

2. Ooppel T, Schuller E, Günther S, Moderer M, Haberkost J, Bieber T, et al. Phenotyping of epidermal dendritic cells allows the differentiation between extrinsic and intrinsic form of atopic dermatitis. *Br J Dermatol* 2000;143:1193-8.
3. Darsow U, Vieluf D, Ring J. Evaluating the relevance of aeroallergen sensitization in atopic eczema with the atopy patch test: a randomized, double-blind multicenter study. *J Am Acad Dermatol* 1999;40:187-93.
4. Darsow U, Ring J. Airborne and dietary allergens in atopic eczema: a comprehensive review of diagnostic tests. *Clin Exp Dermatol* 2000;25:544-51.
5. Jeep S, Paul M, Müller U, Kunkel G. Honeybee venom allergy: immunoblot studies in allergic patients after immunotherapy and before sting challenge. *Allergy* 1996;51:540-6.
6. Wollenberg A, Wen S, Bieber T. Phenotyping of epidermal dendritic cells—clinical applications of a flow cytometric micromethod. *Cytometry* 1999;37:147-55.
7. Majamaa H, Moisiö P, Holm K, Kautiainen H, Turjanmaa K. Cow's milk allergy: diagnostic accuracy of skin prick and patch tests and specific IgE. *Allergy* 1999;54:346-51.
8. Johansson SGO, Hourihane JO, Bousquet J, Bruijnzeel-Koomen C, Dreborg S, Haahela T, et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001;56:813-24.

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## AT<sub>H</sub>2 cytokine inhibitor for airway inflammation in mild asthma

To the Editor:

T<sub>H</sub>2 cytokines stimulate IgE production, airway mucosal mastocytosis, and eosinophilic airway inflammation, thereby playing an important role in the pathogenesis of asthma.<sup>1</sup> We have recently shown that suplatast tosilate (( $\pm$ )-[2-[4-(3-ethoxy-2-hydroxypropoxy) phenylcarbamoyl] ethyl] dimethylsulfonium *p*-toluenesulfonate), a novel selective T<sub>H</sub>2 cytokine inhibitor that suppresses the release of IL-4 and IL-5,<sup>2</sup> has a steroid-sparing effect in patients with severe asthma.<sup>3</sup> In the present placebo-controlled, parallel-group, multicenter study, we compared the benefits of suplatast tosilate with those of inhaled beclomethasone dipropionate (BDP) in mild persistent asthma.

We recruited 43 asthma patients, aged 21 years or older, whose FEV<sub>1</sub> values were at least 70% of predicted normal. All patients had been treated with as-needed short-acting inhaled  $\beta_2$ -agonist alone for at least 8 weeks before the study. After a 2-week run-in period, each patient was assigned to receive for 8 weeks oral suplatast tosilate (200  $\mu$ g twice daily), inhaled BDP (200 mg twice daily), or placebo in tablets identical to those used for suplatast. Distribution of age, sex, FEV<sub>1</sub>, peak expiratory flow rates, or  $\beta_2$ -agonist use did not differ significantly between the 3 treatment groups. At the end of the run-in period (baseline) and at week 4 and week 8 of the treatment period, airway inflammation was assessed by differential cell counts in the sputum obtained by inhaled 5% hypertonic saline.<sup>4</sup> Concentrations of eosinophil cationic protein and mast cell tryptase in the sputum supernatants were also measured by double-antibody radioimmunoassay and immunofluoroassay, respectively.<sup>5</sup> Written informed consent was obtained from each patient, and the study was approved by the Tokyo Women's Medical University Medical Board and the local ethics committees.

During the trial, 5 patients were withdrawn because of missed clinic visits or rejection of sputum induction. Data were available from 13 patients taking suplatast, 13 patients taking BDP, and 12 patients taking placebo. Suplatast tosilate and BDP similarly decreased sputum eosinophil and mast cell counts and concentrations of eosinophil cationic protein and mast cell tryptase at week 8 (Fig 1). Over the 8-week treatment period, the average percentage change from baseline in FEV<sub>1</sub> was 11.2% (95% CI, 8.9% to 13.5%) with suplatast, 10.4% (8.0% to 12.8%) with BDP, and 1.8% (0.6% to 3.0%) with placebo ( $P < .01$  for each active treatment compared with placebo; no significant difference between suplatast and BDP).

Mean morning peak expiratory flow rates increased in the suplatast and BDP groups, and there were no significant differences in changes from baseline levels between the 2 active treatment groups (Fig 2). Findings from physical examinations or laboratory assessments (hematologic, biochemical, and urinalysis studies) performed every 2 weeks did not change significantly from baseline in either group, and no patient withdrew because of adverse side effects.

In asthmatic airways, CD4<sup>+</sup> cells and, to a lesser extent, CD8<sup>+</sup> cells with a type 2 cytokine phenotype are present. These cells produce IL-5 and GM-CSF, which recruit, mobilize, and activate eosinophils, as well as IL-4, an essential cofactor for local and generalized IgE production. This leads to epithelial shedding, mucus hypersecretion, and airway hyperresponsiveness. Thus, inhibitors and/or antagonists directed against T<sub>H</sub>2 cells might hold promise for the treatment of asthma. According to many guidelines, inhaled corticosteroids are the first-line maintenance therapy for mild to moderate asthma. They can reduce T<sub>H</sub>2 cell-mediated airway inflammation but might cause local side effects, such as cough, laryngeal irritation, and oral candidiasis; they might also cause systemic side effects.<sup>6</sup> In addition, because of the ease in taking medication, asthma patients generally prefer oral drugs to inhaled drugs for long-term maintenance therapy.

Our study provides evidence that suplatast tosilate is as effective as BDP in improving pulmonary function and airway inflammation in patients with mild persistent asthma. Therefore, a selective T<sub>H</sub>2 cytokine inhibitor might be considered for the treatment of this subset of the asthmatic population.

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## REFERENCES

1. Kon OM, Kay AB. T cells and chronic asthma. *Int Arch Allergy Immunol* 1999;118:133-5.
2. Yamaya H, Basaki Y, Togawa M, Kojima M, Kuniwa M, Matsuura N. Down-regulation of Th2 cell-mediated murine peritoneal eosinophilia by antiallergic agents. *Life Sci* 1995;19:1647-54.
3. Tamaoki J, Kondo M, Sakai N, Aoshiba K, Tagaya E, Nakata J, et al.

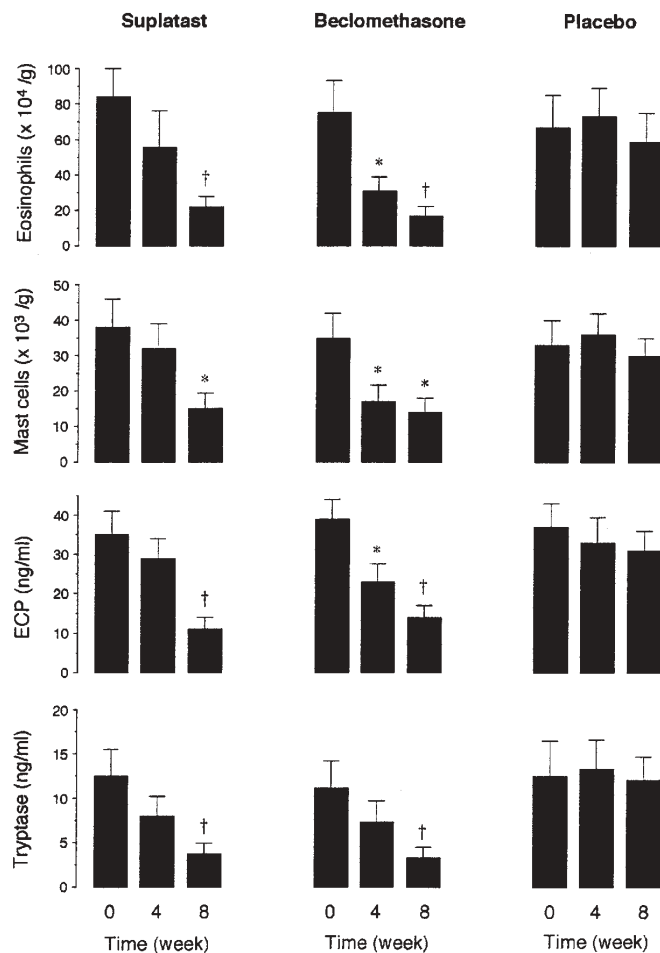


**FIG 1.** Changes in inflammatory markers of induced sputum during an 8-week study of treatment in patients with mild asthma. Values are expressed as means  $\pm$  SEMs. \* $P < .05$  and  $\dagger P < .01$ : significantly different from corresponding values at week 0.

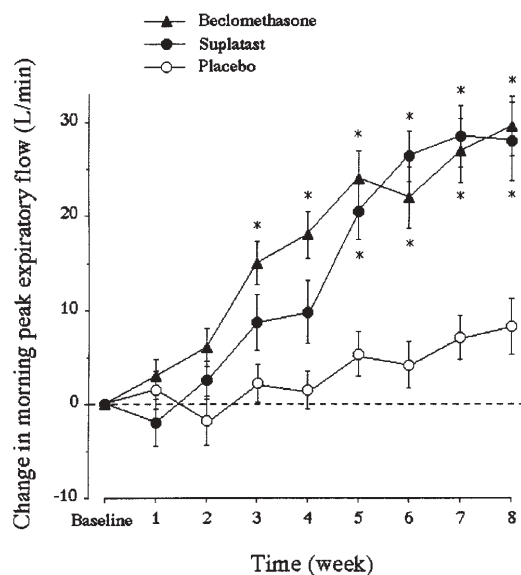


**FIG 2.** Changes in morning peak flow rates from baseline (week 0) during an 8-week study of treatment in patients with mild asthma. Values are expressed as means  $\pm$  SEMs. \* $P < .05$ : significantly different from corresponding values at week 0.

Effect of suplatast tosilate, a  $T_H2$  cytokine inhibitor, on steroid-dependent asthma: a double-blind randomised study. *Lancet* 2000;356:273-8.

- Fahy JV, Liu J, Wong H, Boushey HA. Cellular and biochemical analysis of induced sputum from asthmatic and from healthy subjects. *Am Rev Respir Dis* 1993;147:1126-31.
- Taira M, Tamaoki J, Kondo M, Kawatani K, Nagai A. Serum B12 tryptase level as a marker of allergic airway inflammation in asthma. *J Asthma*. 2002;39:315-22.
- Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. *Arch Intern Med* 1999;159:941-55. doi:10.1067/mai.2003.318

## Fixed drug eruptions caused by tonic water

To the Editor:

Fixed drug eruption (FDE) is a nummular skin lesion that recurs at a given site on re-exposure to a drug. The lesion begins with edema; this is followed by erythema, which darkens to a raised reddish purple color. The lesion or lesions resolve 2 to 3 weeks after drug withdrawal, but they can leave residual hyperpigmentation.<sup>1</sup> The most frequently responsible drug is cotrimoxazole,<sup>2,3</sup> but a number of different drugs, including tetracycline, pyrazolones, barbiturates, aspirin, paracetamol, and many others, have been reported to have induced FDE.<sup>2,4,5</sup>

The origin of FDE is still unclear. Although it is considered a probably immunologic (allergic) drug hypersensitivity reaction,<sup>6</sup> pathogenic mechanisms underlying the appearance of recurrent skin