Role of a Th2 cytokine inhibitor in asthma treatment

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ABSTRACT
The airway wall of asthmatic patients is infiltrated with inflammatory cells, consisting chiefly of eosinophils and T lymphocytes. Among these T lymphocytes, Th2 cells are involved in the regulation of the IgE immune response and local allergic inflammation, which underlie allergic diseases. Various cytokines produced and released by Th2 cells play important roles in the development of many allergic diseases, including asthma, and the exacerbations of their disease states. Therefore, targeting of Th2 cell-derived cytokines is a rational therapeutic strategy for the treatment of asthma. Corticosteroids and immunosuppressive agents can potently inhibit Th2 cytokine-mediated responses, but have no selectivity for Th2 cells: they also exert pharmacological activity against cells other than inflammatory cells, thereby potentially causing adverse side-effects. However, suplatast tosilate is the only specific Th2 cytokine inhibitor that can be used clinically and it has been used widely in Japan as a maintenance drug in the treatment of asthma, atopic dermatitis and allergic rhinitis. There is considerable evidence of the effectiveness of suplatast tosilate in patients with mild asthma or moderate persistent asthma. Furthermore, an effect on cough variant asthma and a steroid-sparing effect have also been reported for suplatast tosilate.

Key words: cough variant asthma, eosinophilic airway inflammation, interleukin-4, interleukin-5, interleukin-13, steroid-sparing effect.

INTRODUCTION
The basic disease state of asthma is chronic airway inflammation. The airway mucosa of asthmatic patients is usually infiltrated with inflammatory cells, consisting chiefly of eosinophils and T lymphocytes, and various chemical mediators and cytokines derived from these cells are closely involved in the pathophysiology of asthma. In particular, Th2 cells predominate in asthma compared with Th1 cells and activated Th2 cells produce and release various cytokines that are involved in the development of allergy, the aggravation of the disease state, airway hyperresponsiveness and airway remodeling. Among these cytokines, interleukin (IL)-5 promotes the differentiation, proliferation and activation of eosinophils and causes eosinophilic airway inflammation. In contrast, IL-4 and IL-13 stimulate B cells to promote IgE production and enhance adhesion molecule expression, mast cell proliferation and mucin secretion. Interleukin-9 enhances the production of IgE, the release of chemical mediators from mast cells and the secretion of mucin. Furthermore, based on previously reported findings on the effects of soluble IL-4 receptor, soluble IL-13 receptor α, monoclonal antibodies to IL-4 and IL-5 and gene targeting, the importance of these Th2 cytokines in the allergic airway responses has been demonstrated.

SUPPRESSION OF ALLERGIC INFLAMMATION BY TH2 CYTOKINE INHIBITOR
In Japan, in 1991, the specific Th2 cytokine inhibitor suplatast tosilate ((+/-)-[2-[4-(3-ethoxy-2-hydroxypropoxy)phenylcarbamoyl]ethyl]dimethylsulfonium P-toluenesulfonate) was developed. Suplatast, at 1–5 µg/mL, suppresses the production of IL-4 and IL-5 by a mouse Th2 clone and human Th2 cell clones specific for Japanese cedar or Derf antigen and also suppresses the antigen-simulated production of IL-13 by cultured basophils. However, with regard to the production of interferon
(IFN)-γ by a purified protein derivative (PPD)-specific Th1 cell clone and murine sensitized T cells and the production of chemokines by monocytes, suplatast is ineffective, even at high concentrations. The Th2 cytokine-inhibitory action of suplatast has also been confirmed in vivo: in a guinea pig model of antigen-induced asthma, a decrease in IL-5 mRNA-expressing CD4+ T cells (Th2 cells) in the airway mucosa has been observed. Moreover, in patients with atopic dermatitis, the production of IL-4 and IL-5 by peripheral blood monocytes is increased 2 weeks after the discontinuation of steroid administration, but the administration of suplatast inhibits the production of these cytokines. Although the inhibitory activity of suplatast in Th2 cytokine production has been confirmed at the mRNA level, its effects on cell surface receptors and signal transduction remain unknown and require further investigation.

**Effects on Mild Persistent Asthma**

The majority of evidence regarding the effects of suplatast in the treatment of asthma concerns patients with mild persistent asthma and the drug has been reported to improve asthma symptoms, respiratory function, airway hyperresponsiveness and airway inflammation. Most basically, this drug is used in combination with inhaled corticosteroids for patients with mild persistent asthma patients and should be dosed chronically, not as needed. It is considered necessary to continue the administration of suplatast, like other anti-allergic drugs in general, for at least 4–6 weeks to evaluate its pharmacological effects.

In an initial uncontrolled study, Sano et al. administered 300 mg suplatast daily for 6 weeks to patients with mild persistent asthma and showed that it improved asthma symptoms and eosinophilic airway inflammation. Subsequently, Sano et al. conducted a case-controlled study and found that the suplatast-administered group showed a gradual increase in peak expiratory flow (PEF) and significant increases in morning and evening PEF in the 5th and 6th weeks, as well as decreases in asthma symptom scores, airway contractile responses to histamine, the number of eosinophils, eosinophil granule-2 (EG2)-positive cells and CD4+ T lymphocytes in airway biopsies, and in eosinophils and EG2-positive cells in induced sputum (Figs 2,3).

Horiguchi et al. also investigated the effects of suplatast (300 mg/day for 4 weeks) in patients with step 1 or 2 asthma and observed an increase in morning PEF, an improvement in airway hyperresponsiveness, a decrease in peripheral blood eosinophils and decreases in serum and induced sputum content of eosinophil cationic protein (ECP). These improvements were more marked in atopic than non-atopic patients.

We compared the effects of suplatast and an inhaled corticosteroid in 43 adult patients with mild persistent asthma. Subjects enrolled in the trial were step 1 patients with a forced expiratory volume in 1 s (FEV1) of over 80% of the predicted value and had symptoms such as stridor, cough and dyspnea fewer than eight times, but...
In that trial, after a 2-week run-in period, patients were divided into three groups and each group received oral suplatast (300 or 400 mg/day), inhaled beclomethasone dipropionate (BDP; 400 µg/day) or an oral placebo for 8 weeks. During the trial, a short-acting inhaled β2-adrenergic receptor agonist alone was administered concomitantly as needed. The degree of airway inflammation was evaluated by eosinophil and mast cell counts in induced sputum and the ECP and tryptase concentrations in the sputum supernatant. As a result, as shown in Fig. 4, all parameters decreased significantly in the suplatast-and BDP-treated groups. These changes were observed only in the BDP group 4 weeks after administration and BDP tended to show an earlier anti-inflammatory effect than suplatast, but the effect was similar in both groups 8 weeks after administration. Therefore, the effect of the usual dose of the Th2 cytokine inhibitor for airway inflammation in mild persistent asthma is equivalent to 400 µg BDP, suggesting its usefulness as an alternative or concurrent drug to inhaled corticosteroids in asthma maintenance therapy. In view of the fact that the prolonged administration of inhaled steroids is associated with the risk of systemic side-effects,17–19 that even short-term administration sometimes causes local side-effects, such as cough and laryngeal discomfort, and that oral drugs generally have a higher compliance rate than inhalants, suplatast should be considered as an option for the long-term maintenance treatment of asthma.

### Effects on Cough Variant Asthma

Although bronchodilators, such as β2-adrenergic receptor agonists and theophylline are effective for the treatment of cough variant asthma, recent studies have indicated that eosinophilic airway inflammation plays an important role in the pathogenesis of the disease.20,21 Therefore, anti-inflammatory drugs should preferentially be chosen for treatment. Shioya et al.22 conducted a double-blind comparative trial of suplatast and a placebo in 20 patients with cough variant asthma and found that the group receiving suplatast (300 mg/day) for 6 weeks showed no significant increase in FEV1 or PEF, nor any improvement in airway hyperresponsiveness to methacholine. However, suplatast treatment caused decreases in the eosinophil count and ECP content in induced
sputum by 75 and 87%, respectively. In addition, the cough scores decreased, as did cough sensitivity to inhaled capsaicin (Fig. 5). We speculate that the mechanism of these effects of suplatast probably involves improvement of eosinophilic airway inflammation owing to the inhibition of IL-5 production, but confirmation of this hypothesis awaits the measurement of cytokine levels in sputum. An improvement in the cough score was noted in the 1st week after the administration of suplatast, suggesting that the effect gained so early may represent a pharmacological effect other than Th2 cytokine inhibition.

**Effects on moderate to severe asthma**

Because the Th2 cytokine inhibitor has no bronchodilating effect, its effect on airflow limitation in moderate to severe asthma is weak and it is difficult to control the disease state by suplatast monotherapy. However, because suplatast is known to have an inhaled steroid-sparing
effect, this drug can be added to reduce the use of inhaled corticosteroids at high doses for step 3–4 asthma. Tamaoki et al.\textsuperscript{23} examined the preventive effect of suplatast against asthma exacerbation occurring when the dose of steroids administered was halved in 85 patients with severe asthma controlled by high doses of BDP. As a result, a reduction in the dosage of BDP to half resulted in lower FEV\textsubscript{1} and PEF, higher asthma symptom scores and more frequent use of a \(\beta_{2}\)-adrenergic receptor agonist in the placebo group, but such exacerbations of asthma were not observed in the suplatast group. When the relapse of asthma was defined as a decrease in FEV\textsubscript{1} or PEF of more than 20% from baseline or the occurrence of asthma symptoms more than 10 times a week, the cumulative rate of steroid reduction-induced relapse was only 13% in the suplatast group compared with 83% in the placebo group, showing a significant difference between the two groups (Fig. 6).

**Evaluation of Th2 Cytokines in Asthma Guidelines**

The newest guidelines for the treatment of asthma are the Japanese Society of Allergology Guidelines for the Diagnosis and Management of Bronchial Asthma (JGL2003).\textsuperscript{24} The Th2 cytokine inhibitors are not indicated for step 1 (mild intermittent) or step 2 (mild

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**Fig. 5** Changes in (a) cough scores and (b) cough threshold for capsaicin in patients with cough variant asthma during treatment with placebo or suplatast tosilate. Data are the mean ± SEM. *P < 0.05 compared with corresponding values for placebo.

**Fig. 6** Kaplan–Meier analysis of the probability of asthma relapse during reduction of beclomethasone propionate (BDP) in patients with severe asthma. Patients receiving suplatast tosilate had a lower risk of relapse than those receiving placebo (\(P < 0.05\) by Wilcoxon single-rank test).
persistent, including cough variant asthma) asthma as drugs for long-term management, but are indicated for step 3 (moderate persistent) and step 4 (severe persistent) asthma as combination therapy with inhaled corticosteroids, slow-releasing theophylline, long-acting 

REFERENCES


