Comparative Evaluation of the Leukotriene Receptor Antagonist Pranlukast versus the Steroid Inhalant Fluticasone in the Therapy of Aged Patients with Mild Bronchial Asthma

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Summary

A comparative study was conducted in elderly subjects with mild bronchial asthma to investigate the clinical usefulness of monotherapy with a leukotriene receptor antagonist in comparison to an inhaled corticosteroid. A total of 41 elderly patients aged 65 years or older with mild bronchial asthma, classified as being in severity step 1 and 2, were randomly assigned to the following two treatment groups: a pranlukast (CAS 103177-37-3, Onon) treatment group of 21 patients and an inhaled corticosteroid treatment group of 20 patients. Patients of the former group received pranlukast 450 mg daily and those of the latter group received fluticasone (CAS 90566-53-3) 200 μg daily for eight weeks. In the reference group, one patient was found to suffer from oral candidiasis 4 weeks after the start of the study. Therefore the evaluation was conducted on the remaining 19 participants. The evaluation parameters examined were obtained by keeping an asthma diary, determinations of PEF (peek expiratory flow), use frequency of β2 stimulants, changes in symptom scores, and medication compliance. Further, measured before and after therapy were the ratio of peripheral blood eosinophils counts, serum ECP (eosinophils cat-ionic protein), ECP levels induced sputum, and forced expiratory volume in one second (FEV1.).

As a result, in the time-course changes of symptoms scores and morning PEF, swift improvement was noted in the pranlukast group. Further, in the variables such as use frequency of β2 stimulants, serum ECP levels, ECP levels induced sputum, and FEV1., an almost comparable level of improvement to the fluticasone group was demonstrated. From the above results, it was deemed that in elderly patients with mild bronchial asthma classified as steps 1 and 2, the pranlukast monotherapy, with superior medication compliance to inhaled therapy, would produce an equivalent level of clinical efficacy to the monotherapy with inhaled corticosteroid (fluticasone 200 μg daily).

Key words

- Antiasthmatics
- Bronchial asthma, elderly
- CAS 103177-37-3
- Leukotriene receptor antagonist
1. Introduction

Advances have been made in the knowledge of physio-pathological and etiological mechanisms involved in allergic diseases: bronchial asthma (hereafter abbreviated to asthma) has come to be recognized as a disease with three outstanding features – viz., exaggerated airway hypersensitivity, reversible airway constriction and allergic airway inflammation [1]. Airway inflammation that is dominated by the presence of eosinophils, in particular, is characterized by the involvement of various cytokines and chemical mediators; and for the treatment of the disease, major efforts are being made to suppress these endogenous substances. There is no question that the current thrust of anti-inflammatory therapy is the use of steroid inhalants. The recent trends toward a reduction in asthmatic mortality and the admittance of fewer patients at hospitals for asthmatic attacks are often attributed to the increasing frequency of steroid inhalant use [2, 3]. However, steroid preparations are plagued by their untoward effects and the emergence of dependency or problems associated with methods of inhalation. For the treatment of aged asthmatic patients who have difficulty in understanding asthma therapy and lack the desire for self care, the importance of managing these problems has been pointed out [4]. In the face of an aging society, the aged asthmatic population will continue to increase and the management of these patients appears to be an urgent issue.

Pranlukast is a cysteiny leukotriene (cys LT) receptor antagonist that has been developed in Japan. It exhibits a potent bronchoconstricting action, suppresses both immediate and delayed reactions to antigen-provocation by inhalation, exhibits anti-inflammatory action suppressing eosinophil infiltration and activation [5–8], and indicates an outstanding clinical efficacy.

According to the “Guideline for the Prevention and Management of Asthma 2003” made public in Japan, pranlukast has been given a certain recognition: its continuous use is recommended for cases of mild and sustained type (step 2), intermediate sustained type (step 3) and severe sustained type (step 4) and its application is considered for the mild intermittent type (step 1). For mild asthma for the aged (steps 1 and 2), however, there have been few comparative evaluations of monotherapy using steroid inhalants or LT receptor antagonists. In the current study, pranlukast alone was administered to aged patients with mild asthma and the result was compared against that of a steroid inhalant.

2. Subjects and method

2.1. Patients

The subjects were 41 ambulatory patients over 65 years who were being treated at our institution for mild asthma (classified as step 1 or 2 according to the “Guideline for the Prevention and Management of Asthma 2003” (Table 1). Asthma in the aged in this study was defined as the asthmatic condition that was found in those 65 years or older and confirmed to be at least 20% reversible with the use of β2 stimulants. Furthermore, those exhibiting evident low attenuation areas (LAA) on computer tomographs were excluded. The study was conducted according to the ethical standards of our medical center, which requires informed consent from each patients (Department of Internal Medicine, Fujita Health University, Toyoake, Japan).

The test design is shown in Fig. 1. Having obtained an informed consent from each person, they were randomly allocated to the test group (n = 21) or the reference group (n = 20). For the former, the dosage of pranlukast was set at 450 mg/day and for the latter, 200 μg/day of fluticasone was given. Both groups remained on the regimen for 8 weeks. In the reference group, one patient was found to suffer from oral candidiasis 4 weeks after the start of the study. Therefore the evaluation was conducted on the remaining 19. Co-medication during the test period was limited to β2 stimulants that were given as needed.

Evaluation was based on the entries in each patient’s “asthma diary”, data on PEF (peak expiratory flow), frequency of the use of β2 stimulating agents, changes in symptom score (based on the scale in Santanello’s symptom diary), and the patient’s compliance to medication. In addition, the following were determined before and after medication: peripheral blood eosinophil ratio, serum ECP (eosinophil cationic protein) level, ECP in the induced sputum and one second value.

2.2. Drugs

Pranlukast (CAS 103177-37-3; Onon®; Ono Pharmaceutical Co., Ltd., Japan) (test drug) is a cys LT receptor antagonist that has been developed in Japan. It exhibits a potent bronchoconstricting action, suppresses both immediate and delayed reactions to antigen provocation by inhalation, exhibits anti-inflammatory action suppressing eosinophil infiltration and activation [5–8], and indicates an outstanding clinical efficacy. Fluticasone (CAS 90566-53-3) was the reference drug. All the experimental drugs were obtained from a pharmacy.

2.3. Statistics

Friedman’s test was employed for statistical analysis. When significance was recognized, a Wilcoxon signed-rank test with Bonferroni correction was conducted for inter-group compar-
Study design

Parameters

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Fig. 1: Study design and parameters.

3. Results

Table 1 shows the backgrounds of the patients. The test group included 8 men and 13 women (mean age, 72.1 ± 5.29 years); and the mean duration of the illness was 9.82 ± 3.60 years. The group included 9 with the atopic type and 12 with the non-atopic type and the severity was represented by step 1 (5) and step 2 (16). The reference group was composed of 7 men and 12 women (mean age, 69.6 ± 5.58 years) and the mean duration of their illness was 9.28 ± 3.02 years. This group included 5 with the atopic type and 14 with the non-atopic type. In regard to the severity of the illness, 4 were found to be in step 1 and 15 in step 2 (Table 1). The patient who developed oral candidiasis 4 weeks later and dropped out of the study was excluded.

Compliance to the medication was found to be 92.8 ± 2.3% and 81.4 ± 4.0% for the test group (n = 21) and the reference group (n = 19), respectively, the percentage being much greater for the former. In the latter, 3 of the 20 patients had difficulty in understanding the instructions given on inhalation therapy until repeated explanations had been provided with the help of their family members.

After one week, the symptom scores improved more eminently in the test group (n = 21, p < 0.01) than the reference group (n = 19, p < 0.05). However, the pattern reversed after 4 weeks (Fig. 2).

After one week, the PEF measured in the morning was found to increase more rapidly in the test group (n = 21, p < 0.01) than in the reference group (n = 19, p < 0.05). After 4 weeks, a greater rise was noted in the latter (Fig. 3).

The frequency of the use of β₂ stimulants by the two groups was expressed as: the test group (n = 21, p < 0.05) and the reference group (n = 19, p < 0.01). Significant reductions were noted in both groups after 8 weeks (Fig. 4).
These findings indicated that the compliance was significantly better in the test group in comparison with the reference group. In examining symptom scores and changes in PEF in the morning, early (one week later) improvement was more significant in the test group than in the reference group. The improvement in the two groups was generally equal in the frequency of use of β₂ stimulants, serum ECP level, ECP contents in the induced sputum and changes in one-second volume.

4. Discussion

Based on the “Guideline for the Prevention and Management of Asthma 2003” [1], steroid inhalants with potent anti-inflammatory actions are firmly established in Japan as the drugs of choice for long-term care of aged patients with mild asthma (steps 1 or 2). However, aged patients are often slow in understanding; despite repeated instructions on how to use the inhalation equipment and encouragement to gargle, they are limited in learning the proper use of steroid inhalants. LT receptor antagonists, on the other hand, are oral agents equipped with a potent broncho-constricting action and an anti-inflammatory effect to suppress eosinophilic infiltration and activation [5–8]; the oral route of administration facilitates patient compliance. Furthermore these agents have shown a possibility to reach the peripheral airway. It has been suggested that LTC₄ is significantly involved in the physiopathology of asthma regardless of a patient’s age or the type of asthma [9].
There are still unanswered questions as to the significance of LT receptor antagonist monotherapy for aged patients with mild asthma. Thus the authors undertook an evaluation of the clinical efficacy of pranlukast monotherapy in comparison with fluticasone in aged patients with mild asthma (steps 1 or 2).

On the topic of a patient’s compliance to medication, the test group, in comparison with the reference group, performed significantly better, suggesting the merit of pranlukast as an oral agent for the aged. In the reference group, on the other hand, one of the 9 participants developed oral candidiasis, indicating a limitation in their capability to learn the inhalation technique. A need to alter the design of inhalation device was also indicated.

After one week, the test group indicated swift improvement in the symptom scores and PEF measured in the morning. The improvement in the frequency of the use of $\beta_2$ stimulants, serum ECP level, ECP content in the induced sputum and one-second value (FEV$_{1.0}$) for the test group was comparable to those of the reference group.

These findings indicated that for aged patients with mild asthma (step 1 or 2), monotherapy using pranlukast is superior to inhalation therapy in patient compliance to medication and comparable to steroid inhalant monotherapy (fluticasone 200 µg/day) in its clinical efficacy.

While steroid inhalants are effective in almost all patients, there are responders and non-responders to the effects of LT receptor antagonists [8]. However, because the latter is given orally, it shows promise for improving airway inflammation by reaching the peripheral airway through systemic circulation. A need for further studies with a larger number of clinical cases was suggested.

Steroid inhalants are still the first-line drugs for long-term care of aged patients with mild asthma. However, LT receptor antagonists are superior in patients’ compliance to medication and the current study confirmed that they produce a reliable anti-asthmatic effect. It was suggested that in future, they may constitute an approach to control asthma in aged patients.

References