Comparison of Effectiveness in Ciclesonide and Fluticasone Propionate on Small Airway Function in Mild Asthma

Makoto Hoshino1,2

ABSTRACT

Background: Inhaled corticosteroids (ICS) are the mainstay of asthma treatment, but conventional ICS may have limited effectiveness in inflammation and patency of small airways. Ciclesonide is delivered and deposited in the peripheral region of the lung as a small particle corticosteroid. The aim of the study is to compare the effects of ciclesonide with fluticasone propionate on small airway function in asthma.

Methods: Thirty mild persistent asthma patients treated with 200 μg of fluticasone propionate were randomized to receive either ciclesonide 200 μg once daily or fluticasone propionate 100 μg twice daily for 8 weeks. Small airway function was assessed by impulse oscillometry (IOS) and percentage of eosinophil induced sputum.

Results: We observed that ciclesonide significantly improved IOS measured resistance of small airways (R5-R20; p < 0.05), distal reactance (X5; p < 0.01), reactance area (AX; p < 0.01), and decreased late-phase sputum eosinophil level (p < 0.01) compared with fluticasone propionate. There were no significant changes in spirometry indices in either group during the study.

Conclusions: These findings suggest that ciclesonide improves small airway function and inflammation compared with fluticasone propionate in mild asthma. This study provides evidence that IOS and late-phase induced sputum allows detection of changes in the small airways that can not be detected by spirometry.

KEY WORDS

asthma, ciclesonide, fluticasone propionate, impulse oscillometry, sputum eosinophils

INTRODUCTION

Bronchial asthma is characterized by chronic inflammation of the airways, and anti-inflammatory treatment with inhaled corticosteroids (ICS) is recommended as the first line therapy. This inflammation usually affects the whole respiratory tract, from the central to the peripheral airways and alveolar tissues. Recently, there is strong evidence that small airways significantly contribute to total airway resistance and several studies have confirmed peripheral airway involvement in asthma. This new insight in the importance of small airway inflammation in asthma has led to the introduction of ICS with small particle sizes that target the site of inflammation.

Ciclesonide (Teijin Pharma, Tokyo, Japan), a novel synthetic small-particle corticosteroid, is administered as an aerosol using a hydrofluoroalkane (HFA)-134a metered-dose inhaler (MDI), and the deposition rate of it is high in the lung with only minimum deposition in the oropharynx area. Additionally, two-dimensional gamma scintigraphy and three-dimensional single photon emission computed tomography showed that mean percent deposition in peripheral regions was higher than in central regions. Clinical studies show that ciclesonide sig-
cantly improves pulmonary function\textsuperscript{8-10} and reduces airway inflammation in patients with asthma.\textsuperscript{11} Recently, Cohen et al.,\textsuperscript{12} reported that ciclesonide improved small airway parameters reflecting alveolar exhaled nitric oxide and airway trapping on computed tomography, though it is still unknown for other small airway function and inflammation. Fluticasone propionate (GlaxoSmithKline, Tokyo, Japan) dry powder inhaler (DPI) is one of the most widely used ICS in the treatment of asthma and is more centrally deposited in the lung because of the larger particle size.\textsuperscript{13} The importance of ICS distribution throughout the whole lung must be acknowledged when patients with stable control asthma are being maintained with fluticasone propionate.

Spirometry is widely used to assess improvements of lung function, but these data are often insensitive to physiological changes such as in mild asthmatic patients.\textsuperscript{14} Impulse oscillometry (IOS) is a technique used to measure respiratory resistance (R) and reactance (X) at each frequency. IOS also provides data with respect to separate measurements for both large and small airway function.\textsuperscript{15}

Induced sputum has been introduced as a reliable, valid, and responsible method to safely obtain airway secretions.\textsuperscript{16} Corrected sputum early in an inhalation period more clearly reflects proximal airway conditions, in contrast to late-phase sputum which reflects peripheral airways.\textsuperscript{17}

Although the clinical efficacy of ciclesonide and fluticasone propionate was equivalent,\textsuperscript{18} there is no study to compare the effect of these drugs on large and small airway resistance separately. We evaluate the efficacy of ciclesonide on small airway function and inflammation assessed by IOS and induced sputum in patients with mild asthma already being treated with fluticasone propionate.

**METHODS**

**SUBJECTS**

Asthma patients were non-smokers, and had a clear history of relevant symptoms, with documented reversible airway obstruction (>12% improvement in forced volume in one second [FEV\textsubscript{1}] either spontaneously or after administration of inhaled β\textsubscript{2} agonists). Asthma was defined according to the American Thoracic Society criteria. All patients attending the hospital had step 2 severity of asthma,\textsuperscript{1} and who presented with stable symptoms for at least 3 months by using dry powder type ICS. Atopy was diagnosed by the presence of one or more specific serum IgE antibodies against common inhalant allergens. The study was approved by the ethics committee of St. Marianna University School of Medicine, and informed written consent to study protocol was obtained from all subjects.

**STUDY DESIGN**

All patients were treated with fluticasone propionate (GlaxoSmithKline) 100 μg twice daily during an 8 week run-in period. At the end of the run-in period, baseline measurements of pulmonary function and sputum induction were performed. Using the envelope method, eligible patients were randomly allocated to either ciclesonide (Teijin Pharm, Tokyo, Japan) 200 μg once daily or fluticasone propionate 100 μg twice daily for an 8 week treatment period. The envelopes were opened by an independent pharmacist involved in neither the diagnosis nor treatment of the patients evaluated. No other asthma medications were permitted except for inhaled β\textsubscript{2} agonists as required. Pulmonary function and induced sputum were repeated after 8 weeks of treatment. Asthma symptoms and control were evaluated with the asthma control test (ACT) developed by QualityMetric Incorporated.\textsuperscript{19} The patients showed good compliance and adherence to treatment with either ciclesonide or fluticasone propionate.

**PULMONARY FUNCTION MEASUREMENTS**

Spirometry and IOS study was done according to the ERS task force recommendations.\textsuperscript{20} The measurements of spirometry function (FEV\textsubscript{1}, FEV\textsubscript{1}/forced vital capacity [FVC], forced expiratory flow 25-75% [FEF25-75%], maximum expiratory flow rate at 50% [MEF50%] and 25% of FVC [MEF25%]) were conducted by FUDAK-77 (Fukuda Electronics, Tokyo, Japan). These parameters except for FEV\textsubscript{1}/FVC are expressed as percentages of predicted values according to the prediction equations of the Japanese Society of Chest Disease.\textsuperscript{21} For IOS, MasterScreen IOS (Jaeger, Wurzburg, Germany) was used. Five IOS parameters were evaluated: (1) airway resistance at 5 Hz (R5), a total index influenced both large and small airways; (2) airway resistance at 20 Hz (R20), an index of large airways; (3) subtracting R5 from R20 (R5-R20), an index of frequency dependence of resistance, reflective of small airways function; (4) reactance at 5 Hz (X5), which is considered to indicate the capacitive reactance in small airways; and (5) an integrated area of low-frequency reactance (AX).\textsuperscript{15,22,23} This parameter included all negative values of respiratory reactance between 5 Hz and the frequency at which reactance is zero, and may reflect small airway function.\textsuperscript{15}

**SPUTUM INDUCTION AND PROCESSING**

After inhalation of 200 μg of salbutamol via a metered dose inhaler, the subjects inhaled 5% hypertonic saline for 15 minutes using an ultrasonic nebulizer (NE-U22, Omron, Tokyo, Japan) and all induced samples were sequentially collected over 30 minutes. We regarded the first induced sputum samples during 15 minutes of inhalation as early-phase samples, while those finally collected after inhalation were taken as...
Effects of Ciclesonide on Small Airways

Table 1  Patients characteristics

<table>
<thead>
<tr>
<th></th>
<th>Ciclesonide group</th>
<th>Fluticasone propionate group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (n)</td>
<td>14</td>
<td>16</td>
<td>0.527</td>
</tr>
<tr>
<td>Gender (Male/Female)</td>
<td>6/8</td>
<td>6/10</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>50.1 ± 14.7</td>
<td>45.3 ± 14.1</td>
<td>0.174</td>
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<tr>
<td>Disease duration (years)</td>
<td>9.8 ± 9.7</td>
<td>12.3 ± 13.0</td>
<td>0.290</td>
</tr>
<tr>
<td>Atopy/Non-atopy</td>
<td>10/4</td>
<td>13/3</td>
<td>0.542</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD.

Table 2  Spirometry function data at baseline and after treatment with ciclesonide or fluticasone propionate

<table>
<thead>
<tr>
<th></th>
<th>Ciclesonide group</th>
<th>Fluticasone propionate group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>After</td>
<td>Before</td>
<td>P-value</td>
<td></td>
</tr>
<tr>
<td>FEV1 (%predicted)</td>
<td>91.9 ± 1.5</td>
<td>93.7 ± 11.4</td>
<td>0.657</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>73.6 ± 11.6</td>
<td>75.2 ± 2.2</td>
<td>0.713</td>
</tr>
<tr>
<td>FEF25-75 (%predicted)</td>
<td>53.9 ± 30.4</td>
<td>59.6 ± 18.8</td>
<td>0.165</td>
</tr>
<tr>
<td>MEF50 (%predicted)</td>
<td>50.9 ± 7.8</td>
<td>57.2 ± 18.1</td>
<td>0.092</td>
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<tr>
<td>MEF25 (%predicted)</td>
<td>35.4 ± 23.2</td>
<td>39.2 ± 7.6</td>
<td>0.161</td>
</tr>
<tr>
<td>After</td>
<td>Before</td>
<td>P-value</td>
<td></td>
</tr>
<tr>
<td>FEV1 (%predicted)</td>
<td>98.6 ± 18.2</td>
<td>99.7 ± 16.8</td>
<td>0.738</td>
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<tr>
<td>FEV1/FVC (%)</td>
<td>75.0 ± 7.1</td>
<td>75.1 ± 6.9</td>
<td>0.884</td>
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<tr>
<td>FEF25-75 (%predicted)</td>
<td>58.5 ± 21.5</td>
<td>58.2 ± 34.2</td>
<td>0.709</td>
</tr>
<tr>
<td>MEF50 (%predicted)</td>
<td>55.2 ± 16.9</td>
<td>53.7 ± 29.6</td>
<td>0.713</td>
</tr>
<tr>
<td>MEF25 (%predicted)</td>
<td>37.7 ± 18.7</td>
<td>36.3 ± 12.7</td>
<td>0.678</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD.

FEV1, forced expiratory volume in one second; FVC, forced vital capacity; FEF25-75, forced expiratory flow 25-75%; MEF50, maximum expiratory flow rate at 50% of FVC; MEF25, maximum expiratory flow rate at 25% of FVC.

late-phase samples. Adequate plugs of sputum were separated from saliva. Sputum was transferred in small amounts and finely distributed and smeared onto microscopic slides. Each smear was air dried and stained with May-Grunwald-Gimsa, and differential cell counts were obtained from 400 non-squamous cells by a blinded investigator.

STATISTICAL ANALYSIS

Data are expressed as mean ± SD. All statistical analyses were performed using Stat View software (SAS Institute, Cary, NC, USA). The results of data were analyzed by using the paired t test, or its equivalent non-parametric Wilcoxon’s signed-rank test for IOS parameters with non-normal distribution. Significance was established at a \( p < 0.05 \) (two-tailed).

RESULTS

A total of 36 patients were approached and agreed to participate in the study. Six patients were unable to tolerate the hypertonic saline challenge. None of them occurred in asthma attack, but these patients were again treated with 200 μg salbutamol after hypertonic inhalation method. Fourteen patients in the ciclesonide group and 16 patients in the fluticasone propionate group completed the study. Patients’ characteristics are shown in Table 1. There was no significant difference between the two groups in terms of clinical data.

The values of spirometry measurements at baseline and 8 weeks after treatment are given in Table 2. None of the spirometry indices showed significant changes in either the ciclesonide or the fluticasone propionate group. At baseline, no significant differences in IOS parameters were observed in patients who were assigned to ciclesonide or fluticasone propionate treatment groups. There were significant improvements in airway resistance R5 (0.35 ± 0.10 to 0.31 ± 0.09 kPa/L/s; \( p < 0.05 \)), R5-R20 (0.08 ± 0.07 to 0.06 ± 0.06 kPa/L/s; \( p < 0.05 \)), reactance X5 (-0.14 ± 0.04 to -0.10 ± 0.04 kPa/L/s; \( p < 0.01 \)), and reactance area A (0.61 ± 0.52 to 0.44 ± 0.42 kPa/L; \( p < 0.01 \)) except for R20 in the ciclesonide group. However, IOS parameters remained unchanged in the fluticasone propionate group (Fig. 1).

In the ciclesonide group, eosinophil percentage in the late-phase sputum significantly decreased from 12.2 ± 6.9% to 6.9 ± 3.2% \( (p < 0.01) \), but did not decrease in the early-phase sputum. In contrast, there were no significant changes in sputum eosinophils in the fluticasone propionate group (Fig. 2).

The ACT scores in the ciclesonide group significantly improved from 21.2 ± 1.9 to 23.3 ± 1.2 \( (p < 0.01) \) and use of rescue β2 inhalation mainly decreased in the 5 items of ACT, however no significant improvements were seen for ACT scores in the fluticasone propionate group (Fig. 3).

DISCUSSION

We demonstrated that treatment with 200 μg ciclesonide once daily can specifically improve parameters reflecting patency and inflammation of small airways in mild asthmatic patients who were treated with 100 μg fluticasone propionate twice daily, even though they were stable from clinical symptoms and ordinary pulmonary function. In order to compare the effects
Fig. 1 Changes in impulse oscillometry (IOS) measured airway resistance of R5, R20, R5-R20, reactance X5, and reactance area (AX) in the ciclesonide- and fluticasone propionate-treated groups. R5, airway resistance at 5 Hz; R20, airway resistance at 20 Hz; R5-R20, airway resistance at 5 to 20 Hz; X5, airway reactance at 5 Hz; AX, integrated area of low frequency reactance. Horizontal bars represent mean values.
of ciclesonide with fluticasone propionate on small airway function, we selected mild persistent asthma treatment with ICS alone, because most asthmatic patients with more step 3 severity had already been medicated with other long-acting β2 agonists, and/or leukotriene receptor antagonists.

In the last decade, therapeutic research related to asthma specially focused on targeting small airways. The sizes of ICS particles strongly affected the aerodynamic properties of the drugs and its delivery to distal airways. Among the ICS, fluticasone propionate-DPI has the largest mass median aerodynamic diameter (MMAD of 5.4 μm) and deposited in the lungs with 10 to 16%. In contrast, the ciclesonide
HFA-MDI delivers small particles (MMAD of 0.9 μm) and achieves delivery of >50% of ciclesonide dose to the lung.6,7 As well, the small particle size of HFA-beclomethasone dipropionate (BDP) has resulted in improved lung deposition with 50 to 60% of the emitted of deposited throughout the Airways.23 Our results showed the lack of significant changes in spirometry function data between ciclesonide and fluticasone propionate treated groups. It had been reported that ciclesonide did not significantly improve small airway parameters such as FEF25-75 and closing volume.12 However, some of the small airway parameters had a large variability, thus reducing statistical power. Furthermore, spirometric data are most commonly reported due in part to the large volume of information on the use of tests such as FEV1 measurement. The IOS is more sensitive in measuring small airway dysfunction and recognizing subtle changes in the Airways.14,26 Frequency dependent changes in resistance have been demonstrated in small airway disease.27 The difference between R5 and R20 (R5-R20) as an index of frequency dependence of resistance was reported to be a sensitive index of peripheral airway obstruction.22 As inductive reactance is negligible at low frequency, X5 can be considered as capacitive reactance and reflects small airway dysfunction.28,29 AX is an index of small airway obstruction complementary to frequency dependence of resistance. The close correlation among spirometric values of FEF25-75 and these IOS parameters are consistent with these indices reflecting small airway function.22 Thus the changes in R5-R20, X5, and AX in this study indicate beneficial small airway effects caused by reaching ciclesonide to the distal Airways. Assessment of respiratory mechanics over time with IOS might offer important information about the pulmonary response of asthmatic patients to therapy that is not reflected by spirometric measurements.

The eosinophil percentage in late-phase sputum showed a significant decrease after treatment with ciclesonide compared with fluticasone propionate. It has been demonstrated that the eosinophil percentages in induced sputum was significantly correlated with those in water obtained by bronchial washing, and bronchoalveolar lavage, suggesting that sputum was useful to evaluate the airway inflammation.30 According to the study of Gershman et al.,17 in sputum collected at each 4 minute interval during 20 minute induction by inhaling 3% saline, sputum samples in early-phase showed higher concentrations of mucin-like proteins originating from proximal Airways, while sputum samples collected 12 minutes after inhalation contained higher levels of surfactant protein (SP)-A, which is more likely to exist in the peripheral Airways alveoli. Although we did not measure SP-A values, we suppose that the 5% hypertonic saline inhalation technique has similar results.31 The large Airways compartment of the lung was sampled in the early phase by sputum induction, and the smaller Airways were sampled in the late phase. We found that in asthma being maintained with fluticasone propionate administration, residual peripheral eosinophilic inflammation was ameliorated by switching to ciclesonide. Our findings are in agreement with a study by Ohbayashi et al. who found that fine particle sizes of ICS (HFA-BDP) can more effectively suppress eosinophilic inflammation in the peripheral Airways for longer term treatment with fluticasone propionate in asthma.32 Using surgically resected lung specimens from asthmatic patients, eosinophils were significantly reduced by treatment with chlorofluorocarbon-BDP or fluticasone propionate in the large Airways, but not in the small Airways.33 Hauber et al. reported that HFA-flunisolide (MMAD of 1.2 μm) effectively reduced eosinophilic inflammation in small Airways by transbronchial biopsy.34 Our results raise the possibility that ciclesonide may be more effective than fluticasone propionate for improving function in the small Airways of asthmatic patients through more effective suppression of peripheral Airways inflammation.

We observed a significant increase of ACT scores after switching fluticasone propionate to ciclesonide. The ACT is a patient administered survey for assessing asthma symptoms, nocturnal symptoms, rescue medications, and role limitations.19 The ACT score is reliable, valid, and responsive to changes in asthma control over time. Although all asthmatic patients showed good compliance and adherence, it may be a possible reason for the difference of drug compliance and side effects between once daily ciclesonide and twice daily fluticasone propionate. Our findings show that the improvement in symptom control after treatment with ciclesonide contributes to changes in pulmonary function and inflammation. Although all asthmatic patients showed good compliance and adherence, it may be a possible reason for the difference of drug compliance and side effects between once daily ciclesonide and twice daily fluticasone propionate. Current asthma guidelines do not recommend preventative treatment for asthma, but our study warrants evaluating the degree of involvement of small Airways and their response to other ICS therapy.

In conclusion, we have demonstrated that ciclesonide improves both small Airways function and inflammation in patients with mild asthma treated with fluticasone propionate. These beneficial findings suggest that IOS and the late-phase induced sputum with hypertonic saline are useful tools to assist in diagnosing and monitoring small Airways involvements in asthma.

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32. Ohbayashi H, Adachi M. Hydrofluoroalkane-beclomethasone dipropionate effectively improves airway eosinophilic inflammation including the distal airways of patients with mild to moderate persistent asthma as compared with fluticasone propionate in a randomized open double-cross study. *Allergol Int* 2008;57:231-9.


34. Hauber HP, Gottfried M, Newman K et al. Effect of HFA-