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Research Article

Long-Acting Beta Agonists Decrease the Cold Development with/without Leukotriene Receptor Antagonists in Asthma Patients Treated with Inhaled Corticosteroids Over Ten Years

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Abstract

Background

Bronchial asthma is a chronic inflammatory disease, and Inhaled Cortico Steroids (ICS) have been the primary therapy for decades. The add-on effects of Leuko Triene Receptor Antagonists (LTRA) and/or Long-Acting Beta Agonists (LABA) on long-term asthma treatment are not sufficiently known.

Methods

The medical records from the outpatient department of National Hospital Organization, Fukuoka Hospital of 82 asthmatic patients who visited regularly and 37 who visited irregularly, beginning in 1998, and who had been treated for 10 years were analyzed to compare the effects of LTRA and/or LABA added on to ICS on respiratory function and symptoms.

Results

After 10 years, the irregular visit group showed significantly higher frequencies of hospitalizations, emergency room visits, asthma exacerbations, and colds than did the regular visit group ($p < 0.05$, each). The irregular group showed significantly decreased Forced Expiratory Volume (FEV) levels ($FEV_{1.0\%predicted}$ ($p < 0.001$)) in the 10^{th} of treatment year compared to the regular visit group.

In the regular visit group, the ratio of patients treated with ICS monotherapy decreased with time, whereas the ratios of patients treated with combination therapy including LTRA and/or LABA increased. Patients who received ICS + LABA or ICS + LABA + LTRA developed significantly fewer colds by the 10^{th} year of treatment than did those who received ICS monotherapy ($p<0.05$, each).

Conclusions

Regular ICS therapy appears to prevent the exacerbation of symptoms and the deterioration of respiratory function in asth-

matics. In addition, LABA with or without LTRA added on to ICS regimens showed a preventive effect against colds.

Keywords: Leukotriene Receptor Antagonists; Long-Acting Beta Agonists; Inhaled Corticosteroids; Adult Asthmatic Patients

Abbreviations:

Inhaled Corticosteroids (ICS);

Forced Expiratory Volume in 1 Second ($FEV_{1.0}$);

Leukotriene Receptor Antagonists (LTRA);

Long-Acting Beta Agonists (LABA);

Introduction

Asthma symptoms are controlled during Inhaled Cortico Steroids (ICS) therapy, but while ICS is discontinued, symptoms worsen and respiratory function deteriorates [1-3]. A 10-year and a 15-year study of adult asthma patients demonstrated that the reduction in forced expiratory volume in 1 second ($FEV_{1.0}$) following treatment was smaller in patients who had received ICS regularly compared to those who had not received ICS or who had used ICS irregularly [4-6]. In addition, a long period of regular ICS treatment was shown to alter asthma severity in a 15-year follow-up study from 1995 to 2010 [4]. 1995 and later, Leukotriene Receptor Antagonists (LTRA) and long-acting beta agonists (LABA) came on the market, followed by the combination of ICS and LABA and/or LTRA, which became popular as a main asthma control strategy[7-9].

The impact of adding on LABA and/or LTRA to ICS regimens on patients' longitudinal asthma history remains unknown. Evaluating lung function and quality of life changes in patients who visit hospitals irregularly is very difficult. The frequencies of their exacerbations or worsening tend to be underestimated because of the extremely small number of their scheduled visits compared with those patients who visit regularly.

In this study, we attempted to evaluate the real-life changes, included lung function and self-reported worsening frequencies compared to the number of scheduled visits, the over 10 years among asthmatic patients treated with ICS therapy, both with and without adding on LABA and/or LTRA.

Materials and Methods

Subjects and Study Design

The medical records of adult patients with bronchial asthma were retrospectively analyzed to assess the effectiveness of long-term, regular ICS therapy and the add-on effect of LTRA and/or LABA in preventing the exacerbation of symptoms and the deterioration of respiratory function.

The study subjects included 153 adult patients with bronchial asthma who first visited the outpatient department of National Hospital Organization, Fukuoka Hospital in 1998 and 1999 (1st year), visited again in 2008 and 2009 (10th year), and visited at least once per year during this 10-year period. All patients were treated as outpatients. Eighty-two patients were eligible for inclusion in the regular visit group (regular group); these patients had visited the hospital regularly each year and received continuous adequate therapy with 80% or greater adherence confirmed by the coincidence of their asthma treatment diaries with prescribed medications. Thirty-seven patients were eligible for inclusion in the irregular visit group (irregular group); these patients had visited only when symptoms occurred and had not received continuous therapy. In addition, the patients in the irregular visit group showed less than 50% adherence, and they had required considerably fewer prescribed ICS cartridges. Thirty-four patients' records were excluded because of complications, prolonged hospitalizations, or not being eligible for either the regular or the irregular group.

The changes in annual hospitalization frequencies, emergency room visits, unscheduled visits, treatment and symptom severity, self-reported worsening frequencies per year compared with scheduled visits, and self-reported cold frequencies per year compared with scheduled visits were compared between the regular and irregular groups and between patients who had been treated with versus without LABA and/or LTRA combined with ICS.

The Fukuoka Hospital Ethics Committee approved the study protocol (20-12). This observational study of existing clinical information did not involve the use of specimens collected from human subjects. A description of the study was provided at the hospital to convey the study details and to obtain general consent. Therefore, informed consent was not obtained from individual subjects.

Compensating the Self-Reported Worsening Frequencies

According to the row numbers of the frequencies of worsening between the regular and irregular groups, under-estimation occurred in the patients in the irregular group due to their extremely small number of scheduled visits. For example, two exacerbations in two scheduled visits in the irregular group and two exacerbations in twelve scheduled visits in the regular group should not be estimated as equal. To lessen this discrepancy, we used compensated frequencies; that is, the row frequencies of self-reported asthma exacerbation or colds were divided by the numbers of scheduled visits and converted to exacerbations per year. For other objective factors, the row data were used for comparison. Asthma worsening was mainly rescued by short acting beta agonist and/or ICS dosage

doubling and/or prednisolon intake for 5 to 10 days.

Statistical Analysis

The statistical software StatMate III (ATMS Co., Ltd., Tokyo, Japan) was used for Mann-Whitney tests to compare exacerbations and respiratory function between the regular and irregular groups and for Kruskal-Wallis tests to compare the medication regimens in the regular visit group, assuming $p < 0.05$ as statistically significant.

Results

Subject Characteristics (at 1st visit in 1998)

Age, sex, disease type, IgE levels and smoking status did not differ between the regular and irregular visit groups (Table 1). Symptoms were significantly milder in the irregular compared to the regular group ($p < 0.001$), and the mean disease duration in the irregular group was significantly longer than that in the regular group ($p < 0.001$; Table 1). The mean (SD) daily dose of ICS in the regular group was 900 (466) mcg of chlorofluorocarbon beclomethasone dipropionate.

Table 1. Patient characteristics at the onset of the study (in 1998).

	Regular visit group, n = 82	Irregular visit group, n = 37	P values
Age, years, mean [SD]	48 [14]	43 [16]	0.10
Sex, Male/female, n (%)	37 (45)/ 45(55)	20 (54)/ 17 (46)	0.30
Type, Atopic/ non-atopic	47(57) /35(43)	20(54)/ 17(46)	0.73
IgE, IU/L	794 [2,598]	783 [1,101]	0.48
Smoking status *	10(12)/ 32(39)/ 40(49)	8(22)/ 11(30)/ 18(49)	0.34
Disease duration, years, mean [SD]	0.8 [2.2]	3.6 [4.7]	<0.001
Treatment severity, n (%) **	0(0)/ 16(19)/ 40(49)/ 26(32)	10(27)/ 13(37)/ 8(22)/ 5(14)	0.09
Symptom severity, n (%) **	9(10)/ 49(60)/ 19(23)/ 6(7)	12(32)/ 20(55)/ 2(5)/ 3(8)	<0.001
Scheduled visits/year	8.2 [4.7]	4.4 [3.7]	p<0.001
Admission/year	0.5 [0.9]	0.3 [1.5]	0.31
Emergency room visits/year	0.3 [0.5]	0.4 [0.7]	0.14
Unscheduled visits/ year	0.3 [0.7]	0.6 [1.2]	0.12
Compensated asthma exacerbation frequencies/year	0.8 [1.3]	1.0 [2.6]	0.33
Compensated cold frequencies/year	1.8 [3.6]	2.9 [5.2]	0.14

*: Current smoker, Ex-smoker, Never-smoker, n (%)

**: Treatment and symptom severity: Mild intermittent, Mild persistent, Moderate persistent, Severe persistent, n (%)

Changes in the Frequencies of Scheduled Visits, Hospitalizations, Emergency Room Visits, and Asthma Exacerbations Over 10 Years

The mean (SD) numbers of scheduled visits per year in the 1st and 10th years did not differ in each group (8.2 (4.7) times/ year and 7.9 (3.7) in the regular group and 4.4 (3.7) and 4.7 (7.0) in the irregular group). The numbers of scheduled visits in the 10th year in both the regular and irregular groups were not significantly different from those in the 1st year ($p = 0.36$ and 0.43).

The hospitalization frequencies of the regular group decreased from the 1st year to the 10th year, (0.3 (0.5) to 0.1 (0.4) times/ year, $p < 0.01$), whereas those of the irregular group did not change (0.4 (0.7) to 0.4 (1.0) times/year, no.s.). The emergency room visit frequencies of the 2 groups were equivalent in the 1st year; however, those of the regular group had decreased to 0.1 (1.7) times/year, whereas those of the irregular group had not changed (0.4 (0.7)) in the 10th year, and this difference between groups was statistically significantly ($p < 0.05$). The numbers of unscheduled visits for the regular and irregular groups were, respectively, 0.8 (1.3)/year and 1.0 (2.6) in the 1st year and 0.2 (0.6) and 1.5 (4.4) in the 10th year, but these changes were not significant. The compensated asthma exacerbation times/year did not differ in the 1st year between groups (1.8 (3.6) vs. 2.9 (5.2)); however, those of the regular group had decreased to 0.4 ((1.7), $p < 0.05$)), whereas those of the irregular group (2.9 (4.7), no.s.) remained the same at the 10th year after treatment. The compensated cold frequencies of the regular and irregular groups in the 1st year were 0.5 (0.9) and 0.3 (1.5), respectively, with no significant difference between groups; however, at the 10th year after treatment, the regular group maintained a cold frequency of 0.3 (0.9), where-

as this frequency increased significantly in the irregular group to 1.2 (3.0) ($p < 0.05$).

Changes in Severity in the Regular and Irregular Groups Over the 10-Year Treatment Period

The treatment severity did not differ between the groups in the 1st year (Table 1), although treatment became more severe in the regular group in the 10th year (Table 2). The symptom severity in the 1st year was significantly milder in the irregular group, although symptoms in this group became significantly more severe in the 10th year ($p = 0.018$).

Table 2. The parameters measured in the 10th year (2008 and 2009).

	Regular visit group (n = 82)	Irregular visit group (n = 37)	P value
Regular visits/year	7.9(3.7)	4.7(7.0)	<0.05
Hospitalizations/ year	0.1(0.2)	0.4(1.0)	0.07
Emergency room visits/year	0.1(0.4)	0.4(0.7)	<0.05
Unscheduled visits/ year	0.2(0.6)	1.5(4.4)	0.09
Compensated asthma exacerbation frequencies/year	0.4(1.7)	2.9(4.7)	<0.05
Compensated cold frequencies/year	0.3(0.9)	1.2(3.0)	0.09
Treatment severity*	7(9)/ 13(16)/ 42(51)/ 20(24)	19(51)/ 8(22)/ 3(8)/ 7(19)	<0.001
Symptom severity*	65(79)/ 10(12)/ 4(5)/ 3(4)	22(59)/ 8(22)/ 2(5)/ 5(14)	0.018

*: Treatment and symptom severity: Mild intermittent, Mild persistent, Moderate persistent, Severe persistent, n (%)

Changes in Respiratory Function in the Regular and Irregular Groups Over the 10-Year Treatment Period

In the regular group, the $FEV_{1.0}$ mean (SD) mL ($FEV_{1.0\%predicted}$ mean (SD)) increased by 442 (488) mL (16.8 (18.3) %) in the 1st year and then gradually decreased by 103 (442) mL (4.7 (15.4) %) until the 10th year (Figure 1). The average annual reduction during the 10 years was 37.6 (43.5) mL (0.5 (1.7) %). In the irregular group, the $FEV_{1.0}$ ($FEV_{1.0\%predicted}$) decreased by 56 (221) mL (1.1 (8.1) %) in the 1st year and decreased further by 554 (347) mL (13.3 (12.9) % over the 10 years. The average annual reduction $FEV_{1.0}$ was 55.4 (34.7) mL (1.3 (1.3) %). The $FEV_{1.0}$ ($FEV_{1.0\%predicted}$) measurements over the 10-year period were significantly lower in the irregular group compared to the regular ($p < 0.001$) visit group.

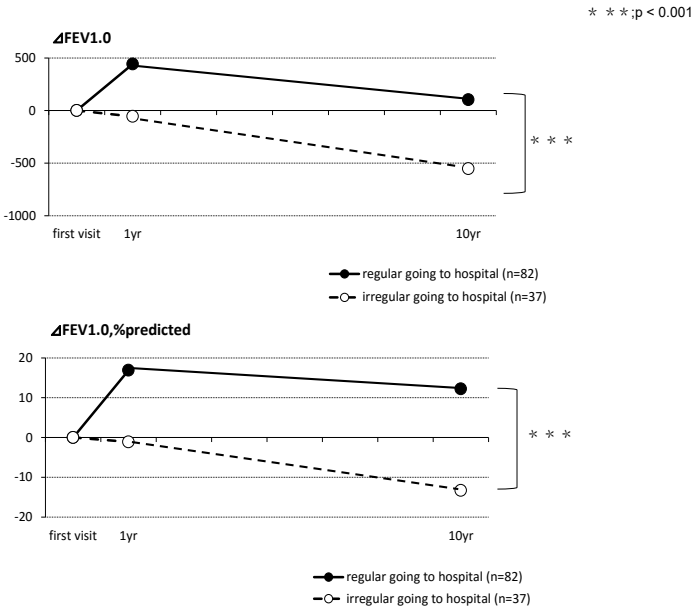

Figure 1. Change in $FEV_{1.0}$ Over Time.

Graphs illustrate the changes over time in the FEV1.0%predicted and FEV1.0. Data are expressed as mean values at the first visit, 1 year later, and 10 years later for the regular visit group (solid line with black circles) and the irregular visit group (dashed line with white circles). Reductions after 10 years are compared between the regular and irregular visit groups.

Changes in Medication Regimens in the Regular Visit Group Over the 10-Year Treatment Period

In Japan, around 1998 to 2001, ICS was started to be used as monotherapy or in combination with LTRA (ICS + LTRA; Figure 2). LABA was introduced in 2002 and was used in combination with ICS (ICS + LABA) or with ICS and LTRA (ICS + LTRA + LABA). Over time, many patients were switched from ICS monotherapy to combination therapy. The medication regimens in the 1st year of this study included ICS monotherapy (81% of the subjects) or ICS + LTRA (19%), whereas the regimens in the 10th year consisted of ICS monotherapy (32%), ICS + LTRA (16%), ICS + LABA (26%), or ICS + LTRA + LABA (26%). The mean ICS dosages for these treatment regimens were 756 (202), 756 (285), 1020 (221), and 1087 (221) mcg/day, respectively.

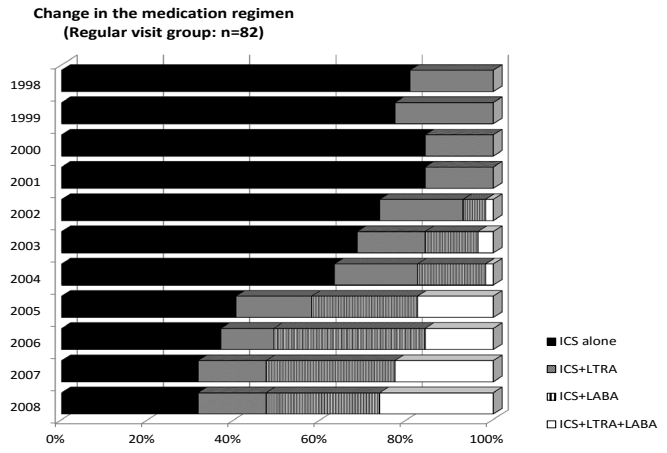

Figure 2. Changes in Medication Regimen in the Regular Visit Group.

Graph illustrates changes in medication regimen from the first visit (1998) over the next 10 years. Data are expressed as the proportions of patients receiving ICS monotherapy (black bar), ICS + LTRA (gray bar), ICS + LABA (striped bar), and ICS + LTRA + LABA (white bar).

LABA ($p < 0.05$) therapy.

The frequencies of hospitalization in the 1st year for the ICS monotherapy patients and the ICS + LTRA patients were 0.3 (0.5) and 0.2 (0.4), respectively, with no significant difference between groups. The frequencies of hospitalization in the 10th year for the ICS monotherapy, ICS + LTRA, ICS + LABA, and ICS + LTRA + LABA patients did not differ. The frequencies of emergency room visits in the 10th year for each group of patients also did not differ. The compensated cold frequencies in the 10th year for the ICS monotherapy, ICS + LTRA, ICS + LABA and ICS + LTRA + LABA patients were 0.9 (1.5), 0.1 (0.3), 0.1 (0.2) and 0.1 (0.3), respectively. The cold frequencies were significantly lower in the ICS + LABA and ICS + LTRA + LABA patients than in the ICS monotherapy patients ($p < 0.05$ for each).

Discussion

In this study, two main conclusions were found. First, the frequencies of hospitalizations, emergency room visits, unscheduled visits, asthma exacerbations, cold developments and severity improved over the 10-year treatment period in patients who were regularly treated with ICS included treatment but not in those who were treated irregularly.

Table 3. The exacerbation rates for each medication regimen over the 10-year treatment period in the regular visit group.

	1st year		10th year			
	ICS	ICS+LTRA	ICS	ICS+LTRA	ICS+LABA	ICS+LTRA+LABA
Regular visits/year	7.9(4.9)	9.4(3.7)	6.8(4.0)	8.0(2.4)	7.4(3.5)	9.8(3.7)
Hospitalizations/year	0.3(0.5)	0.2(0.4)	0.1(0.2)	0.0(0.0)	0.0(0.0)	0.1(0.4)
Emergency room visits/year	0.8(0.9)	0.7(0.9)	0.4(0.7)	0.2(0.7)	0.1(0.3) *	0.3(0.6)
Unscheduled visits/year	0.7(0.9)	1.3(2.1)	0.3(0.7)	0.3(0.7)	0.1(0.3)	0.3(0.6)
Compensated exacerbations/year	2.0(3.5)	2.1(3.8)	1.3(3.1)	0.4(1.3)	0.1(0.2)	0.3(0.7)
Compensated cold frequencies/ year	0.4(0.9)	0.6(0.9)	0.9(1.5)	0.1(0.3)	0.1(0.2) *	0.1(0.3)

The results are expressed as the mean (SD). *: $p < 0.05$ compared to patients treated with ICS monotherapy
Abbreviations: ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; LABA, long-acting beta agonist.

The Exacerbation Rates for Each Medication Regimen over the 10-Year Treatment Period in the Regular Visit Group

The mean number of scheduled visits in the 1st year was 7.9 (4.9) for patients on ICS monotherapy (n = 66) and 9.4 (3.7) for those taking ICS + LTRA (n = 16); there was no significant difference in visits between these regimens (Table 3). The mean numbers of scheduled visits in the 10th year for patients treated with ICS monotherapy (n = 27), ICS + LTRA (n = 13), ICS + LABA (n = 21), and ICS + LTRA + LABA (n = 21) were 6.8 (4.0), 8.0 (2.4), 7.4 (3.5), and 9.8 (3.7), respectively. The number of visits for ICS + LTRA + LABA patients was significantly higher than for those receiving ICS monotherapy ($p < 0.05$) and ICS +

The decrease of $FEV_{1.0}$ per year was different between irregular and regular groups. Second, LABA addition on to ICS and LABA and LTRA addition on to ICS decreased the frequencies of colds in regularly treated asthmatic patients.

In the regular visit group, all frequencies of asthma exacerbations and colds decreased in the 10-year period, although this result was not observed in the irregular visit group. Lange at al. reported the deterioration of lung function in adult asthma patients over the 15-year period from 1976 to 1994; these authors observed was a significantly greater reduction in the ventilatory function of adults with asthma compared with

those without asthma, with an annual $FEV_{1.0}$ reduction of 38 mL in the former and 22 mL in the latter group [6]. Adults with asthma appear to experience a progressive decline in respiratory function compared to adults without asthma [10], although regular ICS treatment can improve asthma symptoms [4]. Treatment severity was not decreased over the 10-year treatment period, however, the symptom severity improved significantly, the percentage of mild intermittent symptoms increased from 11% to 79%, and the percentage of moderate and severe symptoms decreased in the regular visit group. In contrast, symptom severity did not improve in the irregular visit group. Thus, regular treatment with moderate doses of ICS improved asthma symptoms over the 10-year treatment period.

The current study also explored the effects on longitudinal asthma symptoms of adding on LABA or LABA and LTRA to ICS. The period from 1998 to 2008 corresponded roughly to the period when asthma guidelines were revised annually. In our study, the main asthma treatment regimen options were expanded from two (ICS monotherapy and ICS + LTRA) to four (ICS monotherapy, ICS+LTRA, ICS+LABA, and ICS+LTRA+LABA) over the 10-year study period. These options were made available after the introduction of LABA in 2001 in Japan [11]. For patients who visited the hospital regularly, the combinations of LABA and/or LTRA with ICS were more effective than ICS monotherapy. As the duration of treatment increases, it can become difficult to control asthma with ICS alone, and better control can be achieved by combining ICS with LTRA, LABA, or both. Patients treated with either ICS + LABA or ICS + LTRA + LABA showed significantly fewer colds over the 10-year treatment period than did those treated with ICS alone. These findings support the notion that ICS in combination with LABA or LABA + LTRA is more effective in preventing exacerbations than ICS alone. According to a review by the Cochrane Collaboration, LABA is more effective than LTRA as an adjunctive therapy to ICS in terms of emergency visit rates, use of rescue medications, quality of life, number of symptom-free days, daytime symptom scores, number of nighttime awakenings, and patient satisfaction [10]. Moreover, LABA may protect against infection through the suppression of airway IL-8 levels or neutrophil numbers [12], however, the increase risk of fatal serious adverse events of LABA addition to ICS cannot definitively ruled out [13].

One of the limitations of this study was that it was not prospective, which made it difficult to establish the true adherence to medication. We attempted to compare the effects of regular ICS inhalation with irregular inhalation, which reduced the number of subjects and made the study itself retrospective. In addition, it was difficult to obtain information on true asthma exacerbations in our patients, particularly for those who did not visit the hospital regularly; thus, we compensated for this limitation by also including the numbers of scheduled visits in the analysis. We believe that this correction reduced the inaccuracy of the irregular visit patients' asthma control levels. In addition, our study could not clarify the effects of the different mean ICS dosages between ICS+LABA patients and ICS+LTRA patients on the results and the former treatment profile different between the regular and irregular patients.

Conclusions

Based on previous reports and our present study results, it is suggested that regular ICS therapy can prevent the deterioration of respiratory function to a greater extent than the insufficient use of ICS [14]. Our results also show that cold frequencies may also be decreased by adding LABA on to ICS therapy.

Permissions-IRB Approval:

The Fukuoka Hospital Ethics Committee approved the study protocol (20-12). This observational study of existing clinical information did not involve the use of specimens collected from human subjects. A description of the study was provided at the hospital to convey the study details and to obtain general consent. Therefore, informed consent was not obtained from individual subjects.

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