Improved Case of Bronchial Asthma by Re-administration of Pranlukast from Montelukast: Evaluation of Eosinophilic Inflammation in the Peripheral Airway

Hiroyuki Ohbayashi

ABSTRACT

Background: Pranlukast and Montelukast are Cysteinyl leukotriene receptor antagonists with almost the same pharmacological activity. However, I will describe a case in which these drugs showed different therapeutic effects on clinical symptoms during the daytime and eosinophilic inflammation in the peripheral airway.

Methods: A 70-year-old male patient with non-atopic bronchial asthma who was treated with 400 μg/day of Budesonide Turbuhaler® (BUD-TH) changed from Pranlukast (225 mg, twice daily) to Montelukast (10 mg, one tablet before sleeping), resulting in worsening clinical symptoms consisting of sputum and cough in the daytime, mainly at lunch time. Due to the fact that the symptoms did not improve sufficiently, instead of increasing the dose of BUD-TH, we investigated the clinical symptoms and pulmonary functions as well as measured the mean eosinophil count, eosinophil cationic protein (ECP) and eotaxin in the hypertonic saline-induced sputum prior to administration of Pranlukast, and 4 and 8 weeks after the re-administration of Pranlukast from Montelukast.

Results: Following the re-administration of Pranlukast, the clinical symptoms disappeared within a few days and pulmonary function improved within 4 weeks. Eosinophils in the induced sputum almost completely disappeared for 4 weeks. The sputum ECP and eotaxin before and 4 weeks after the re-administration of Pranlukast changed from 700 μg/l to 192 μg/l, and 69.9 pg/ml to 30.6 pg/ml, respectively. After 8 weeks, no sputum induction was found.

Conclusions: The clinical difference between these two similar antagonists may be caused by the time difference relating to when and how often each drug is administered, suggesting the existence of the lunchtime dip.

KEY WORDS

asthma, eosinophil cationic protein (ECP), eotaxin, induced sputum, Pranlukast

INTRODUCTION

Cysteinyl leukotriene (CysLT) receptor antagonists are defined as drugs for the long-term control of asthma in the Guide for Asthma Management and Prevention published by the Global Institute for Asthma (GINA)1 and in the Asthma Prevention and Management Guidelines 2003 (JGL).2 At present, the CysLT1 receptor antagonists used in Japan are Pranlukast, Montelukast and Zafirlukast. These three drugs show almost the same levels of CysLT1 receptor antagonism.3 Although no significant differences in clinical effects were found in a comparative study of Pranlukast and Montelukast,4 both drugs differ in the type of the drug form; a capsule or a small tablet, and the daily administrative time; when and how often each drug is taken. In daily use, the recommended daily dose of Pranlukast for adults is 4 cap-
sutures (450 mg/day), taken twice daily (after breakfast and dinner), while the recommended daily dose of Montelukast is 10 mg/day taken once prior to sleeping.

Drug compliance is highly dependent on the drug form and the administration time, especially in elderly asthmatic patients. The author has often encountered patients who found it difficult to take capsules or wished to decrease the number of capsules they were required to take, often resulting in an administrative change from Pranlukast to Montelukast. However, I have also experienced not a few patients who then requested re-administration of Pranlukast, due to aggravated subjective symptoms which developed after the change of drugs. The case report given below involves one such patient.

In this case report, in addition to evaluating the changes in clinical symptoms and pulmonary functions, I also investigated the eosinophil count, eosinophil cationic protein (ECP) and eotaxin in the hypertonic saline-induced sputum before and after the re-administration of Pranlukast from Montelukast.

**CLINICAL SUMMARY**

The patient was a 70-year-old male with non-atopic bronchial asthma who visited our department in February 2001 and was given Beclomethasone dipropionate (BDP), a steroid inhalant, at a dose of 800 μg/day, based on Step 3 of the "Severity Criteria for Bronchial Asthma" developed by the Japanese Society of Allergy. In May 2002, his asthma was under effective control using 400 μg/day of Budesonide Turbuhaler® (BUD-TH), a steroid inhaler, 100 mg/day of theophylline, 2 mg/day of a Tulobuterol patch, and 450 mg/day of Pranlukast. In November 2002, because of his good stable asthmatic condition, the patient requested a decrease in the number of oral drug capsules. Therefore, 4 capsules of Pranlukast were changed into one tablet of Montelukast at bedtime. For several weeks after the change, his asthmatic condition showed no remarkable change, and then the amount of sputum and cough gradually increased in the daytime, in particular at lunchtime. In June 2004, he had a moderate asthma attack and was admitted to our hospital. After admission, BUD-TH was increased to 600 μg/day and wheezing and breathing difficulty quickly improved, but the sputum associated with cough persisted during the daytime. Again based on the patient’s request, Montelukast was replaced with Pranlukast in September 2004. A few days afterwards, the sputum associated with cough at daytime disappeared spontaneously and completely. According to his daily asthma diary and a detailed interview with his family, his drug compliance was confirmed as almost 100% over this course. His clinical course for the two months is shown in Figure 1.

**PATHOLOGICAL FINDINGS**

In order to investigate the relationship between the changes of his asthmatic condition and eosinophilic inflammation in his peripheral airway, the induced sputum tests were performed before and after the change from Montelukast to Pranlukast. Prior to performing the each test, the purpose, methods and risks of the test were explained to the patient in detail each time, in accordance with the code of ethics at our hospital which is based on the Declaration of Helsinki of 1995 (as revised in Edinburgh 2000). After informed consent was obtained, the test was conducted. The patient inhaled a 10% salt solution for 15 minutes using an ultrasonic nebulizer, and the induced sputum was collected by a deep cough after gargling. The saliva component was removed from the collected sputum, and a smear preparation of the viscous sputum component was made. This was then stained with Wright-Giemsa stain. The mean number
of eosinophils per 5 microscopic views (×400) was obtained, based on the following criteria: per 5 views, one or less eosinophil, (−); one to less than 10, (+); 10 to less than 20, (2+); 20 or more, (3+). The sputum ECP and eotaxin levels were determined according to the method of Motojima et al. Induced sputum was kept at 4°C from the time of collection to sample preparation; samples were always prepared within 6 hours. The sputum ECP and eotaxin levels were determined using an ECP FEIA kit (Pharmacia & Upjohn Diagnostics AS, Uppsala, Sweden) and an eotaxin ELISA kit (R&D Systems, MN, USA), respectively. The mean eosinophil count and the ECP and eotaxin levels in induced sputum immediately before, and 4 and 8 weeks after re-administration of Pranlukast were determined according to the method of Motojima et al. Induced sputum was kept at 4°C from the time of collection to sample preparation; samples were always prepared within 6 hours. The sputum ECP and eotaxin levels were determined using an ECP FEIA kit (Pharmacia & Upjohn Diagnostics AS, Uppsala, Sweden) and an eotaxin ELISA kit (R&D Systems, MN, USA), respectively. The mean eosinophil count and the ECP and eotaxin levels in induced sputum immediately before, and 4 and 8 weeks after re-administration of Pranlukast are shown in Table 1. Pulmonary function data from April 2002, i.e., before the initial change from Pranlukast to Montelukast, to November 2004 are shown in Table 2. All pulmonary function data were measured between 11 a.m. and noon. Four weeks after the change from Montelukast to Pranlukast, the eosinophil count in induced sputum was negative, and sputum ECP and eotaxin were markedly decreased. Furthermore, 8 weeks after this change, no sputum could be induced. The pulmonary function values were aggravated after the change from Pranlukast to Montelukast and then improved after re-administration of Pranlukast (Table 2).

**Table 1** Results of hypertonic saline-induced sputum tests

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Eo</th>
<th>ECP (μg/l)</th>
<th>Eotaxin (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before re-administration of Pranlukast</td>
<td>(+)</td>
<td>700</td>
<td>69.9</td>
</tr>
<tr>
<td>4 weeks later</td>
<td>(−)</td>
<td>192</td>
<td>30.6</td>
</tr>
<tr>
<td>8 weeks later</td>
<td></td>
<td>no sputum induction</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Eo = eosinophil, ECP = eosinophil cationic protein

**Criteria for Eosinophils**

<table>
<thead>
<tr>
<th>Mean counts of eosinophils in 5 HPF (X)</th>
<th>Judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>X &lt; 1</td>
<td>(−)</td>
</tr>
<tr>
<td>1 &lt; or = X &lt; 10</td>
<td>(+)</td>
</tr>
<tr>
<td>10 &lt; or = X &lt; 20</td>
<td>(2+)</td>
</tr>
<tr>
<td>20 &lt; or = X</td>
<td>(3+)</td>
</tr>
</tbody>
</table>

**Table 2** Changes in pulmonary function test data with time

<table>
<thead>
<tr>
<th>Time Point</th>
<th>%VC (%)</th>
<th>%FVC (%)</th>
<th>%FEV1.0 (%)</th>
<th>V50 (L/sec)</th>
<th>V25 (L/sec)</th>
<th>V25/H (L/sec/m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002.4</td>
<td>70.6</td>
<td>55.1</td>
<td>72.9</td>
<td>1.11</td>
<td>0.68</td>
<td>0.46</td>
</tr>
<tr>
<td>2002.11 change from Pranlukast to Montelukast</td>
<td>72.4</td>
<td>57.8</td>
<td>68.4</td>
<td>1.02</td>
<td>0.39</td>
<td>0.27</td>
</tr>
<tr>
<td>2003.4</td>
<td>62.7</td>
<td>58.3</td>
<td>64.0</td>
<td>0.83</td>
<td>0.54</td>
<td>0.36</td>
</tr>
<tr>
<td>2003.10</td>
<td>61.7</td>
<td>53.5</td>
<td>69.6</td>
<td>0.57</td>
<td>0.66</td>
<td>0.44</td>
</tr>
<tr>
<td>2004.6 dose of BUD-TH increased from 400 μg/day to 600 μg/day</td>
<td>46.6</td>
<td>42.8</td>
<td>61.3</td>
<td>0.88</td>
<td>0.64</td>
<td>0.44</td>
</tr>
<tr>
<td>2004.9 (before change of drugs)</td>
<td>49.1</td>
<td>49.1</td>
<td>65.4</td>
<td>0.86</td>
<td>0.74</td>
<td>0.50</td>
</tr>
<tr>
<td>2004.9 change back to Pranlukast from Montelukast</td>
<td>51.2</td>
<td>50.1</td>
<td>71.4</td>
<td>1.06</td>
<td>0.73</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Abbreviations: VC = vital capacity, FVC = forced vital capacity, FEV 1.0 = forced expiratory volume during 1 second

DISCUSSION

Pranlukast and Montelukast are CysLT1 receptor antagonists with almost the same pharmacological anti-LT activity, although their administered doses and drug forms are different. In the present case, the patient experienced subjective asthma symptoms after switching from Pranlukast to Montelukast which then improved after a change back to Pranlukast. This was objectively proved based on the results from the pulmonary function data. Collectively, the objective and subjective results suggest that Pranlukast and Montelukast had a different clinical effect in this patient.
In addition to exerting strong LT receptor antagonism, CysLT1 receptor antagonists suppress eosinophil activation, leading to reduction of serum ECP,6,7 and inhibit cellular infiltration of inflammatory cells in bronchial mucosa,8 as well as eosinophilic migration through suppression of eotaxin, an eosinophilic migration factor.9 However, a direct comparison of eosinophil suppression has not been performed for Montelukast and Pranlukast. We therefore found the different suppression effects of Montelukast and Pranlukast in the present case to be of particular interest, and we examined the eosinophilic conditions of the peripheral airway before and after the change of drugs, using the induced-sputum method described above. It is generally accepted that hypertonic saline-induced sputum in this study can be used to determine the main conditions of the peripheral airway,10,11 and this method has recently received attention due to its clinical applicability; it is easily performed for outpatients and shows good reproducibility.12,13 In the present case, markedly reduced levels of eosinophils, ECP and eotaxin were found in the induced sputum after re-administration of Pranlukast, compared to the levels during treatment with Montelukast, suggesting that Pranlukast is able to reduce peripheral airway eosinophilic inflammation and implying that there may be a clinical difference between Pranlukast and Montelukast in this respect.

In trials in normal volunteers in Japan, the time to reach the peak Pranlukast concentration in blood was 5.2 ± 1.1 hr and the half-life (t1/2) was 1.15 ± 0.13 hr, suggesting that Pranlukast administration twice a day is necessary to maintain an effective blood concentration of 30 ng/ml.14 On the contrary, the peak blood Montelukast concentration was reached in 3.9 ± 1.5 hr and the t1/2 was 4.57 ± 0.39 hr, suggesting that Montelukast repeat administration at bedtime allows a sufficient blood concentration to be maintained until noon the next day.15 However, pharmacokinetics can differ on an individual basis, and in the present case the patient showed asthma symptoms before noon, suggesting that the blood concentration of Montelukast may have already decreased below an effective concentration before noon. As shown in Figure 2, in Pranlukast-treated patients the drug concentration in the blood remained almost at its peak concentration around noon. Hence, there may be significant differences in the blood concentrations of Pranlukast and Montelukast at this time of day.

Aggravated asthma symptoms that occur early in the morning are considered to be caused by a morning "dip", and Montelukast is administered at bedtime to suppress such symptoms. However, at the 2004 American College of Chest Physician (ACCP) Annual Congress, Medarov gave a very interesting presentation,16 in which it was reported that the pulmonary function data of 4800 asthma patients showed a lunch-time dip around noon, i.e., the lowest pulmonary function occurred at this time, as well as a morning dip. In the present case, the patient also showed aggravated symptoms with low pulmonary function before noon during treatment with Montelukast, consistent with data from Medarov. Re-administration of Pranlukast twice a day improved the symptoms of the patient, and therefore I concluded that a difference in blood concentration between Pranlukast and Montelukast may be one of the reasons for the clinical difference between the two drugs in the patient.

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16. Medarov BI. Hour-to-hour variation of FEV1 / FVC. CHEST 2004;126:744S.