Effects of Pranlukast, a Cysteinyl Leukotriene Antagonist, on Bronchial Responsiveness to Methacholine in Aspirin-Intolerant Asthmatics Treated with Corticosteroids

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ABSTRACT

Cysteinyl leukotrienes (cysLTs) are considered to be the most important mediator involved in the pathogenesis of aspirin-intolerant asthma (AIA). However, the role of cysLTs in the baseline condition of the pathophysiology of AIA when not exposed to non-steroidal antiinflammatory drugs (NSAIDs) as well as that in the pathophysiology of aspirin-tolerant asthma remains to be elucidated. Therefore, we evaluated the effect of pranlukast, a potent, selective cysLT receptor antagonist, on bronchial responsiveness to methacholine, a non-specific stimulus, in 7 well-controlled aspirin-intolerant asthmatics receiving oral or inhaled corticosteroid treatment. Pranlukast was orally administered at a dose of 225 mg twice daily to all patients for 4 weeks, and the methacholine challenge test was performed before and after pranlukast treatment. The methacholine provocative concentration producing a 20% fall in forced expiratory volume in 1 second (PC20-FEV1) was calculated as an index of bronchial hyperresponsiveness (BHR). The geometric mean values of PC20-FEV1 significantly (p = 0.028) increased from 0.34 mg/dl to 0.61 mg/dl after pranlukast treatment. No significant differences were observed in the baseline values of forced vital capacity (FVC) or FEV1 before and after pranlukast treatment. These findings suggest that antagonism of endogenous cysLT by pranlukast may be responsible for the improvement of BHR to methacholine.

Key words: Pranlukast, Cysteinyl leukotriene, Bronchial responsiveness, Aspirin-intolerant asthma

MATERIALS AND METHODS

The subjects consisted of 7 well-controlled AIA patients on corticosteroid treatment, who were diagnosed by sulpyrine challenge test or by a history of asthmatic attack induced by NSAIDs (Table 1). All the subjects were non-smokers. Informed consent was obtained from all patients after the purpose of the study was explained. These patients had been treated with medication without any modification (see Table 1) for 6 months before pranlukast treatment.

Pranlukast was orally administered at a dose of 225 mg twice daily to all patients for 4 weeks. Concomitant medication was continued without...
### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Type</th>
<th>Severity</th>
<th>Complication</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62</td>
<td>F</td>
<td>Ext</td>
<td>Moderate</td>
<td>AR/CS/NP</td>
<td>BDP (µg/day) 600</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>F</td>
<td>Int</td>
<td>Severe</td>
<td>AR/CS/NP</td>
<td>BDP (µg/day) 400</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>F</td>
<td>Ext</td>
<td>Moderate</td>
<td>AR/CS/NP</td>
<td>BDP (µg/day) —</td>
</tr>
<tr>
<td>4</td>
<td>53</td>
<td>M</td>
<td>Ext</td>
<td>Severe</td>
<td>CS</td>
<td>BDP (µg/day) 1200</td>
</tr>
<tr>
<td>5</td>
<td>27</td>
<td>M</td>
<td>Ext</td>
<td>Moderate</td>
<td>AR/CS/NP</td>
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</tr>
<tr>
<td>6</td>
<td>65</td>
<td>F</td>
<td>Ext</td>
<td>Mild</td>
<td>CS/NP</td>
<td>BDP (µg/day) 100</td>
</tr>
<tr>
<td>7</td>
<td>66</td>
<td>F</td>
<td>Int</td>
<td>Severe</td>
<td></td>
<td>BDP (µg/day) —</td>
</tr>
</tbody>
</table>

BDP: Beclomethasone dipropionate; Theo: Theophylline; PSL: Prednisolone; F: Female; M: Male; Ext: Extrinsic asthma; Int: Intrinsic asthma; AR: Allergic rhinitis; CS: Chronic sinusitis; NP: Nasal polyp; I: Inhaled administration; O: Oral administration.

### Results

The geometric mean values of PC20-FEV1 significantly increased from 0.34 (GSEM: 1.71) mg/ml to 0.61 (GSEM: 1.56) mg/ml after pranlukast treatment (p = 0.028, Wilcoxon signed-ranks test) (Fig. 1). No significant differences were observed in the baseline values of FVC or FEV1 before and after pranlukast treatment (Table 2).

### Discussion

It has been observed that the baseline urinary excretion of LTE4, expression of LTC4 synthase in bronchial specimens, and sensitivity to inhalation of LTE4 in patients with AIA are significantly higher than those in patients with aspirin-tolerant asthma. Thus, patients with AIA are considered to have both an increased basal production of cysLTs and an increased bronchial responsiveness to cysLTs even when not exposed to NSAIDs.

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**Fig. 1.** Effect of oral administration of pranlukast on bronchial responsiveness to methacholine in aspirin-intolerant asthmatics undergoing oral or inhaled corticosteroid treatment. Group values are expressed as geometric means with geometric standard errors of the mean. PC20-FEV1 indicates the concentration of methacholine producing a 20% fall in forced expiratory volume in 1 second.
In the present study, pranlukast significantly improved baseline BHR to methacholine in well-controlled aspirin-intolerant asthmatics with oral or inhaled corticosteroid treatment, and the increase in PC_{20}-FEV_1 was 1.8 times. On the other hand, pranlukast did not affect baseline pulmonary function. Since all patients in the present study had been well controlled with the concomitant treatment, these findings suggest that antagonism of endogenous cysLTs by pranlukast may be responsible for the improvement of BHR to methacholine.

Fujimura et al. reported that oral pranlukast significantly improved baseline BHR to methacholine with an increase of 1.6 times in PC_{20}-FEV_1, accompanied by no improvement of baseline pulmonary function in mild stable asthmatics without inhaled or oral corticosteroid therapy. Although the severity of the disease and profiles of concomitant treatment were different from those in the present study, the effect of pranlukast on BHR to methacholine in our patients was somewhat higher, suggesting the importance of cysLTs in the baseline condition of the pathophysiology of AIA.


REFERENCES
