Usefulness of Suplatast Tosilate in Patients with Mild Bronchial Asthma —Comparison with Beclomethasone Dipropionate

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ABSTRACT

Background: Suplatast tosilate is a type 2 (Th2) cytokine inhibitor that blocks the production of IgE antibodies and the invasion of tissues by eosinophils during an allergic reaction. Suplatast tosilate ameliorates asthma symptoms and airway hypersensitivity by inhibiting production of the Th2 cytokines interleukin (IL)-4 and IL-5.

Methods: In the present study, a comparative examination of the therapeutic effects of suplatast tosilate was carried out in patients with mild intermittent and mild persistent asthma by randomly allocating 35 adult patients to a suplatast tosilate group (n = 18; 100 mg suplatast tosilate three times daily) and a beclomethasone dipropionate (BDP) group (n = 17; 200 µg BDP twice daily) for 6 weeks of treatment.

Results: The suplatast tosilate group required more time than the BDP group to show improvement in peak expiratory flow, but at week 6 the change from baseline was nearly the same in both groups. A significant improvement was observed for both groups in the peripheral blood eosinophil ratio, serum eosinophil cationic protein (ECP) levels, induced sputum ECP levels, forced expiratory volume in 1 second, and airway hypersensitivity, but induced sputum ECP level was lower in the BDP group than in the suplatast tosilate group. Total IgE levels decreased in the suplatast tosilate group only.

Conclusions: We conclude that suplatast tosilate may be useful in long-term management of mild bronchial asthma.

KEY WORDS

airway hypersensitivity, anti-allergic agents, antiasthmatic drugs, bronchial asthma, inflammatory mediators

INTRODUCTION

The Type 2 helper T cell (Th2) cytokines interleukin (IL)-4 and IL-5 are known to be involved in the modulation of immunoglobulin E (IgE) production by B cells, as well as in the differentiation, proliferation, and activation of eosinophils.1 Suplatast tosilate, a dimethylsulfonium anti-allergy drug that blocks IgE antibody production and eosinophilic issue invasion by inhibiting the Th2 cytokines IL-4 and IL-5, is associated with clinical improvement of asthma symptoms and reductions in airway hypersensitivity.2,3

In recent years, supplementary treatment with suplatast tosilate has been reported useful in decreasing steroid dosage for patients with severe asthma.4 Researchers have also reported that in patients suffering from mild intermittent and mild persistent bronchial asthma, suplatast tosilate inhibited eosinophilic airway inflammation and thus reduced airway hypersensitivity. These effects were particularly pronounced in atopic asthma.5 However, there are only a few studies available that compare the usefulness of suplatast to inhaled steroids.

The present study is a prospective randomized
comparing the usefulness of suplatast tosilate with beclomethasone dipropionate (BDP), an inhaled steroidal agent that is currently the drug of first choice, controlled study in patients with mild intermittent and mild persistent asthma in such treatment.

**METHODS**

Subjects included 35 mild bronchial asthma outpatients at the Department of Respiratory Tract Medicine, 2nd Education Hospital, Fujita Health University. The group consisted of 12 men and 23 women 19 to 74 years of age. Atopic asthma was diagnosed in 17 cases and non-atopic asthma in 18 cases, with 13 cases meeting the criteria for step 1 (mild intermittent) asthma and 22 cases for step 2 (mild persistent) asthma according to the 2003 Guidelines for Prevention and Control of Asthma. No patients were using bronchodilators or steroidal or anti-allergy drugs (Table 1). No significant difference was found between the two groups in any of these categories.

The study design is shown in Figure 1. All patients were provided with informed consent and the study design was approved by the university ethics committee. After a 2-week run-in period, the patients were randomly allocated to the suplatast tosilate-treated group (18 patients) or the BDP-treated group (17 patients).
Changes in PEF: Changes in peak expiratory flow during 6 weeks of treatment in adult patients with intermittent and mild persistent asthma: suplatast tosilate group (n = 18, 100 mg suplatast tosilate three times daily) and BDP group (n = 17, 200 μg BDP twice daily).

Table 2  Changes in inflammatory markers

<table>
<thead>
<tr>
<th></th>
<th>Suplatast tosilate</th>
<th>BDP</th>
<th>Change between groups</th>
<th>p value</th>
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<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
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<tr>
<td>eosinophils</td>
<td>5.385±0.924</td>
<td>3.769±0.482*</td>
<td>5.300±0.761</td>
<td>4.200±0.646*</td>
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<td>serum ECP</td>
<td>18.7±3.27</td>
<td>14.1±2.15*</td>
<td>23.17±4.49</td>
<td>11.07±1.74*</td>
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<tr>
<td>sputum ECP</td>
<td>627.9±233.5</td>
<td>14.1±2.15*</td>
<td>307.4±117.6*</td>
<td>23.17±4.49</td>
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<tr>
<td>total IgE levels</td>
<td>184.8±112.2</td>
<td>170.7±106.7*</td>
<td>211.8±127.9</td>
<td>225.1±147.4</td>
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<tr>
<td>FEV₁₀</td>
<td>2328.3±133.3</td>
<td>238.3±135.3*</td>
<td>1963.3±130.6</td>
<td>2096.6±118.4*</td>
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<tr>
<td>Dmin</td>
<td>2.393±0.64</td>
<td>3.087±0.882*</td>
<td>3.217±0.697</td>
<td>4.848±0.808*</td>
</tr>
</tbody>
</table>

* p<0.05 between values ** p<0.01 between values

Fig. 2  Changes in PEF. Changes in peak expiratory flow during 6 weeks of treatment in adult patients with intermittent and mild persistent asthma: suplatast tosilate group (n = 18, 100 mg suplatast tosilate three times daily) and BDP group (n = 17, 200 μg BDP twice daily).

Results are shown as mean ± SD. We used the Mann-Whitney U test to compare independent data between the two groups, the Wilcoxon signed rank test to compare paired data between the two groups, using the ECP-Kit (Pharmacia Diagnostics, Uppsala, Sweden). Sputum samples were collected by hypertonic saline induction as described by Pin. The sputum was frozen immediately and stored at −20°C or below. At the time of measurement, the saliva portion was removed. The remaining sample was combined with 4 volumes of physiological saline (5-fold dilution), agitated, and then centrifuged at 4000 g for 30 minutes at 4°C. Measurements were performed on the supernatant with anECP-Kit. Airway hypersensitivity (Dmin) was determined by astograph (TCK-6000, Chest Corp., Japan).
and the Frieden test for comparison of paired data among three or more groups. Intergroup comparison using the Mann-Whitney U test with Bonferroni correction was performed on all statistically significant data.

RESULTS

1) Changes in PEF (Fig. 2)

PEF increased significantly from week 1 in the BDP group and stabilized after week 2 ($P < 0.02$). In the suplatast tosilate group PEF increased significantly from week 2 ($P < 0.03$) and reached the nearly the same maximum level as in the BDP group at week 6 (Fig. 2). However, from week 1 to week 4 the BDP group showed significantly greater elevation of PEF than the suplatast tosilate group.

2) Changes in peripheral eosinophil ratio, serum ECP level, induced sputum ECP level, IgE titer, FEV1.0, and airway hypersensitivity (Dmin), and comparison of differences between groups (Table 2).

The peripheral blood eosinophil ratio decreased significantly after 6 weeks of treatment in both the suplatast tosilate group ($P < 0.02$) and the BDP group ($P < 0.02$). There was no significant difference in this change between the two groups.

Serum ECP values also decreased significantly after 6 weeks of treatment in both groups (suplatast tosilate $P < 0.04$, BDP $P < 0.02$). Again, we found no significant difference in change between the two groups.

The induced sputum ECP level decreased significantly after 6 weeks of treatment in both the suplatast tosilate group ($P < 0.02$) and the BDP group ($P < 0.008$), with a more pronounced decrease in the BDP group. A comparison of the difference between the two groups showed a significantly greater decrease in the BDP group.

Total IgE levels decreased significantly after 6 weeks of treatment in the suplatast tosilate group ($P < 0.05$). There was no significant difference in change between the two groups.

There was a significant increase in FEV1.0 in both the suplatast tosilate group ($P < 0.05$) and the BDP group ($P < 0.03$) after 6 weeks of treatment. We found no significant difference in change between the two groups.

Dmin increased significantly after 6 weeks of treatment in both the suplatast tosilate group ($P < 0.05$) and the BDP group ($P < 0.02$), with no significant difference in change between the two groups.

DISCUSSION

Allergic inflammation results from a complex interaction between invading cell groups such as mast cells, eosinophils, basophils, T lymphocytes, and macrophages, and local structural cells such as vascular endothelial cells, airway epithelial cells, and fibroblasts. Conventional explanations of mechanism of onset of allergic disease have focused on the functions of eosinophils, mast cells, and basophils, which work as effectors in allergic inflammation. However, in recent years the important role of cytokines produced by lymphocytes, particularly T cells, has become more obvious.

Helper CD4+ T cells are divided into two subsets, Th1 and Th2. Th1 cells which mainly produce interferon-γ and IL-2, are involved in delayed hypersensitivity reactions, cellular immunity, and induction of IgG2a antibody. Production Th2 cells which produce IL-4, IL-5, IL-6, and IL-10, are involved in humoral immunity, and induce production of antibodies such as IgG1 and IgE.

The onset of the allergic response is attributed to a shift in the balance between Th1 and Th2 cells, toward excess Th2. As a result, excessive amounts of IL-4 and IL-5 are available to stimulate production of IgE antibody by B cells and to promote differentiation and proliferation of eosinophils. The Th 2-cell-predominant state appears to play an important role in the clinical condition of bronchial asthma.

There has been considerable research on the effects of suplatast tosilate on Th2 cytokine production. Findings from experimentally induced asthma in guinea pigs indicate that suplatast tosilate specifically inhibited IgE antibody production, and blocked tissue invasion by eosinophils through the inhibition of IL-4 and IL-5 production. Using a mouse model of asthma, Zhao et al. found that suplatast tosilate inhibited IL-4, IL-5, and IL-13 in bronchoalveolar lavage fluid, decreased airway invasion by eosinophils, and reduced airway hypersensitivity. Shim et al. also reported that suplatast tosilate inhibited the increase of IL-4 and IL-13 in bronchoalveolar lavage fluid. In bronchial mucosal biopsy specimens from patients with bronchial asthma, Sano et al. reported that suplatast tosilate decreased both the eosinophil count and the number of cells testing positive for a monoclonal antibody to ECP (EG2+). In addition, in bronchial asthma test findings stratified by degree of severity, Tamaoki et al. reported that suplatast tosilate was useful for reducing steroid dose in patients with severe asthma. In mild asthma, suplatast tosilate was reported to inhibit eosinophilic airway inflammation and airway hypersensitivity by significantly reducing peripheral blood eosinophils, serum ECP levels, and induced sputum ECP levels. These results were particularly prominent in cases of atopic asthma.

In our study we compared the therapeutic effects of suplatast tosilate and BDP in patients with mild bronchial asthma. Criteria for mild bronchial asthma as defined at step 1 is the presence of airway hypersensitivity and chronic airway inflammation, even though asthma symptoms may be mild. This study involved patients who met the criteria for either step 1 or step 2.

The suplatast tosilate group required more time to show improvements in PEF than the BDP group.
BDP was associated with significantly higher PEF values than suplatast tosilate during weeks 1 through 4, but suplatast tosilate results were almost identical to those for BDP by the fifth or sixth week. The suplatast tosilate group also showed significant improvements in the peripheral blood eosinophil ratio, ECP levels in serum and induced sputum, total IgE levels, FEV\textsubscript{1.0}, and Dmin. The BDP group had lower levels of induced sputum ECP, a parameter closely associated with damage to the airway mucosa as a result of inflammation. Total IgE levels were inhibited only in the suplatast tosilate group. Although the differences between baseline and posttreatment findings was not statistically significant in either group, these findings show that oral suplatast tosilate decreased total IgE levels, an effect not demonstrated with inhaled steroids. A comparison of baseline and posttreatment findings in the suplatast tosilate group and the BDP group also showed that BDP was associated with a significantly greater improvement than suplatast tosilate in sputum ECP levels only. These findings suggest that by decreasing the level of eosinophil ECP in peripheral blood, suplatast tosilate inhibited eosinophilic inflammation of the airway and thus blocked the development of airway hypersensitivity.

These results suggest that oral suplatast tosilate has nearly the same therapeutic usefulness as inhaled BDP 400 μg/day in patients with mild asthma. However, long-term management of bronchial asthma, there is no doubt that inhaled steroids are the treatment of first choice. The results of this study suggest that suplatast tosilate may become a first-line treatment option for mild asthma. In cases where there are problems with compliance when using inhaled steroids, limits on the use of inhaled steroids, or complications of allergic sinusitis or atopic dermatitis, suplatast tosilate may prove useful in the long-term management of bronchial asthma. Further study of the drug’s long-term effects are needed.

**CONCLUSION**

We prospectively compared the therapeutic effects of suplatast tosilate and BDP in 35 patients with intermittent and mild persistent asthma by randomly allocating patients a suplatast tosilate group (18 patients, 100 mg three times daily) or a BDP group (17 patients, 200 μg twice daily) for 6 weeks of treatment.

1. The suplatast tosilate group required more time than the BDP group to show improvements in PEF. BDP treatment was associated with significantly higher PEF values during weeks 1 through 4, but suplatast tosilate showed results almost identical to those for BDP by the fifth or sixth week.

2. Both groups showed significant improvement in the peripheral blood eosinophil ratio, serum ECP levels, induced sputum ECP levels, FEV\textsubscript{1.0}, and Dmin. However, induced sputum ECP levels were lower in the BDP group than in the suplatast tosilate group.

3. Total IgE levels decreased only in the suplatast tosilate group.

We conclude that suplatast tosilate may be useful in the long-term management of mild bronchial asthma.

**REFERENCES**


