

Addition of Leukotriene Receptor Antagonists to Inhaled Corticosteroids Improved QOL of Patients with Bronchial Asthma Surveyed in Suburban Tokyo, Japan

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ABSTRACT

Background: Bronchial asthma is a chronic inflammatory disease that has a severe impact on health worldwide.

Methods: A survey of 10,771 patients with bronchial asthma in the Tama region, Tokyo was conducted for 5 years to examine treatment and quality of life (QOL). Subjects were patients aged ≥ 16 years and their physicians who replied to a questionnaire sent in November from 2002 to 2006. Symptoms of bronchial asthma, visits to an emergency room, use of drugs, and severity of asthma were investigated.

Results: Asthmatic symptoms improved over the 5 years, with a reduction in the number of emergency room visits. Since inhaled corticosteroids (ICS) were used by $>80\%$ of patients in 2002, we suspected that increased use of concomitant leukotriene receptor antagonists (LTRA) and long-acting β_2 agonists (LABA) might have contributed to these findings. The effects of these drugs were compared between ICS + LTRA ($n = 45$) and ICS + LABA ($n = 54$) groups of patients. There was no significant difference in the ICS dose between these groups. In the ICS + LABA group, 18.5% and 22.2% of patients visited an emergency room before and after initiation of combination therapy, respectively, with no statistically significant difference. In contrast, the rate of emergency room visits in the ICS + LTRA group decreased from 24.4% to 6.6% after addition of LTRA.

Conclusions: These results suggest that the frequency of visits to an emergency room was decreased by complementing the anti-inflammatory effect of ICS with further treatment of inflammation, particularly with LTRA.

KEY WORDS

bronchial asthma, inhaled corticosteroids, leukotriene receptor antagonists, quality of life, survey

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Received 1 December 2010. Accepted for publication 11 February 2011.

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INTRODUCTION

Bronchial asthma is a chronic inflammatory disease of the airways¹ that is commonly treated with anti-inflammatory agents such as inhaled corticosteroids (ICS) and leukotriene receptor antagonists (LTRA). Use of these drugs has decreased the rates of hospitalization and death due to asthma attacks. In Japan, more than 6,000 people died from asthma in the 1990s, whereas the total number of deaths in the current century was less than 2,500 by 2008.² Asphyxiation caused by a severe attack is a major cause of death in asthma, and most cases involve sudden death.³ The pathology of asthma includes airway inflammation, which leads to airway obstruction due to smooth muscle contraction, mucosal swelling, increased airway secretion, and airway wall remodeling.⁴ Autopsies show that patients with asthma who died suddenly had chronic inflammation in the airways and that death was due to aggravation of inflammation.³ Therefore, inappropriate daily management of asthma can induce severe attacks that can result in death, which indicates the importance of long-term asthma control with treatment against airway inflammation.⁵

In Finland, a 10-year comprehensive program has decreased the hospitalization period and deaths due to asthma, despite an increase in the number of patients with asthma. This program has also contributed to reduction of healthcare costs. The main strategy is to initiate treatment with ICS at an early stage. As a result, ICS are prescribed for 80% of patients in Finland,⁶ in contrast to 15% in Japan in 2005.⁷ Therefore, it is important for the government, allergists and primary care physicians in Japan to cooperate with each other in promoting standard treatment with ICS to decrease mortality due to asthma. Furthermore, elderly patients (aged ≥ 60 years) accounted for 90% of deaths due to asthma in Japan,⁸ and this percentage has increased year by year. This makes it important to improve asthma treatment for elderly patients in order to decrease mortality due to asthma. Elderly patients in Japan often have age-associated respiratory dysfunction, complicated chronic obstructive pulmonary disease (COPD) and poor adherence to inhalants, all of which may reduce ICS distribution to peripheral tissues and result in incomplete treatment of inflammation.

To examine trends in asthma treatment, local hospitals and primary care physicians in Tama region, 130 facilities in total, established the Tama Research Group on QOL in Bronchial Asthma. We conducted a survey in a total of 10,771 bronchial asthma patients over 5 years from 2002 to 2006 using a questionnaire prepared by the Tama Research Group to evaluate the conditions and QOL of patients with asthma. Tama region is located in the western part of Tokyo and consists of commercial, industrial and agricul-

tural zones. It has an area of 1,169.49 km² and a population of approximately 4 million. Based on this survey, we analyzed whether an increase in ICS use improved asthma control in the region and whether addition of LABA or LTRA to ICS changed the QOL of asthma patients.

METHODS

The survey was conducted each November from 2002 to 2006. The subjects were outpatients diagnosed with bronchial asthma in hospitals, respiratory clinics and general clinics in Tama region. All the subjects gave informed consent. This study was approved by the ethics committee of the Tama Research Group to evaluate the conditions and QOL of patients with asthma.

The questionnaire used in the survey was prepared by the Tama Research Group on QOL in Bronchial Asthma, consisting of questions for patients and physicians to define management and severity of bronchial asthma and self-assessment by patients, based on the Asthma Prevention and Management Guidelines 1998 (JGL 1998) of the Japanese Society of Allergology⁹ (Table 1). The questionnaire included 13 questions for patients on current subjective symptoms, incidence of symptoms, time of symptom appearance, sleep, effects on daily life, compliance with drug regimens, and visits to an emergency room. The questionnaire also included questions for physicians regarding treatment and severity. Based on the Asthma Prevention and Management Guidelines 1998 (JGL1998) of the Japanese Society of Allergology,⁹ severity of asthma was classified into Steps 1 to 4, which are also valid in the latest version of the Asthma Prevention and Management Guidelines 2009.¹⁰ The ICS dosage indicated by a physician in the questionnaire was converted to the amount of beclomethasone dipropionate (BDP) in the dosage. Based on the definition of the Global Initiative for Asthma (GINA) control level¹¹ (Table 2), patients who answered "No" to questions 3, 5, 6 and 12 in the Tama original questionnaire (which were consistent with the items for the GINA control level) were considered to have asthma that was controlled.

To determine which medication would have additional effects to those of ICS on decreasing the number of emergency visits, we selected 54 cases that utilized LABA in addition to ICS (ICS + LABA group) and 45 cases with LTRA in addition to ICS (ICS + LTRA group). We checked their effects one year after initiation of LABA or LTRA, focusing on ICS dose and emergency visits. Patient background factors with a possible association with visits to an emergency room due to an asthma attack were also analyzed.

Statistical analysis was performed using a chi-square test for the asthma control level. A Wilcoxon test was used to compare frequencies of visits to an emergency room before and after initiation of combi-

Table 1 Questionnaire on QOL of patients with bronchial asthma**Request for participation in the questionnaire survey**

We are conducting this survey with the goals of understanding your asthma condition and improving treatment. We appreciate your cooperation. (Please check ☐ for each item that applies.)

Age _____ Sex (Male/Female) _____ Date of answering the survey _____ year _____ month _____ day _____

1. Are you being or have you been treated for an allergic disease other than asthma? (check all that apply)

- ☐ None ☐ Hay fever ☐ Allergic rhinitis ☐ Atopic dermatitis ☐ Allergic mucositis ☐ Nasal polyp
☐ Maxillary empyema, sinusitis ☐ Urticaria ☐ Other _____

2. What kinds of symptoms do you have at present? (check all that apply)

- ☐ None ☐ Cough ☐ Sputum that is difficult to cough up ☐ Noisy and whistling breath
☐ Difficulty with breathing ☐ Other _____

3. How many times do you have these symptoms?

- ☐ Never ☐ Twice or less per week ☐ More than twice per week ☐ Almost every day

4. When do the symptoms occur? (check all that apply)

- ☐ Never ☐ Early morning ☐ Morning ☐ At work or during exercise
☐ Afternoon ☐ Evening ☐ Night ☐ During sleep

5. Do you sleep well at present?

- ☐ I sleep well. ☐ I do not sleep well due to difficulty with breathing.
☐ I sometimes do not sleep well due to difficulty with breathing.

6. Does asthma disturb your daily life (work, housekeeping, school, etc.) ?

- ☐ No ☐ Sometimes ☐ Often ☐ Frequently
☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor

7. How have you felt over the last 2 weeks?

- ☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor

8. For how long have you used your regular inhaled drug?

- ☐ Not used ☐ Less than 3 months ☐ 3-6 months ☐ 6 months to 1 year ☐ More than 1 year

9. How well do you inhale your regular inhaled drug as instructed?

- ☐ I can inhale my regular drug as instructed ☐ A: Fair ☐ B: Not well enough
 If A or B was checked: What is the reason for the difficulty? (check all that apply)

- ☐ I don't know how to use an inhaler. ☐ I don't feel an effect of the inhaled drug.
☐ It is a nuisance. ☐ I cannot use the drug due to suffering from asthma.
☐ I forget to inhale the drug. ☐ I am worried about attracting attention from others.
☐ I am anxious about adverse reactions.

10. For how long have you used an oral drug for asthma?

- ☐ Not used ☐ Less than 3 months ☐ 3-6 months ☐ 6 months to 1 year ☐ More than 1 year

11. Do you take oral drugs for asthma as instructed?

- ☐ I can take oral drugs as instructed ☐ A: Fair ☐ B: Not enough
 If A or B was checked: What is the reason? (check all that apply)

- ☐ I don't feel an effect of the oral drug. ☐ It is a nuisance. ☐ I forget to take the drug.
☐ I am anxious about adverse reactions.

12. Have you visit an emergency room due to an asthma attack?

- ☐ No ☐ Within the last month. ☐ Within the last 3 months. ☐ Within the last 6 months.

☐ Yes, but not within the last 6 months.

13. What level do you consider your asthma to be?

- ☐ Mild ☐ Moderate ☐ Severe

The following items should be completed by a physician.

Patient's name (initial) _____ Medical chart number _____ Disease period _____ years

Please describe the current treatment.

■ Medication (please check ☐ for an item that applies) . If the drug is not listed, please put the drug name in parentheses after "other".

- ☐ No use of drugs
☐ Inhaled corticosteroid (_____ μ g/day)
 Becotide Aldecin Flutide Pulmicort Qvar Other (_____)
☐ Inhaled β_2 agonist (repeat or single use)
 Mepit Sultanol Airomir Serevent Other (_____)
☐ Oral β_2 agonist
 Meptin Venetlin Hokunalin Berotec Atcock Other (_____)
☐ Patched β_2 agonist
 Hokunalin Tape
☐ Theophylline
☐ Theo-Dur Theolong Slo-bid Uniphyl Unicon Other (_____)
☐ Leukotriene receptor antagonist
 Onon Accolate Singular Kipres
☐ Oral antiallergic drug
 (Drug name _____)
☐ Oral corticosteroid
 (Drug name _____)
☐ Other (desensitization, etc.)
 (_____)

■ Please check ☐ to indicate the asthma stage of your patient in accordance with the guidelines in the Appendix.

☐ Step 1 ☐ Step 2 ☐ Step 3 ☐ Step 4

■ What are the criteria you use when determining the asthma stage?

- ☐ The dose of inhaled corticosteroids ☐ Symptoms
☐ Both the dose of inhaled corticosteroids and symptoms

Medical institution _____ Physician's name _____

Table 2 Levels of asthma control

Characteristic	Controlled	Partly Controlled	Uncontrolled
Daytime symptoms	None (twice or less/week)	More than twice/week	Three or more features of partly controlled asthma present in any week
Limitation of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/rescue treatment	None (twice or less/week)	More than twice/week	One in any week
Lung function (PEF or FEV1)	Normal	<80% predicted or personal best	
Exacerbations	None	One or more/year	

Patients who answered "No" to 4 questions in the Tama original questionnaire that were consistent with the items on the GINA control scale were considered to have asthma that was "completely controlled."

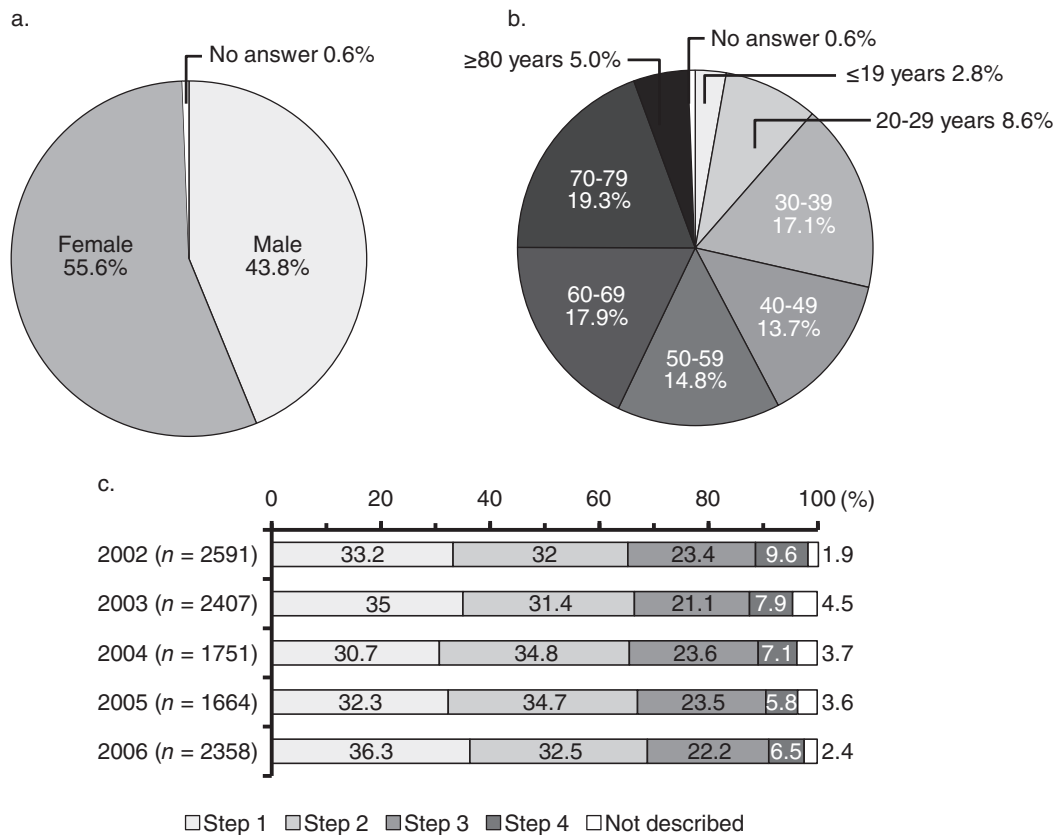


Fig. 1 Background of 10,771 asthma patients surveyed from 2002 to 2006. Severity distribution by (a) sex, (b) age and (c) year.

nation therapy. Multivariate analysis was used to identify background factors with a significant association with visits to an emergency room due to an asthma attack. A *p* value of <0.05 was considered to be significant in all analyses.

RESULTS

The number of respondents to the questionnaire on QOL in Bronchial Asthma were 1,591 in 2002, 2,407 in 2003, 1,751 in 2004, 1,664 in 2005 and 2,358 in 2006, giving a total of 10,771 respondents for the 5 years. Twenty-three patients repeatedly participated

in the survey every year for five years; 53 patients for consecutive four years, 126 for consecutive three years, 866 for consecutive 2 years. Although exact response rate of the survey was not known, more than 90% of patients and all doctors answered the questionnaire. For each year, 60% of patients were recruited from hospitals, while 20% were enrolled from respiratory clinics with the remaining 20% from general clinics. Males and females comprised 43.8% and 55.6% of the subjects, respectively (0.6% gave no answer). By age, 12.2%, 17.1%, 13.7%, 14.8%, 17.9%, 19.3%, and 5.0% were <29, 30-39, 40-49, 50-59, 60-69, 70-79 and ≥80

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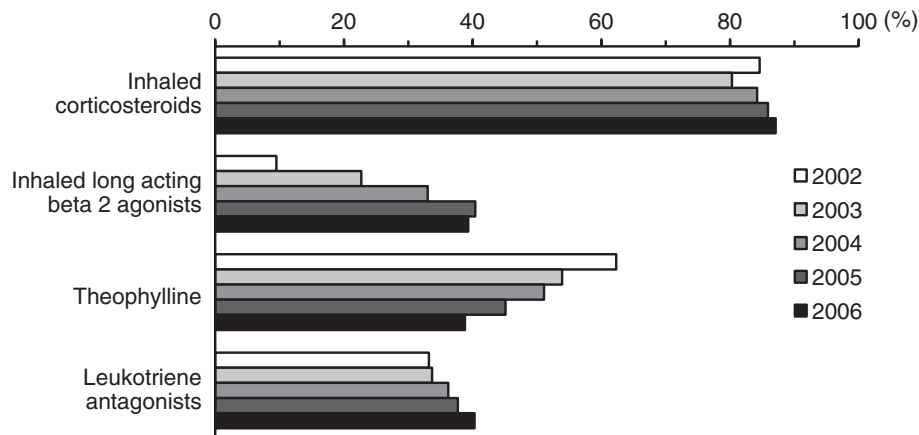


Fig. 2 Changes in treatment over 5 years. The percentage of patients treated with ICS showed little change, while treatment with LABA and LTRA increased.

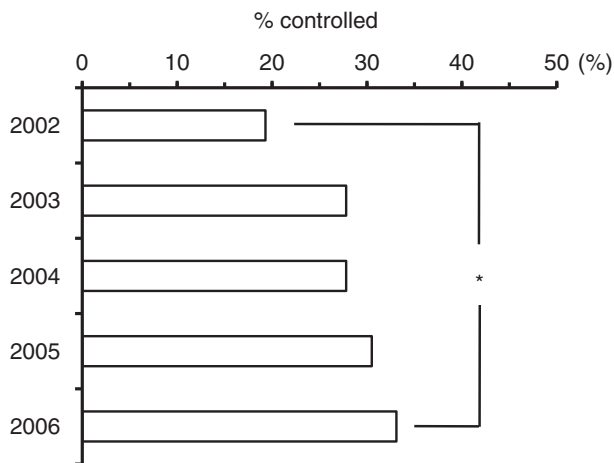


Fig. 3 Changes in cases with controlled asthma based on the GINA classification, using answers to the Tama original questionnaire. * $p < 0.05$ (χ^2 test).

years old. The severity distribution was 33.5%, 33.8%, 22.8% and 7.4% in Steps 1, 2, 3 and 4, respectively, with no significant change in this distribution over 5 years (Fig. 1). ICS were used in >80% of patients, again with no significant change in this rate over the 5-year period. Use of LTRA and LABA increased and that of theophylline decreased over 5 years (Fig. 2).

The percentage of patients with controlled asthma based on the GINA classification was significantly lower in 2006 than in 2002 (Fig. 3). No changes in the incidence of symptoms, sleep disorder and disturbance in daily life were found over 5 years; however, visits to an emergency room due to an asthma attack decreased from 34.9% of patients in 2002 to 19.3% in 2006 (Fig. 4).

Multivariate analysis of patient background factors was performed to identify factors with an association

with visits to an emergency room due to an asthma attack. This analysis was performed using data pooled over the 5 years of the study. Divergence between the asthma stage and the patient's recognition of severity was found to be significantly related to visits to an emergency room. In other words, the risk for a visit to an emergency room increased in patients who considered their condition to be more severe than their asthma stage as assessed by a physician (Fig. 5).

To determine the cause of the reduction in frequency of visits to an emergency room, effect of combined therapy with ICS was evaluated. LTRA and LABA were chosen for this analysis because use of these agents as concomitant drugs increased over the 5-year study period. The backgrounds of 54 patients in the ICS + LABA group and 45 patients in the ICS + LTRA group are shown in Table 3. The mean ages were 51.0 ± 20.0 years in the ICS + LABA group and 54.4 ± 18.1 years in the ICS + LTRA group. The severity distribution of patients in the ICS + LABA group was 11 (20.4%), 24 (44.4%), 15 (27.8%) and 2 (3.7%) in Steps 1, 2, 3 and 4, respectively, and for patients in the ICS + LTRA group it was 12 (26.7%), 18 (40.0%), 12 (26.7%) and 2 (4.4%), respectively. The ICS doses (converted to BDP) were 745 ± 351 and 680 ± 283 $\mu\text{g}/\text{day}$ before and one year after initiation of combination therapy, respectively, in the ICS + LABA group. The respective doses in the ICS + LTRA group were 657 ± 356 and 686 ± 319 $\mu\text{g}/\text{day}$, with no significant difference between groups. The percentages of patients who visited an emergency room due to an asthma attack were 18.5% before and 22.2% in the first year after initiation of combination therapy in the ICS + LABA group, with no significant difference between these rates. In contrast, visits to an emergency room due to an asthma attack significantly decreased from 24.4% before to 6.6% in the first year after initiation of combination therapy in the ICS + LTRA group

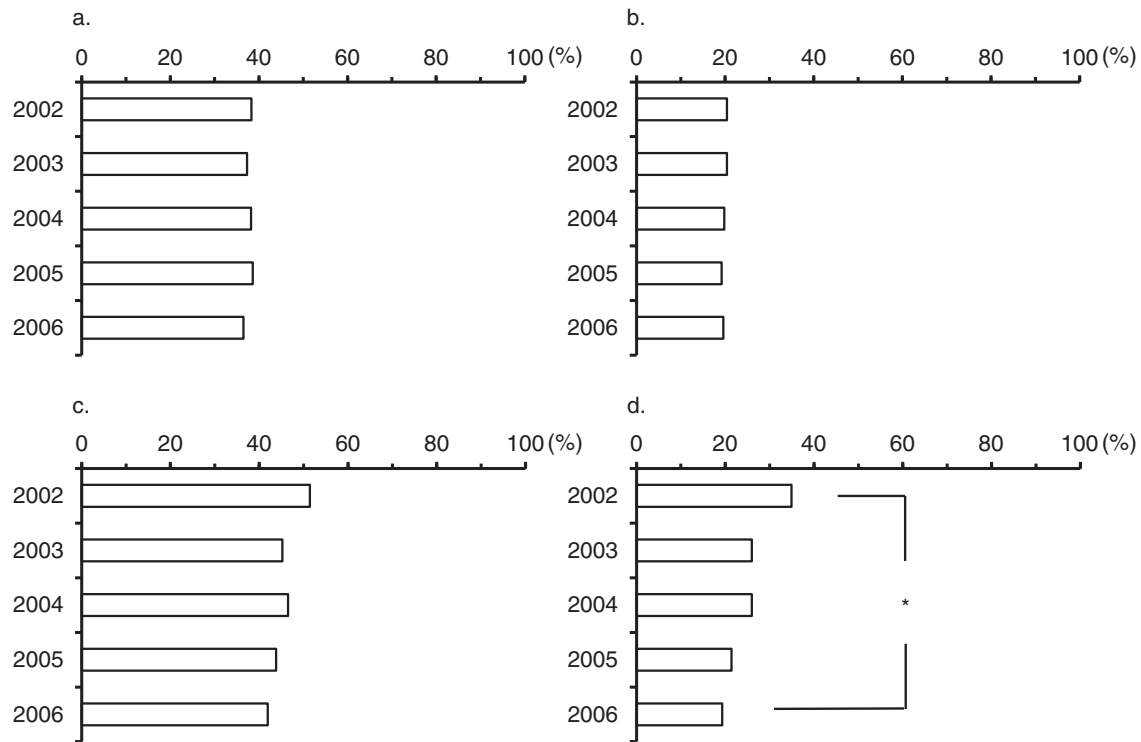


Fig. 4 Changes over 5 years in asthma symptoms, sleep disorder, disturbance in daily life, and visits to an emergency room due to an asthma attack, based on answers to 4 questions on the Tama original questionnaire. **a:** Symptoms occurring twice or more/week (patients who answered “twice or more/week” and “almost every day”); **b:** Sleep disorder (patients who gave answers other than “I sleep well”); **c:** Disturbance of daily life (patients who gave answers other than “No”); and **d:** Frequency of visits to an emergency room due to an asthma attack (patients who gave answers other than “Never”). * $p < 0.05$ (χ^2 test).

(Fig. 6).

DISCUSSION

In this study, we followed patients with bronchial asthma in Tama region, Tokyo, Japan for 5 years and found that the frequency of visits to an emergency room due to an asthma attack was reduced over time. Although these data might have been collected in different group of patients, the severity of bronchial asthma and the ICS dose were similar, which indicates that the subjects had a similar treatment background. Since clinics and hospitals participating in the survey were knowledgeable about current asthma management, more than 80% of the patients were taking ICS throughout the survey period, which exceeded the average ICS usage (15% in 2005) in Japan. This suggests that increased use of concomitant drugs contributed to the reduction in visits to an emergency room. Therefore, the effects of LTRA and LABA on the frequency of visits to an emergency room were evaluated. Our data indicated that a combination of ICS and LTRA resulted in a significant decrease in the frequency of visits to an emergency room in the one year after initiation of combination

treatment. These results demonstrate the efficacy of LTRA for treatment of bronchial asthma. As for patients' selection, we did not provide any selection criteria whether to add LTRA or LABA to ICS to better manage the particular patients. In fact, each doctor independently decided additional medication, resulting in better QOL in LTRA + ICS group.

The Gaining Optimal Asthma control (GOAL) study confirmed the efficacy of the combination of a LABA (salmeterol) and an ICS (fluticasone propionate, Flutide), but total control of asthma with salmeterol-fluticasone propionate (SFC) therapy was only achieved in 41% of patients.¹² Bateman *et al.* showed that patients treated with ICS and LABA in combination had a lower risk for acute and severe deterioration of asthma compared to those treated with ICS alone; however, no difference in asthma-related hospitalization and death or the risk for asthma-related endotracheal intubation was found between the groups.¹³ Therefore, an increase in the rate of total control of asthma and decreased asthmatic death requires a combination of an anti-inflammatory drug with ICS.

LTRA are oral drugs that have a strong anti-

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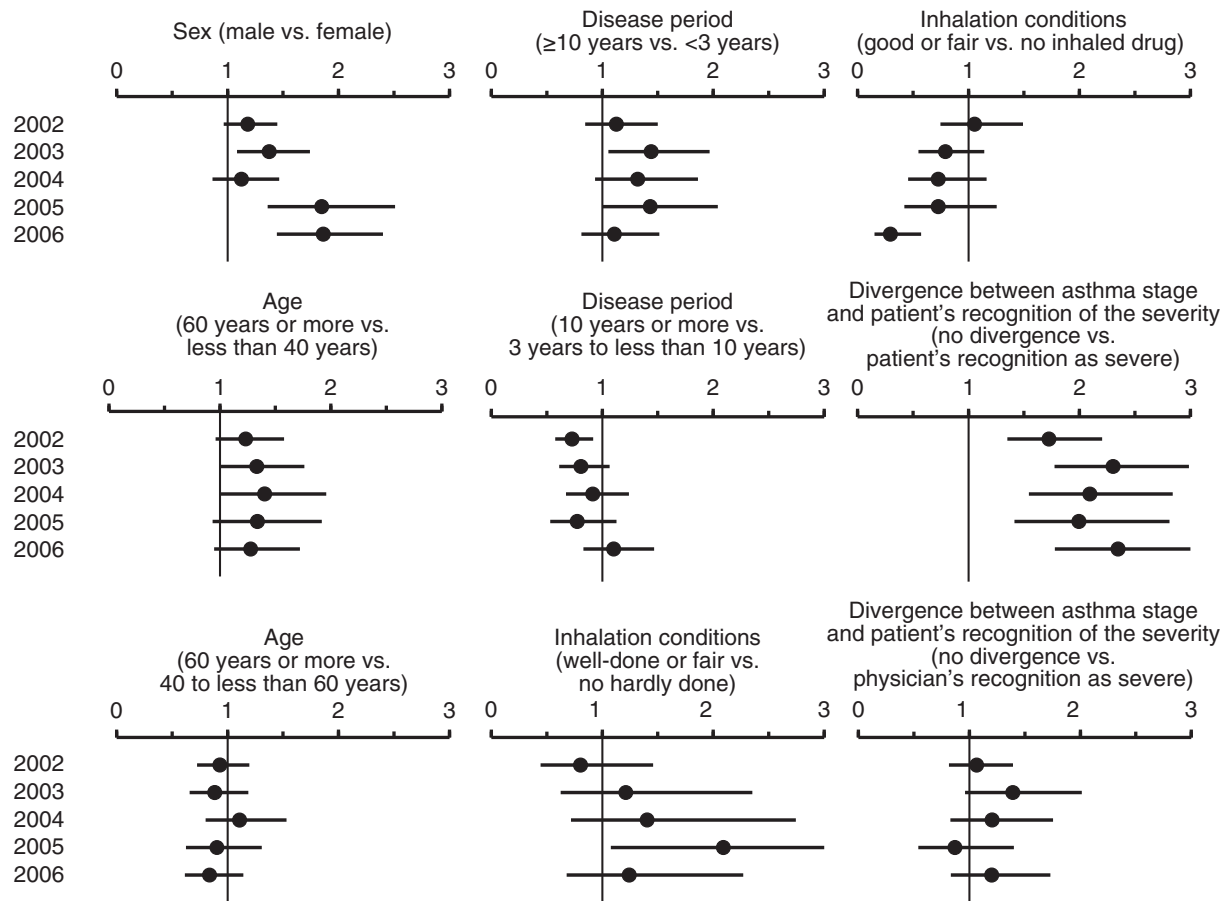


Fig. 5 Multivariate analysis of background factors with a possible association with visits to an emergency room due to an asthmatic attack. The odds ratio (●) and 95% confidence interval (—) are shown.

Table 3 Background of patients in the ICS + LABA and ICS + LTRA groups

	ICS + LABA (n = 54)	ICS + LTRA (n = 45)
Male/Female (number of patients)	25/29	20/25
Age (years)	51.0 ± 20.0	54.4 ± 18.1
Asthmatic stage (number of patients)		
Step 1	11	12
Step 2	24	18
Step 3	15	12
Step 4	2	2
Dose of ICS (μg/day)		
Before combination therapy	745 ± 351	657 ± 356
At 1 year after combined therapy	680 ± 283	686 ± 319

Data are shown as the number of patients or the mean ± SD.

inflammatory effect on the peripheral airway via systemic delivery. The oral route of delivery gives good compliance in elderly patients for whom inhalation is difficult. The concept of a dual pathway of inflammation has been proposed: i.e., there are two kinds of airway inflammation that are treatable and untreatable by ICS and LTRA has an inhibitory effect on in-

flammation that is untreatable by ICS.¹⁴ Airway infection is the major factor that induces a bronchial asthma attack. Several studies have shown that treatment with an LTRA for respiratory syncytial (RS) virus infection improved the severity of bronchiolitis and inhibited exacerbation of asthma.¹⁵⁻¹⁷ This suggests that LTRA have a strong effect on inflammation

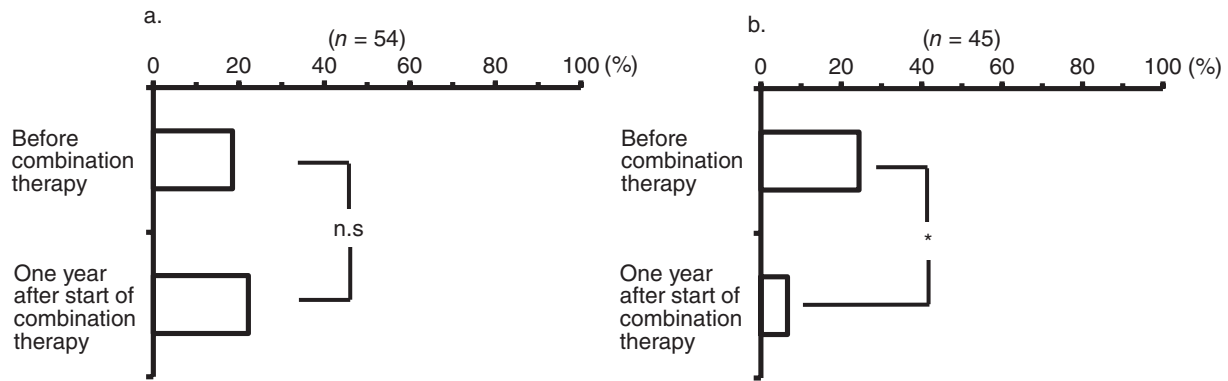


Fig. 6 Frequency of visits to an emergency room due to an asthmatic attack in groups treated with ICS and different concomitant drugs. **a:** ICS + LABA, **b:** ICS + LTRA. * $p < 0.05$ (Wilcoxon test).

caused by viral infection. Allergic rhinitis, a common complication of asthma, may also be involved in exacerbation of inflammation in the lower respiratory tract, and LTRA may inhibit the actions of leukotriene related to both diseases.¹⁸ The additional effects of LTRA beyond those of treatment with ICS may be responsible for the reduction in emergency room visits.

Multivariate analysis showed that the frequency of visits to an emergency room increased when there was a gap of between the perception of doctors and patients about medical conditions, especially in cases where doctors under diagnosed the conditions. Therefore, better control of asthma symptoms requires improved treatment and promotion of guideline-based evaluation and treatment. Programs aimed at reducing the death rate from asthma have been promoted for 10 years in Finland, and this strategy is very commendable.⁶ In Japan, further education is required to improve the understanding of asthma as an inflammatory disease and to promote the use of guidelines based on the relationship between primary care practitioners and specialists. The increased percentage of patients under good asthma control suggests that a survey on asthma conditions for 5 years can improve the attitudes of specialists, primary care physicians, and the patients themselves. When most of the asthma patients use ICS, the importance of additional drugs may be highlighted. In this study, use of additional LTRA proved to be helpful to improve the QOL of asthma patients.

ACKNOWLEDGEMENTS

We would like to express our sincere gratitude for the cooperation of all the physicians in the hospitals and clinics that received the survey.

REFERENCES

1. Bousquet J, Michel FB. International consensus report on diagnosis and management of asthma. *Allergy* 1992;**47**: 129-32.
2. [Annual population survey report from the Ministry of

Health, Labour and Welfare of Japan 2008] (in Japanese). Available at: <http://www.mhlw.go.jp/toukei/saikin/hw/ji nkou/geppo/nengai08/toukei6.html>. Accessed June 3, 2009.

3. Bousquet J, Jeffery PK, Busse WW, Johnson M, Vignola AM. Asthma. From bronchoconstriction to airways inflammation and remodeling. *Am J Respir Crit Care Med* 2000;**161**:1720-45.
4. Sumi Y, Hamid Q. Airway remodeling in asthma. *Allergol Int* 2007;**56**:341-8.
5. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000;**343**:332-6.
6. Haahtela T, Tuomisto LE, Pietinalho A *et al.* A 10 year asthma programme in Finland: major change for the better. *Thorax* 2006;**61**:663-70.
7. Adachi M, Ohta K, Morikawa A, Nishima S. [Asthma insights & reality in Japan 2005]. *Alerugi* 2006;**55**:1340-3.
8. Nakazawa T, Dobashi K. Current asthma deaths among adults in Japan. *Allergol Int* 2004;**53**:205-9.
9. Ministry of Health and Welfare, Japan. Asthma prevention and management guidelines. *Int Arch Allergy Immunol* 2000;**121** (Suppl 1):1-77.
10. Japanese Society of Allergy. [Asthma Prevention and Management Guideline 2009, Japan]. Tokyo: Kyowa Kikaku, 2009;92-113 (in Japanese).
11. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Updated 2009. Available at: <http://www.ginasthma.org>.
12. Bateman ED, Boushey HA, Bousquet J *et al.* Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med* 2004;**170**:836-44.
13. Bateman E, Nelson H, Bousquet J *et al.* Meta-analysis: effects of adding salmeterol to inhaled corticosteroids on serious asthma-related events. *Ann Intern Med* 2008;**149**: 33-42.
14. Peters-Golden M, Henderson WR Jr. Leukotrienes. *N Engl J Med* 2007;**357**:1841-54.
15. Bisgaard H, Zielen S, Garcia-Garcia ML *et al.* Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. *Am J Respir Crit Care Med* 2005;**171**:315-22.
16. Johnston NW, Mandhane PJ, Dai J *et al.* Attenuation of the September epidemic of asthma exacerbations in children: a randomized, controlled trial of montelukast added

- to usual therapy. *Pediatrics* 2007;**120**:e702-12.
17. Robertson CF, Price D, Henry R *et al*. Short-course montelukast for intermittent asthma in children: a randomized controlled trial. *Am J Respir Crit Care Med* 2007;**175**:323-9.
18. Bjerner L. Time for a paradigm shift in asthma treatment: from relieving bronchospasm to controlling systemic inflammation. *J Allergy Clin Immunol* 2007;**120**:1269-75.