Allergology International. 2009;58:389-393
DOI: 10.2332/allergolint.08-OA-0068

ORIGINAL ARTICLE

Effect of Suplatast Tosilate on Antileukotriene Non-Responders with Mild-to-Moderate Persistent Asthma

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ABSTRACT

Background: Immunomodulatory therapy has been recently introduced for the management of asthma. Suplatast tosilate (ST), a new immune-modifying drug, is known to improve the airway function by inhibiting the release of Th-2 cytokines. However, its efficacy as a controller listed in the guideline, Global Initiative for Asthma 2005 has not been established. In this study we investigated the role of ST in leukotriene receptor antagonist (LTRA) non-responders with mild-to-moderate persistent asthma before initiating corticosteroids inhalation therapy.

Methods: This was a prospective open-level clinical trial. LTRAs was given to 41 patients with asthma for 4 weeks and clinical efficacy was assessed using daily symptom scores. The 10 patients, aged 2.5–8.5 years, who failed to show clinical improvement, were defined as LTRA non-responders. After a 1-week washout period, the efficacy of ST was investigated and compared with LTRA non-responders for the following 4 weeks.

Results: LTRA non-responders showed a significant improvement in the average symptom score, peak expiratory flow, use of rescue medication and the proportion of symptom-free days with ST therapy.

Conclusions: ST is a good choice for patients who have failed to respond to LTRAs. ST should therefore be added to the list of treatment options for such patients.

KEY WORDS

antileukotriene non-responders, bronchial asthma, children, suplatast tosilate, Th2 cytokines

INTRODUCTION

Asthma is a chronic common disorder with an increased incidence, especially among children. Treatment for asthma has been designed to avoid irritating symptoms and serious attacks, minimize the use of rescue medication, to allow productive and physically active lives, and to have optimal lung function. Daily controller medications recommended in the Global Initiative for Asthma for children with mild-to-moderate persistent asthma, include inhaled glucocorticosteroids as a first-line therapy and sustained-release theophylline, sodium cromoglycate, or LTRA as treatment options.[1]

ST is a new drug expected to serve as a daily controller alone, or to be used concurrently with inhaled glucocorticosteroids. ST has a mechanism different from any other therapy by blocking the allergic reaction upstream via regulating the production of Th2-cytokines.[2] It also inhibits production of tissue- injuring substances produced by mast cells and eosinophils.[3] ST could therefore be considered as a new option in the stepwise approach toward corticosteroid inhalation therapy, while also possibly reducing the glucocorticosteroid dose when used concurrently.[4]

Health care professionals should always seek methods to minimize treatment and medication in order to minimize side effects while maintaining control. Inhaled glucocorticosteroids are anti-inflammatory agents which are effective, long-term, preventive medications in reducing asthma attacks. However, possible side effects such as adrenal suppression and growth delay, must always be considered, to avoid hindering children's growth and developmental process.[5] On the other hand, LTRAs are well-known controller medications used solely or concurrently

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Received 2 December 2008. Accepted for publication 2 March 2009.

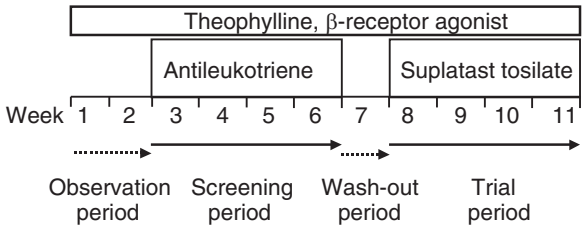

Fig. 1 A schematic drawing of the study design. After a 2-week observation period, antileukotriene was given to patients for 4 weeks, during the screening period. The patients were classified as antileukotriene non-responders if their average symptom score over the first half (weeks 3 and 4) and second half (weeks 5 and 6) of the screening period were not significantly less compared to the observation period (weeks 1 and 2). After a 1-week wash-out period for LTRA, suplatast tosilate was administered to the antileukotriene non-responders for a 4-week trial period.

with glucocorticosteroids. LTRA acts as an antagonist for leukotrienes and inhibits bronchoconstriction and inflammation.[6] However, there are poor responders to LTRA who require additional glucocorticosteroid therapy or increased doses of glucocorticosteroids.[7]

This clinical trial was undertaken prospectively to determine the role of ST as a second-line treatment in LTRA non-responders with mild-to-moderate persistent asthma, not yet treated by corticosteroid inhalation therapy.

METHODS

PATIENTS

Men and women were eligible for the study and were enrolled from June 2004 to May 2005 if they met the following criteria: under 15 years of age but over 1 years-old; having a medical history of asthma and classified as mild-to-moderately persistent by the Global Initiative for Asthma; and did not respond to 4 weeks of LTRA therapy. Patients previously treated with daily inhaled or oral corticosteroids were excluded. Written informed consent was obtained from each patient or guardian and patient anonymity was protected using documents and methods approved by the ethical review board of Juntendo University Hospital.

STUDY DESIGN

This 11-week study was approved by the institutional review board (Fig. 1). The investigation was carried out in accordance with the Declaration of Helsinki of 1995. Forty-one patients with mild-to-moderate persistent asthma were observed during the screening period to evaluate their responsiveness to LTRAs. After a 2-week observation period, Pranlukast (7 mg/kg/day in 2 separate doses) or Montelukast (4 mg, once a day) was given during the 4-week screening period. The use of theophylline and beta-agonist was continued if the patient had been receiving medication prior to this study. Rescue medication was available throughout the study period. Parents recorded the daily symptom-score list,[8] and the use of rescue medication and peak expiratory flow on a daily card. The daily symptom-score list included the following 4 questions: 1) Did you notice your child coughing or wheezing last night, 2) Was your child awake due to coughing or wheezing last night, 3) Did you notice coughing, wheezing, or shortness of breath today, 4) Did these airway symptoms interfere with the activities of your child. The screening period was divided into the first and second-second period each lasting for 2 weeks. Patients were eligible if the average symptom scores for both the first and second-second half of the screening period failed to show a significant decrease in comparison to that observed during the observation period. A washout period of 1 week was given, based on the pharmacokinetic data.[9]

After the 1-week washout period for LTRA, patients entered the trial period. ST was administered at 6 mg/kg/day in 2 separate doses for 4 weeks. The parents continued to record their daily card evaluations throughout the study period.

ASSESSMENT OF EFFICACY AND SAFETY

The trial period was divided into the first and second-second period, each lasting for 2 weeks. The outcome measures included the average number of symptoms per day, the number of symptom-free days, the peak expiratory flow and the use of rescue medication for the first and second-second half of the intervention period. Patients were examined between 8 a.m. and 5 p.m., at the beginning and end of the observation, screening and trial periods. Safety assessment was made by examining adverse events and physical examinations.

STATISTICAL ANALYSES

All statistical tests were performed using two-sided Student's *t*-tests.

RESULTS

A total of 41 patients were eligible for enrollment. The background characteristics and disposition of patients are shown in Table 1. Thirty-one patients were classified as LTRA responders, from results showing a significant decrease or improvement in the averages of symptom-scores over the first and second half of the screening period compared to that of the observation period. The 10 patients who failed to show any significant improvement in the average symptom-score by LTRA administration, were classified as LTRA non-responders and entered the trial period after a 1-week washout period.

Table 1 Baseline characteristics and patient disposition

	LTRA responder	LTRA non-responder
Number of patients	31	10
Male/Female (%)	71.0/29.0	60.0/40.0
Age (years)	5.2±3.8	5.4±2.0
Range (years)	1.0−14.5	2.5−8.5
Type of LTRA (%)		
Pranlukast/Montelukast	100.0/0	80.0/20.0
Daily symptom-score		
Week 1−2	1.46±0.93	1.67±1.10
Week 3−4	0.57±0.61**	1.57±1.15
Week 5−6	0.48±0.58**	1.59±1.06

LTRA, leukotriene receptor antagonist. Data are expressed as the means±SD. * $p < 0.01$ *vs.* week 1−2.

EFFICACY

The average symptom score over the second half of the LTRA screening period was 1.59 (SD 1.06), while the average scores in the first and second half of the ST trial period were 0.16 (SD 0.32) and 0.32 (SD 0.28) respectively. The symptom scores decreased significantly in both phases of the ST trial period in comparison to the second half of the LTRA screening period (paired Student's *t*-test, $p < 0.005$, 0.004, respectively; Fig. 2a).

The proportion of symptom-free days in the second half of the LTRA screening period was 45.0% (SD 29.4) which increased significantly to 92.1% (SD 16.0) and 83.6% (SD 18.8) respectively (paired *t*-test, $p < 0.0005$, 0.002; Fig. 2b) in the first and second half of the ST trial period.

The average peak expiratory flow in the second half of the LTRA screening period was 153.3 l/minute (SD 7.6) and those of the average in the first and second half of the ST trial period were 168.3 l/minute (SD 16.1) and 170.0 l/minute (SD 13.2) respectively. In the second half of the ST trial period, a significant increase was observed in comparison to the second half of the LTRA screening period ($n = 3$, paired Student's *t*-test, $p < 0.004$; Fig. 2c).

The average use of rescue medication in the second half of the LTRA screening period was 0.67 times/day (SD 0.43) and that of the average in the first and second half of the ST trial period were 0.08 times/day (SD 0.15) and 0.13 times/day (SD 0.19) respectively, thus revealing a significant decrease in both phases (paired Student's *t*-test, $p < 0.006$, 0.003; Fig. 2d).

SAFETY

No adverse events were reported throughout the study period and no significant abnormalities were found in the physical examination findings.

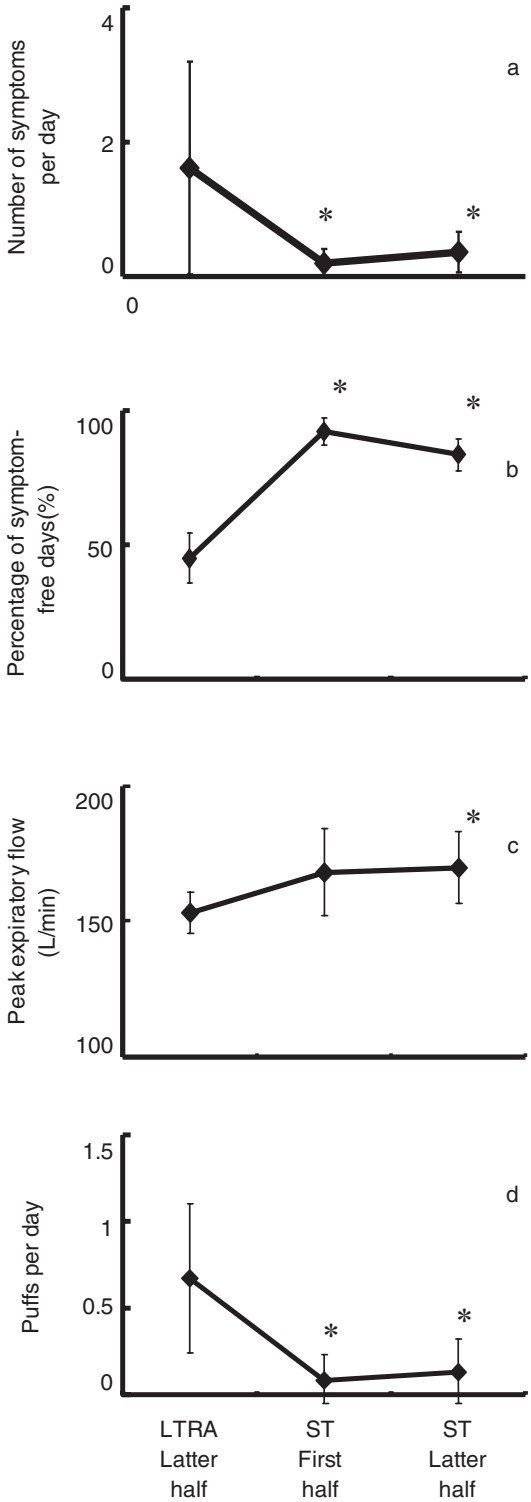

Fig. 2 **a**) Average symptom score, **b**) Proportion of symptom-free days, **c**) Average peak expiratory flow ($n = 3$) and **d**) Average use of rescue medication over the second half of the LTRA screening period (weeks 5 and 6) was compared to the average during the first (weeks 8 and 9) and second (weeks 10 and 11) half of the ST trial period. *$p < 0.05$.

DISCUSSION

We set out to determine the role of ST in LTRA nonresponders with mild-to-moderate persistent asthma before initiating corticosteroid inhalation therapy.

The results of this clinical trial demonstrated that in patients who had not responded to LTRA, a significant improvement occurred after initiation of ST regarding to symptom scores, the number of symptom-free days, peak expiratory flow and use of rescue medication.

Asthma is a chronic inflammation of the lower airways accompanied by hypersensitivity and airway obstruction. Eosinophils play a major role in the allergic inflammation of asthma contributing to tissue injury, vascular leakage, mucus secretion, and airway smooth muscle contraction.[10] Eosinophils produce tissue-injuring substances, such as major basic protein and eosinophil cationic protein (ECP), which cause epithelial cell damage.[11] Reactive oxygen species are also released, resulting in airway tissue injury[12] and airway hypersensitivity. Eosinophils stimulate fibroblasts through TGF-β[13] and GM-CSF,[14] thus promoting subepithelial collagen deposition, and thickening and remodeling of the basement membrane. Production of leukotriene C4 by eosinophils also causes contraction of the bronchial smooth muscle.[15] Th2 cells have been implicated in the local infiltration and activation of eosinophils by the following mechanism. First, Th2 cells produce IL-4 and 13 which upregulates the expression of cell adhesion molecules in the vascular endothelial cells.[16] Secondly, Th2-cell-mediated production of chemokines, such as RANTES and eotaxin, is also involved in the pathogenesis of eosinophilic infiltration.[17] IL-5, also released from Th2 cells, is involved in the activation of eosinophils by promoting their growth, differentiation and chemotaxis.[18] Finally, GM-CSF produced by Th2 cells induces eosinophilic elongation and degranulation resulting in tissue damage.[19]

Horiguchi *et al*.[3] reported that 4 weeks of treatment with ST reduced the peripheral blood eosinophil count, serum level of ECP, ECP level in induced sputum, and inhibited airway hyper-responsiveness. The difference in response to ST and LTRA in each patient may depend upon the pathogenic mechanism of asthma which is heterogeneous in each patient. ST acts through a new concept of blocking the allergic reaction by regulating the production of Th2-cytokines, resulting in the inhibition of eosinophilic migration and activation, to and at the inflammatory site, while LTRA only partially blocks the role of eosinophils in asthma.

Several studies have suggested that there are responders and nonresponders for both LTRA in addition to ST therapy. Approximately 20% of the patients with mild-to-moderate asthma ranging from 3 to 15 years of age have been reported to be nonresponders to ST.[20,21] Analyses of single-nucleotide polymorphisms, gene expression, proteomes, and metabonome have been conducted recently in the hope of obtaining an effective basis for tailored medicine. DNA sequence variants ALOX5 and LTC4S in the leukotriene C (4) synthase genotype is predictive of the clinical response to LTRA.[22,23] Routinely-measured laboratory parameters, such as the percentage of eosinophils and the basophil counts are also good candidates for predicting the response to ST.[24] A combination of several predictors may serve as an indicator for choosing the type of anti-allergic agent to meet the individual needs of all patients and obtain the best effect for each treatment.

Further studies are needed to test the efficacy of ST as a first-line treatment for asthma, since the effectiveness of early intervention using ST can expect to suppress the allergic march. Yoshihara reported that ST given at the food allergy stage, several months after birth, decreased the eosinophil count and increased the Th1/Th2 ratio, suggesting that it was useful in the primary prevention of atopic asthma.[25] On the other hand, the add-on effects of ST in patients treated with various doses of inhaled corticosteroids was reported to improve pulmonary function.[4,26] Moreover, a steroid sparing effect was observed in patients taking high doses of corticosteroids ($\geq$1500 μ/day) to control symptoms in a double-blind, randomized study by Tamaoki *et al*.[4]

The most recent guidelines for the diagnosis and treatment of asthma recommend a low-to-medium dose of glucocorticosteroids for mild-to-moderate persistent patients. The option to be used solely or concurrently with inhaled glucocorticosteroids are sustained release theophylline, long acting beta-agonist, sodium cromoglycate and LTRA. The results from our study indicate that ST should be added to the list of treatment options as it could be a good alternative for patients who have failed to respond to LTRA.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. You Aoyagi and Dr. Yoshikazu Ohtsuka, of the Department of Pediatrics, Juntendo University School of Medicine, for their expertise and contributions.

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