Long-term monotherapy with suplatast tosilate in patients with mild atopic asthma: A pilot comparison with low-dose inhaled fluticasone

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Summary

Background and objective: Suplatast tosilate is a Th2 cytokine inhibitor that is effective for controlling persistent asthma. However, the longterm efficacy of suplatast is unknown. We compared the clinical efficacy of long-term monotherapy with suplatast tosilate with a low dose of inhaled steroids in patients with mild atopic asthma.

Methods: A total of 32 patients with mild atopic asthma were randomly assigned to receive suplatast (n = 15) or fluticasone (n = 17). In the suplatast group, 100 mg of suplatast was given orally 3 times a day (total daily dose = 300 mg) for 2 years. In the fluticasone group, 100 μ g of fluticasone was inhaled twice a day (total daily dose = 200 μ g) for 2 years.

Results: In the suplatast group, the improvements in peak expiratory flow (PEF) rate and forced expiratory volume in 1 second (FEV₁) and the changes in the symptom diary scale and frequency of **B2** stimulant inhalation were generally similar to those in the fluticasone group, and efficacy was maintained for 2 years. Improvements in inflammatory indices, such as the sputum eosinophil cationic protein (ECP) level and exhaled nitric oxide concentration, were comparable in the suplatast and fluticasone groups. The improvement in airway hyperresponsiveness was also similar in the 2 groups. The peripheral blood eosinophil percent change, serum ECP level, and total IgE antibody titer improved only in the suplatast group.

Corresponding author: Takahiko Horiguchi E-mail: <u>ta-hori@fujita-hu.ac.jp</u> Submitted date: 4/8/2010 Accepted date: 16/3/2011 *Conclusions:* Long-term treatment with suplatast significantly improved symptoms and inflammatory indices in patients with mild atopic asthma. Along with fluticasone, suplatast is considered a useful drug for the management of mild atopic asthma. (Asian Pac J Allergy Immunol 2011;29:134-42)

Key words: mild atopic asthma, suplatast tosilate, inhaled steroids, nitric oxide and airway hyper-responsiveness

Introduction

Our understanding of the etiology of bronchial asthma has improved considerably. Reversible airway obstruction, airway hyper-responsiveness, and chronic airway inflammation are now acknowledged to have important roles in the basic pathogenesis of the disease. The asthmatic response is associated with infiltration of inflammatory cells, involving mainly eosinophils, T lymphocytes, and mast cells. In particular, type 2 helper T cells (Th2 cells) produce and release many cytokines participating in the onset and development of allergy. Interleukin (IL)-4 and IL-13 are known to modulate IgE production by B cells. IL-5 is involved in the differentiation, proliferation, and activation of eosinophils¹.

Suplatast tosilate, antiasthmatic an drug developed in Japan, inhibits the production of IL-4 and IL-5, thereby decreasing IgE antibody titers, suppressing eosinophilic infiltration, and improving asthmatic symptoms and airway hyperresponsiveness². We previously reported that 4 weeks of treatment with suplatast significantly improved peripheral blood eosinophil percent change, eosinophil cationic protein (ECP) levels in serum and induced sputum, and airway hyperresponsiveness in patients with mild asthma. These changes were particularly marked in patients with atopic asthma³. We also previously compared the effectiveness of suplatast, given for 6 weeks, with

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Figure 1. Study design: PEF: peak expiratory flow, ECP: eosinophil cationic protein, $FEV_{1,0}$: forced expiratory volume in one second

that of inhaled beclomethasone dipropionate (400 μ g/day) in adults with mild asthma. We found that the degrees of improvement in peak expiratory flow (PEF), peripheral blood eosinophil percent change, ECP levels in serum and induced sputum, forced expiratory volume in 1 second (FEV₁), and airway hyper-responsiveness were generally similar in the 2 treatment groups⁴. However, long-term studies of suplatast are scarce, and many aspects of the clinical effectiveness of this drug remain unclear. We therefore compared the clinical effectiveness of 2 years of monotherapy with suplatast with that of monotherapy with the inhaled steroid fluticasone (200 μ g/day) in adults with mild atopic asthma.

Methods

This study was an open-labeled randomized trial. The study group comprised 32 adults (15 men and 17 women) with mild atopic asthma who presented at the Department of Respiratory Internal Medicine of Fujita Health University Second Educational Hospital. The severity of asthma according to the 2006 Asthma Prevention and Management guidelines⁵ was step 1 (mild intermittent) in 17 patients and step 2 (mild persistent) in 15. Patients who had evidence of serum-specific IgE antibodies to allergens other than cedar pollen in the environment were regarded as having atopic asthma. The study design is shown in Figure 1. After 1 month of observation, informed consent to participate in the study was obtained from all patients before enrollment. Medication remained unchanged during the observation period of 1 month. Fifteen patients were randomly assigned to receive suplatast and 17 to receive fluticasone. In the suplatast group, 100 mg of suplatast was given orally 3 times a day (total daily dose = 300 mg) for 2 years. In the fluticasone group, 100 μ g of inhaled fluticasone was given twice a day (total daily dose = 200 μ g) for 2 years. Table 1 shows the demographic characteristics of the patients in the suplatast group and the fluticasone group. There were no significant differences between the treatment groups in any demographic characteristic.

All patients were asked to keep an asthma diary to record peak expiratory flow (PEF) in the morning, frequency of the use of β 2-stimulant inhalation, symptom score, and treatment compliance, which were used as parameters. The time course of the symptom score was evaluated according to Santanello's symptom diary scale. Symptom scores were calculated for 1-week periods after 12 months and 24 months of treatment and were compared with the baseline symptom score during the week before the start of treatment. PEF before treatment was compared with the values after 1, 3, 6, 12, and 24 months of treatment. The frequency

Table 1. Characteristics : Data are expressed as medians, with ranges in parentheses. P values were obtained by the Wilcoxon signed-rank test.

	Suplatast tosilate (n=15)	Fluticasone (n=17)	P value
Sex: Male/ Female	6/9	7/10	0.593
Mean age (range)	56 (39-75)	62 (36-81)	0.288
Mean asthma duration	3 (2-5)	3 (2-6)	0.551
Asthma severity:	10 /5	7/10	0.543
PEF (L/min)	452 (300-620)	428 (300-460)	0.345
Frequency of β2 stimulant	2 (0-4)	2 (0-5)	0.641
Symptom diary scale	2 (1-5)	2 (1-5)	0.884
Peripheral blood eosinophil percent change	5 (1-8)	3 (1-6)	0.061
Serum ECP level (µg/L)	20.6 (2-35.9)	15.6 (2-30.2)	0.435
Sputum ECP level (µg/L)	476 (24-2100)	622 (86-2260)	0.624
Total IgE (IU/ml)	346 (124-870)	252 (148-640)	0.667
FEV ₁ (predosing) (ml)	40 (17.7-125)	52.5 (10.8-136)	0.236
Exhaled NO levels (ppb)	2420 (930-3100)	2180 (1130-2800)	0.126
Dmin	2.45 (0.8-4.5)	3.08 (1.08-5.8)	0.084

of β 2-stimulant inhalation and the symptom diary scale before treatment were compared with the values after 12 and 24 months of treatment. Peripheral blood eosinophil percent change, serum ECP levels, induced sputum ECP levels, total IgE antibody titers, FEV₁, exhaled nitric oxide (NO) concentrations, and airway hyper-responsiveness on astography were assessed at baseline and after 12 and 24 months of treatment, and the values were compared. In this study, the primary outcome was PEF. Secondary outcomes were the frequency of the use of β 2-stimulant inhalation, symptom score, peripheral blood eosinophil percent change, serum ECP levels, induced sputum ECP levels, total IgE antibody titers, FEV₁, exhaled nitric oxide (NO) concentrations, and airway hyper-responsiveness on astography. To measure serum ECP levels, venous blood samples were collected and allowed to stand for 60 minutes at room temperature. The serum was then isolated and stored at -20°C or lower. Serum ECP levels were measured with the use of an ECP kit (Pharmacia, Diagnostics, Uppsala, Sweden). Sputum was induced with hypertonic saline as described by Pin et al.⁶. Whole sputum samples were collected, and saliva was discarded macroscopically. Immediately after collection, sputum samples were stored at -20° C or below. The

sputum samples were diluted with 4 volumes of physiologic saline (1:5 dilution) and stirred. The diluted serum was centrifuged for 30 minutes at 4000 x g and a temperature of 4°C. The supernatant was assayed with the use of the ECP kit. Exhaled NO concentrations were measured with the use of a NOA280i analyzer (Sievers Instruments, Boulder, $(CO, USA)^7$. Airway hyper-responsiveness to methacholine (minimum dose of methacholine, Dmin) was determined by astography (TCK-6000, Chest Corp., Japan). The results are expressed as median values. The statistical significance of differences between the 2 groups was calculated by the Wilcoxon signed-rank test. The Kruskal-Wallis test was used to compare variables among 3 or more groups. In case of significant differences, the Mann-Whitney U test with Bonferroni corrections was used to compare groups. Differences between the suplatast group and the fluticasone group were determined by the Wilcoxon signed-rank test at each time of assessment (at 1, 3, 6, 12, and 24 months for PEF and at 12 and 24 months for the other parameters).

During the study period, short-acting β_2 stimulants were given only as needed for asthmatic attacks. Drugs used to treat other diseases were not changed.

This study was approved by the Fujita Health University ethics committee.

Results

Twenty Time course of PEF (Figure. 2)

After 1 month of treatment, PEF significantly increased in both the suplatast group and the fluticasone group (p < 0.0001). After 3 months, the PEF reached a plateau. The effectiveness of treatment was maintained for 24 months (p < 0.0001).

There were no significant differences of PEF between the suplatast group and the fluticasone group at any of the assessment times.

Time course of frequency of $\beta 2$ stimulant inhalation (Figure. 3a)

After 12 months of treatment, the frequency of $\beta 2$ stimulant inhalation significantly decreased in both the suplatast group (p = 0.020) and the fluticasone group (p = 0.041). The effectiveness of treatment was maintained for 24 months in both the suplatast group (p = 0.007) and the fluticasone group (p = 0.0053).





Changes in peak expiratory flow in the morning during 24 months of treatment in mild atopic asthma: Suplatast tosilate group (n=15, 100mg suplatast tosilate three times daily) and Fluticasone group. (n=17, 100 μ g twice daily) Changes of PEF at 1month, 3months, 6months, 12months and 24months significantly increased in comparison to baseline in both the suplatast group and the fluticasone group.

There were not significant differences between two groups at any of the assessment times.

There were no significant differences in the use of inhaled β 2-stimulants between the suplatast group and the fluticasone group at 12 or 24 months.

Time course of symptom diary scale (Figure. 3b)

After 12 months of treatment, the symptom diary scale significantly decreased in both the suplatast group (p = 0.0002) and the fluticasone group (p = 0.0030). The effectiveness of treatment was maintained for 24 months in both the suplatast group (p = 0.0004) and the fluticasone group (p = 0.0053).

There were no significant differences in the symptom diary scale between the suplatast group and the fluticasone group at 12 or 24 months.

Time course of peripheral blood eosinophil percent change (Figure. 4a)

Peripheral blood eosinophil percent change did not change significantly in either the suplatast group or the fluticasone group.

There were no significant differences in the peripheral blood eosinophil percent change between

the suplatast group and the fluticasone group at 12 or 24 months.

Time course of serum ECP levels (Figure. 4b)

In the suplatast group, the serum ECP levels significantly decreased after 12 months of treatment (p = 0.0141). Treatment effectiveness was maintained for 24 months (p = 0.0054). In the fluticasone group, there was no significant change in the serum ECP level. There were no significant differences of serum ECP levels between the suplatast group and the fluticasone group at 12 or 24 months.

Time course of ECP levels in induced sputum (Figure. 4c)

ECP levels in induced sputum significantly decreased after 12 months of treatment in both the suplatast group (p = 0.0021) and the fluticasone group (p = 0.0019). Decreased ECP levels were maintained for 24 months in both the suplatast group (p = 0.0016) and the fluticasone group (p = 0.0014).



Figure 3a. Changes in frequency of β_2 stimulant inhalation :

Changes in frequency of β_2 stimulant inhalation per week in the suplatast group and the fluticasne group.

Changes in frequency of β_2 stimulant inhalation at 12 months and 24 months significantly decreased in comparison to baseline in both the suplatast group and the fluticasone group.

There were not significant differences between two groups at 12 or 24 months.

Figure 3b. Changes in symptom diary scale :

Changes in symptom diary scale in the suplatast group and the fluticasne group.

Changes in symptom diary scale at 12 months and 24 months significantly decreased in comparison to baseline in both the suplatast group and the fluticasone group.

There were not significant differences between two groups at 12 or 24 months.



Figure 4a. Changes in peripheral blood eosinophil percent change :

Changes in peripheral blood eosinophil percent change in the suplatast group and the fluticasne group.

There were not significant differences in comparison to baseline in either the suplatast group or the fluticasone group at 12 or 24 months, and there were not significant differences between two groups at 12 or 24 months.

Figure 4b. Changes in serum ECP level :

Changes in serum eosinophil cationic protein level in the suplatast group and the fluticasone group.

In the suplatast group, changes in serum ECP level at 12 months and 24 months significantly decreased in comparison to baseline.

There were not significant differences in comparison to baseline in the fluticasone group at 12 or 24 months, and there were not significant differences between two groups at 12 or 24 months.

Figure 4c. Changes in sputum ECP level :

Changes in sputum eosinophil cationic protein level in the suplatast group and the fluticasone group.

Changes in sputum ECP level at 12 months and 24 months significantly decreased in comparison to baseline in both the suplatast group and the fluticasone group.

There were not significant differences between two groups at 12 or 24 months.

Figure 4d. Changes in total IgE RIST level

Changes in total IgE RIST level in the suplatast group and the fluticasone group.

*p < 0.05: in comparison to baseline

In the suplatast group, changes in total IgE RIST level at 12 months and 24 months significantly decreased in

There were no significant differences in ECP levels in induced sputum between the suplatast group and the fluticasone group at 12 or 24 months.

Time course of total IgE antibody titers (Figure. 4d)

In the suplatast group, the total IgE antibody titer significantly decreased after 12 months of treatment (p = 0.0128). The effectiveness of treatment was maintained for 24 months (p = 0.0189). In the fluticasone group, there was no significant change in total IgE antibody titers. There were no significant differences in the total IgE antibody titer between the suplatast group and the fluticasone group at 12 or 24 months.

*Time course of FEV*₁ (*Figure. 5a*)

After 12 months of treatment, the FEV₁ significantly increased in both the suplatast group (p < 0.0001) and the fluticasone group (p = 0.0104). The effectiveness of treatment was maintained for 24 months in both the suplatast group (p < 0.0001) and the fluticasone group (p = 0.0102). There were no significant differences in FEV₁ between the suplatast group and the fluticasone group at 12 or 24 months.

Time course of exhaled NO concentrations (*Figure. 5b*)

After 12 months of treatment, exhaled NO concentrations significantly decreased in both the suplatast group (p = 0.0005) and the fluticasone group (p = 0.0248). Effectiveness was maintained for 24 months in both the suplatast group (p = 0.0002) and the fluticasone group (p = 0.0303). There were no significant differences in the exhaled NO concentration between the suplatast group and the fluticasone group at 12 or 24 months.

Time course of airway hyper-responsiveness to methacholine (minimum dose of methacholine, Dmin) (Figure. 5c)

After 12 months of treatment, airway hyperresponsiveness significantly decreased in both the suplatast group (p = 0.0044) and the fluticasone group (p = 0.0034). The effectiveness of treatment was maintained for 24 months in both the suplatast group (p = 0.0077) and the fluticasone group (p = 0.0062). There were no significant differences in airway hyper-responsiveness to methacholine between the suplatast group and the fluticasone group at 12 or 24 months.

There was no significant difference in treatment compliance between the two groups during the administration period $(85.7 \pm 5.4\%)$ in the suplatast

group vs. $81.6 \pm 4.9\%$ in the fluticasone group). No patient had drug-related side effects in either group.

Discussion

The Global Initiative for Asthma⁸ discouraged the use of anti-inflammatory therapy for the management of mild intermittent asthma (step 1). In 2006, however, the Asthma Prevention and Management guidelines⁵ recommended low-dose inhaled steroids for the treatment of mild asthma. In patients with mild asthma, airway hyperresponsiveness is associated mainly with eosinophilic inflammation. If left untreated, airway remodeling may occur, causing the disease to become less responsive to treatment. Early initiation of aggressive anti-inflammatory therapy may inhibit airway inflammation and thereby normalize airway hyper-responsiveness. It is widely accepted that inhaled steroids are currently the most useful antiinflammatory agents. However, the 2006 Asthma Prevention and Management guidelines approved the concomitant use of suplatast in patients with atopic asthma.

Experimentally, suplatast has been shown to inhibit eosinophilic infiltration of tissue by suppressing the production of the Th2 cytokines, IL-4 and IL-5 in a guinea pig model of asthma². In a mouse model of asthma, suplatast inhibited the production of IL-4, IL-5, and IL-13 in bronchoalveolar lavage fluid, thereby suppressing eosinophilic infiltration and hyper-responsiveness of the airway⁹. Clinically, Sano et al. reported that suplatast decreased the eosinophil count and the EG2-positive cell count in bronchial-biopsy specimens from patients with bronchial asthma¹⁰. We previously reported that suplatast significantly decreases the peripheral-blood eosinophil count and ECP levels in serum and induced sputum, thereby inhibiting eosinophilic inflammation and airway hyper-responsiveness in patients with mild asthma³. We also reported that the degree of improvement in mild asthma was similar in patients given suplatast for 6 weeks and those given 400 µg of inhaled beclomethasone⁴. However, the mechanism of action of suplatast differs from that of other antiallergic drugs. Suplatast inhibits the production of IL-4, IL-5, and IL-13, resulting in a gradual response to treatment. Suplatast is thus usually given for prolonged periods, but long-term studies are scarce. We therefore compared the effect of 2 years of monotherapy with suplatast with that of monotherapy with 200 µg/day of fluticasone in patients with mild atopic asthma. The Japanese



Figure 5a. Changes in FEV_1 :

Changes in forced expiratory volume in one second in the suplatast group and the fluticasone group.

Changes in FEV_1 at 12 months and 24 months significantly increased in comparison to baseline in both the suplatast group and the fluticasone group.

There were not significant differences between two groups at 12 or 24 months.

Figure 5b. Changes in nitric oxide :

Changes in exhaled nitric oxide concentrations in the suplatast group and the fluticasone group.

Changes in nitric oxide at 12 months and 24 months significantly decreased in comparison to baseline in both the suplatast group and the fluticasone group. There were not significant differences between two groups at 12 or 24 months.

Figure 5c. Changes in Dmin :

Changes in airway hyperresponsiveness to methacholine (minimum dose of methacholine,Dmin) in the suplatast group and the fluticasone group.

Changes in Dmin at 12 months and 24 months significantly decreased in comparison to baseline in both the suplatast group and the fluticasone group.

There were not significant differences between two groups at 12 or 24 months.

guidelines recommend continued use of low-dose inhaled steroids for the treatment of mild intermittent asthma and continued use of FP-DPI (100-200 µg/day) for mild persistent asthma. In the present study, only patients with mild asthma were targeted and treated with continued use of FP-DPI (200 μ g/day). The improvements in PEF and FEV₁ in the suplatast group were not different to those in the fluticasone group, and treatment effectiveness was maintained for 2 years. As for inflammatory indices, the degree of improvement in sputum ECP levels was not different in the suplatast group and the fluticasone group. Exhaled NO concentrations are considered to correlate with ECP levels in sputum and in serum and most closely reflect chronic airway inflammation¹¹. This variable can be measured promptly and repeatedly and is regarded to be an accurate diagnostic and therapeutic index of asthma¹². The inclusion of exhaled NO concentrations in the assessment of treatment response has been reported to lead to better control with fewer drugs than guideline recommendations¹³. In our study, the improvement in airway inflammation was not different in the suplatast group and the fluticasone group. The degree of improvement in airway hyper-responsiveness was also not different in the groups. Improvements in peripheral blood eosinophil percent change, serum ECP levels, and total IgE antibody titers were seen only in the suplatast group. Taken together, our results suggest that suplatast inhibits the production of the Th2 cytokines IL-4, IL-5, and IL-13, thereby antibody decreasing IgE titers, inhibiting eosinophilic infiltration of tissue, and improving asthmatic symptoms and inflammatory indices. Treatment effectiveness was maintained for 2 years.

In conclusion, our results suggest that monotherapy with suplatast is a useful option for the long-term management of mild atopic asthma.

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