarbon formulation. After the baseline period, 311 patients were given once-daily 100, 200 or 400 μg of ciclesonide or placebo for an 8-week treatment period without the use of a spacer. The primary efficacy variable was morning PEF.

Results: Changes in the morning PEF (least squares mean) at the end of the study were 4.23 L/min ($P < 0.001$) in the 100 μg group, 3.75 L/min ($P < 0.001$) in the 200 μg group, –0.40 L/min ($P < 0.001$) in the 400 μg group, as compared with –24.95 L/min in the placebo group. In the ciclesonide groups, the PEF remained at the same level as the baseline period. No large differences were observed between the placebo group and the ciclesonide groups regarding safety.

Conclusion: Once-daily administration of ciclesonide at doses of 100, 200 or 400 μg was shown to be effective in adult patients with mild to moderate asthma. Ciclesonide is considered to have favourable safety profiles and be well tolerated.

Key words: ciclesonide, inhaled corticosteroid, mild to moderate asthma, once-daily, on-site-activation.

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INTRODUCTION

Bronchial asthma is characterized by chronic inflammation of the airways, and inhaled corticosteroids (ICSs) are recognized as a first-line therapy for the long-term management of persistent asthma of all severities.[1–3] However, long-term treatment with high doses of ICSs raises concerns about systemic side-effects such as reduced adrenal function[4–6] and reduced bone density.[6,7] In addition, ICSs cause local side-effects such as candidiasis of the oropharynx[8,9] and hoarseness.[9,10] The prescription rates of ICSs are reported to be not high.[11–13] Safer and more tolerable ICSs are therefore necessary for the optimal treatment of asthma patients.

Ciclesonide, a novel synthetic corticosteroid, is a pro-drug that is converted by esterases on-site in the lungs to its active metabolite, desisobutyl-ciclesonide (des-CIC), which has a high binding affinity to glucocorticoid receptors and exerts a potent anti-inflammatory activity.[14,15] As ciclesonide and des-CIC are highly lipophilic,[15] they are considered to be retained longer in the lung tissue. Furthermore, des-CIC is expected to show prolonged anti-inflammatory action because it forms fatty acid conjugates at the C-21 position in the lung tissue.[16] This conjugation is reversible, resulting in prolonged pulmonary residence time.[17] Ciclesonide shows low oral bioavailability (1%)[18] and high plasma protein binding rate (99%)[19] and is rapidly metabolized and inactivated in the liver.[20] These features are expected to lead to a reduction in systemic exposure after inhalation of ciclesonide and thus to a reduction in systemic side-effects. In addition, because ciclesonide is formulated as a solution, rather than a suspension, and is delivered by a pressurized metered dose inhaler using hydrofluoroalkane (HFA)-134a as the propellant, the deposition rate of ciclesonide is high in the lung (52%), with only minimum deposition in the oropharyngeal area.[21,22] As ciclesonide is not easily activated in the oropharynx,[23,24] a reduction in local side-effects is expected. The use of a spacer is recommended for the available pressurized metered dose inhalers to improve drug delivery into the lungs or to avoid drug deposition in the oral cavity.[1,2] However, the use of a spacer is considered unnecessary for ciclesonide because of its formulation properties. Therefore, the product is highly portable and simple to use, and these attributes are expected to contribute to good compliance by patients.

In this study, the efficacy and safety of once-daily administration of 100, 200 or 400 μg of ciclesonide were compared with those of placebo in adult patients with mild to moderate bronchial asthma.

METHODS

Patients

From 50 medical institutions in Japan, 435 adult patients aged between 16 and 75 years were recruited into this study. The patients had mild to moderate bronchial asthma according to the Japanese guideline for asthma treatment[1] and had been treated with 400–800 μg/day of chlorofluorocarbon formulation of beclomethasone dipropionate (BDP) or 200–400 μg/day of fluticasone propionate for more than 4 weeks. Of these patients, 311 whose mean morning PEF during the last week of the 4-week baseline period was from 60% to 90% of their predicted PEF were randomly allocated into four treatment groups. The predicted PEF was calculated from regression equations for predicting PEF[25] in Japanese patients. Patients with respiratory complications that may have influenced the evaluation, or patients who had been hospitalized, treated in the emergency room for asthma or treated with systemic steroids within 4 weeks before the baseline period were excluded from the study.

Ethics

The protocol was reviewed and approved by the Institutional Review Boards of all the participating institutions. Written informed consent was obtained from all patients before initiation of the study.

Study design

This was a multicentre, randomized, placebo-controlled, double-blind and parallel group comparative study. During the 4-week baseline period, the patients received chlorofluorocarbon-BDP at a dose of 400 μg/day. At the end of the baseline period, patients who were judged eligible were randomly allocated into fourtreatment groups and received once-daily administration of 100, 200 or 400 μg (ex-valve dose, equivalent to 80, 160 or 320 μg ex-actuator, respectively) of ciclesonide or placebo in the evenings during the following 8-week treatment period. The use of a spacer was not permitted. The patients visited their institutions every 2 weeks. Concomitant use of systemic steroids, theophylline for injection and beta agonists for injection were not permitted. Other anti-asthmatics and treatments were allowed on the condition that they had been used before the baseline period.

Outcome measurements

Each day, patients recorded their morning and evening PEF, asthma symptoms, and use of anti-asthmatics in a designated asthma diary. The PEF was measured using a peak flow meter (Personal Best; Respironics, Murrysville, PA, USA). Mean values for PEF, use of rescue medication and asthmatic score during the treatment period, were the average of daily measures over a two-week period. The means calculated for the last week of the baseline period were defined as the baseline. Use of rescue medication was evaluated based on the number of times per day inhaled short acting beta agonists were recorded in the asthma diary. According to the rating standard of the Japanese Society of Allergology, the asthmatic

score was calculated as the sum of the symptom score based on the asthmatic symptoms and of the therapy score based on the use of asthma medication.[26] An increase in asthma score is associated with worsening asthma and a decrease means improvement. Spirometric measurements were conducted in the institutions every four weeks during the treatment period. Adverse events were assessed for their relationship to the study medications by the clinical investigators. Laboratory tests and vital sign measurements were conducted in the institutions at the start and at the end of the treatment period.

Statistical analysis

The primary variable, the change in morning PEF from the baseline to the end of treatment period, was analysed by analysis of covariance (ANCOVA). Fifty institutions had been grouped into four blocks in advance and the block was used as a covariate in the analysis. In consideration of multiplicity, each treatment group of ciclesonide was compared with the placebo group using a closed testing procedure. The overall type I errors of all three tests, ciclesonide 400 μg versus placebo, 200 μg versus placebo and 100 μg versus placebo, were controlled below the level of significance.

Each ciclesonide group was compared with the placebo group in terms of change in morning PEF every two weeks, change in evening PEF at the end of the treatment period and change in spirometric measurements once every four weeks using the two-sample *t*-test. Comparison of each ciclesonide group with the placebo group in terms of change in use of rescue medication and change in asthmatic score was conducted using the two-sample Wilcoxon test. The analysis of the dose–response relationship was conducted using the Jonckheere–Terpstra test. The two-sided significance level was set at 5% and the one-sided significance level at 2.5%. In analyses, except for the ANCOVA of the primary variable, no adjustments for multiplicity were conducted.

RESULTS

Patient population

Of the 435 patients enrolled in the study, 311 patients were randomly allocated to four groups: the ciclesonide 100 μg group, the 200 μg group, the 400 μg group and the placebo group. Table 1 shows the demographic and baseline characteristics of the patients in each group. The baseline morning PEF (% of predicted PEF) differed among groups ($P = 0.059$, one-way analysis of variance). Analyses using the Pearson's product–moment correlation efficient and Spearman's rank correlation coefficient showed that the differences did not affect the results of the efficacy assessments.

Table 1 Patient demographic and baseline characteristics ($n = 311$)

Parameter	Placebo	Ciclesonide 100 μg†	Ciclesonide 200 μg†	Ciclesonide 400 μg†	*P*-value
Patients (*n*)	79	78	71	83	—
Gender, male/female (*n*)	42/37	45/33	33/38	51/32	0.282
Age (years)	51.0 ± 16.3	50.8 ± 15.0	52.3 ± 15.9	52.1 ± 15.3	0.914
Height (cm)	160.24 ± 8.66	162.30 ± 8.76	161.16 ± 8.66	162.08 ± 8.39	0.418
Weight (kg)	59.58 ± 10.21	61.54 ± 11.52	61.40 ± 11.25	61.90 ± 11.12	0.551
Morning PEF (% of predicted)	73.5 ± 7.8	71.9 ± 8.5	74.0 ± 7.9	75.3 ± 7.8	0.059
Severity, mild/moderate (*n*)	27/52	18/60	16/55	26/57	0.268
ICS treatment before baseline period (*n*)					0.291
BDP; ≥400 μg/day and <800 μg/day	37	37	22	28	
BDP; ≥800 μg/day	3	4	6	7	
FP; ≥200 μg/day and <400 μg/day	14	13	18	21	
FP; ≥400 μg/day	25	24	25	27	
Morning PEF (L/min)	360.41 ± 83.90	367.31 ± 86.16	357.31 ± 87.82	385.97 ± 89.72	0.159
Evening PEF (L/min)	367.28 ± 97.72	375.25 ± 90.19	362.81 ± 87.32	389.81 ± 89.17	0.264
Use of rescue medication (times/day)	0.40 ± 1.00	0.57 ± 1.32	0.42 ± 1.15	0.51 ± 1.20	0.589
Asthmatic score	4.95 ± 3.68	6.49 ± 5.00	5.72 ± 4.58	5.78 ± 4.70	0.334
FEV_1 (L)	2.30 ± 0.83	2.31 ± 0.73	2.25 ± 0.76	2.32 ± 0.79	0.951
FEV_1% (%)	69.84 ± 13.27	70.95 ± 10.36	73.14 ± 9.98	70.00 ± 11.53	0.269
FVC (L)	3.29 ± 0.95	3.26 ± 0.88	3.06 ± 0.94	3.30 ± 0.96	0.380
%FVC (%)	103.61 ± 16.62	101.47 ± 18.38	97.87 ± 15.43	101.50 ± 19.40	0.258

Data are presented as mean ± SD except for patients, gender, severity and ICS treatment before the baseline period. The data of morning PEF, evening PEF, use of rescue medication and asthmatic score are the means in the last one week of the baseline period. %FVC, percentage of predicted FVC. The data of FEV_1, FEV_1%, FVC and %FVC are the measurements at the start of the treatment period.

†Ex-valve dose, equivalent to 80, 160 or 320 μg ex-actuator, respectively.

BDP, beclomethasone dipropionate; FP, fluticasone propionate; ICS, inhaled corticosteroids.

Table 2 Analysis of change in morning PEF from baseline to the end of study[†]

Treatment	Number of patients	LSMean ± SEM		Median[§]
		Change (L/min)	*P*-value[‡]	Change (L/min)
Placebo	79	–24.95 ± 4.34	—	–18.57
100 μg	78	4.23 ± 4.79	<0.001	–0.69
200 μg	71	3.75 ± 4.80	<0.001	0.71
400 μg	83	–0.40 ± 4.26	<0.001	3.57

[†]Change from the start of treatment period to week 8 or termination of administration.
[‡]Comparison of each ciclesonide group with the placebo group (analysis of covariance)
[§]The analysis of dose–response relationship was conducted using the Jonckheere–Terpstra test. Dose–response relationship was statistically significant ($P < 0.001$) when the placebo group was included and not significant ($P = 0.339$) when the placebo group was excluded from the analysis.
LSMean, least squares mean.

Data obtained from the 311 patients in the treatment groups were used in the analyses of efficacy and safety. Of these, 33 patients (17 in the placebo group, five in the ciclesonide 100 μg group, four in the 200 μg group and seven in the 400 μg group) withdrew from the study. The reasons for withdrawal were aggravation of asthma (25 patients), adverse events (four patients) and withdrawal of consent (four patients).

Morning PEF

The least squares mean and SEM (LSMean ± SEM) of change in morning PEF from the baseline to the end of the study for all four groups are listed in Table 2. All the ciclesonide groups showed a significant difference from the placebo group ($P < 0.001$ for all groups). The dose–response relationship was significant ($P < 0.001$) when the placebo group was included and was not significant ($P = 0.339$) when the placebo group was excluded from the analysis.

In all ciclesonide groups, change in morning PEF from baseline, analysed each two weeks, differed significantly from that in the placebo group from week 2 onwards (Fig. 1).

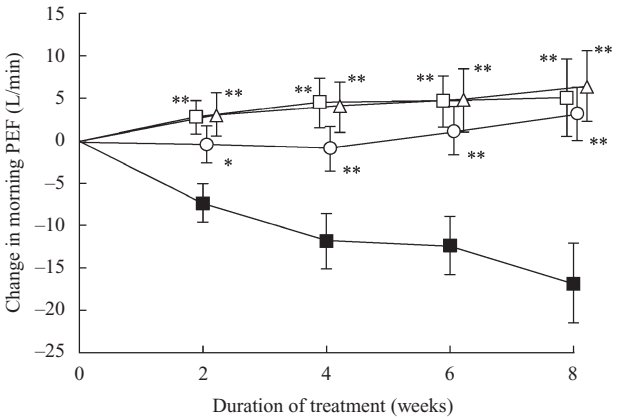

Figure 1 Change from baseline in morning PEF at each time point (mean ± SEM). ■ Placebo, □ 100 μg ciclesonide, △ 200 μg ciclesonide, ○ 400 μg ciclesonide. *$P < 0.05$, **$P < 0.01$.

Evening PEF

Changes in evening PEF (mean ± SEM) from baseline to the end of the study were 1.58 ± 3.70 L/min ($P < 0.001$) in the 100 μg group, 3.38 ± 4.39 L/min ($P < 0.001$) in the 200 μg group and –2.64 ± 3.57 L/min ($P = 0.001$) in the 400 μg group compared with –23.28 ± 4.77 L/min in the placebo group.

Use of rescue medication

Mean changes in the use of rescue medication from baseline to the end of the study were 0.64 times/day in the placebo group, –0.20 times/day in the 100 μg group, 0.01 times/day in the 200 μg group and –0.03 times/day in the 400 μg group. The change in the use of rescue medication in the 100, 200 and 400 μg groups differed significantly from that in the placebo group ($P < 0.001$, $P = 0.007$ and $P = 0.001$, respectively).

Asthmatic score

The change in asthmatic score is shown in Figure 2. The asthmatic score worsened in the placebo group, whereas the score remained at the same level as that during the baseline period in the ciclesonide groups.

Spirometric measurements

The change in spirometric measurements is shown in Table 3. The FEV_1 at the end time point of the study in the placebo group decreased from the value at the start of the treatment period. In the 100, 200 and 400 μg groups, the FEV_1 remained at the same level as

that at the start of the treatment period. The change in FEV_1 in the ciclesonide groups differed significantly from that in the placebo group.

Safety

In the treatment period, adverse events were observed in 46 patients (58.2%) in the placebo group, 42 patients (53.8%) in the 100 μg group, 35 patients (49.3%) in the 200 μg group and 48 patients (57.8%) in the 400 μg group. Adverse events observed in more than 5% of each study group were nasopharyngitis (26 patients, 32.9%) and headache (four patients, 5.1%) in the placebo group; and nasopharyngitis (67 patients, 28.9%) and upper respiratory tract inflammation (12 patients, 5.2%) in the ciclesonide groups. There was no dose-dependent relationship between the occurrence of adverse events and the ciclesonide groups. Serious adverse events during the treatment period were aggravation of asthma symptoms in the placebo group ($n = 2$) and gastric cancers (one in each of the 200 and 400 μg groups). No causal relationship between the adverse events and the study medications were found. Two patients with skin rashes (one in the 100 μg group and one in the 200 μg group), for whom a causal relationship to the study medications could not be excluded, led to their withdrawal from the study. One case of somnolence occurred in the 100 μg group and for this adverse event a causal relationship with the study medication could not be excluded.

Abnormal laboratory tests occurred in four patients in the placebo group (increase in eosinophil percentage ($n = 1$), increased alanine aminotransferase (ALT; $n = 1$), increased γ-glutamyltransferase (γ-GTP; $n = 1$) and urine glucose present ($n = 1$)). In the treatment groups, abnormal laboratory tests occurred in one patient in the 100 μg group (increase in eosinophil percentage) and three patients in the 400 μg group (increased serum creatinine ($n = 1$), decreased platelet count ($n = 1$), urine protein present ($n = 2$), increases in both aspartate aminotransferase (AST) and ALT ($n = 2$)).

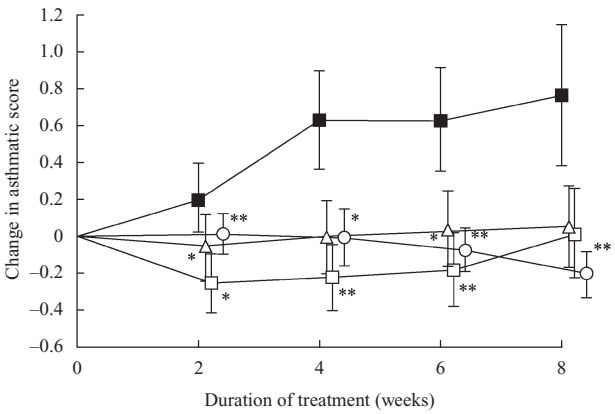

Figure 2 Change from baseline in asthmatic score (mean ± SEM). ■ Placebo, □ 100 μg ciclesonide, △ 200 μg ciclesonide, ○ 400 μg ciclesonide. *$P < 0.05$, **$P < 0.01$.

DISCUSSION

In this study, once-daily administration of ciclesonide at doses of 100, 200 and 400 μg was found to be

Table 3 Change in spirometric measurements at each time point

Item	Treatment	Fourth week		End time point of study	
		Change†	*P*-value§	Change‡	*P*-value§
FEV_1 (L)	Placebo	–0.10 ± 0.31	—	–0.15 ± 0.34	—
	100 μg	0.02 ± 0.23	0.008	–0.01 ± 0.24	0.003
	200 μg	–0.03 ± 0.21	0.110	0.02 ± 0.18	<0.001
	400 μg	0.04 ± 0.27	0.003	–0.03 ± 0.26	0.011
FEV_1% (%)	Placebo	–1.40 ± 6.90	—	–2.68 ± 7.54	—
	100 μg	0.13 ± 4.55	0.117	0.25 ± 4.52	0.004
	200 μg	–0.84 ± 4.86	0.584	–0.61 ± 4.66	0.052
	400 μg	–0.34 ± 5.70	0.306	–0.78 ± 6.69	0.099
FVC (L)	Placebo	–0.11 ± 0.28	—	–0.12 ± 0.40	—
	100 μg	0.00 ± 0.23	0.009	–0.04 ± 0.23	0.150
	200 μg	0.00 ± 0.25	0.021	0.06 ± 0.19	0.001
	400 μg	0.06 ± 0.28	<0.001	–0.03 ± 0.28	0.093
%FVC (%)	Placebo	–3.62 ± 9.06	—	–4.09 ± 13.92	—
	100 μg	–0.95 ± 7.95	0.063	–1.71 ± 7.45	0.191
	200 μg	–0.28 ± 7.98	0.025	1.65 ± 6.40	0.002
	400 μg	1.65 ± 8.69	<0.001	–0.75 ± 9.07	0.076

In the placebo group, significant decreases in all of spirometric measurements were observed at fourth week and the end time point of study, except fourth week of FEV_1% (paired *t*-test, $P < 0.05$). %FVC, percentage of predicted FVC.

†Change from the start of treatment period to fourth week (mean ± SD).

‡Change from the start of treatment period to eighth week or termination of administration (mean ± SD).

§Comparison of each ciclesonide group versus placebo group (two-sample *t*-test).

superior to placebo with respect to the primary variable of change in morning PEF. Superiority of all ciclesonide groups to placebo was further confirmed with regard to evening PEF, use of rescue medication, asthmatic score and FEV_1. These results clearly show that ciclesonide is effective for the treatment of patients with mild to moderate asthma. Chapman *et al*. have shown the efficacy of once-daily administration of ciclesonide at doses of 200 μg and 800 μg with efficacy indices of morning PEF and probability of experiencing lack of efficacy.[27]

No dose-response relationship was observed among the ciclesonide groups in this study. Based on the morning PEF (% of predicted PEF), use of rescue medication, asthmatic score at the baseline period and spirometric measurements at the start of the treatment period, the patients enrolled in this study were considered to have relatively mild symptoms of asthma and had been well controlled with BDP at 400 μg/day during the baseline period. The morning PEF decreased and the asthmatic score worsened throughout the study in the placebo group, while in all the ciclesonide groups the level of symptoms remained the same as during the four-week baseline period, in which patients had been given 400 μg/day of BDP. This shows that asthma patients of the same severity as those enrolled in this study can be treated with 100 μg/day (the minimum dose in the study) of ciclesonide to control their asthma symptoms.

Demonstrating a clear dose–response relationship in clinical studies of ICSs using morning PEF and FEV_1 as parameters is rather difficult, especially in well-controlled patients.[28–30] The dose–response range for ICSs is narrow; potent effects are present at low doses; and the dose-response curve becomes flat within the recommended dose range.[31,32] In addition, patients with asthma of similar severity show great diversity and enrolling patients with comparable clinical features is difficult.[28]

As ciclesonide is not easily activated in the oropharynx, it is expected to cause fewer local side-effects such as hoarseness and oral candidiasis.[23,24] Oral bioavailability of ciclesonide (1%) is the lowest of the ICSs.[18] Ciclesonide and des-CIC have a high plasma protein-binding rate (99%). It is suggested that free compounds that exert systemic action are practically not present in the systemic circulation,[19] so systemic side-effects should be less compared with other available ICSs.

The ciclesonide groups reported similar adverse events to those reported by the placebo group in this study. No adverse event was found to be dose-dependent. Two cases of rash occurred only in the ciclesonide groups, but rash has also been reported with other available ICSs[33,34] and is unlikely to be specific to ciclesonide. Somnolence was also observed in a patient treated with 100 μg of ciclesonide, but this was mild and not of clinical importance.

This study showed that once-daily ciclesonide (100, 200 or 400 μg) was superior to placebo in the maintenance of asthma control in adult patients with mild to moderate asthma. Ciclesonide was well tolerated up to 400 μg/day and showed an adverse events profile comparable to that of placebo.

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