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ORIGINAL ARTICLE

Clinical Evaluation of Leukotriene Receptor Antagonists in Preventing Common Cold-like Symptoms in Bronchial Asthma Patients

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ABSTRACT

Background: We investigated the possibility of preventing common cold-like symptoms as a previously unknown benefit of leukotriene receptor antagonists (LTRAs) .

Methods: A total of 279 adult patients with bronchial asthma referred to our hospital between June and December 2004 were retrospectively analyzed. Patients were divided into LTRA treated and untreated groups. Frequency of acute exacerbations and number of visits to emergency rooms and of hospital admissions were analyzed as indicators of frequency of infections and asthma exacerbation over the previous 12 months.

Results: Irrespective of inhaled corticosteroid (ICS) use, frequency of infections was significantly lower in the LTRA treated group (0.3 ± 0.7 times/year) than in the LTRA untreated group (1.6 ± 4.2 times/year) ($P < 0.05$), suggesting that LTRA therapy prevents common cold-like symptoms. Frequency of acute exacerbations and number of hospital admissions were significantly lower in the LTRA treated versus LTRA untreated group (0.4 ± 0.8 versus 2.7 ± 4.3 times/year and 0.0 ± 0.2 versus 0.4 ± 0.7 times/year, respectively; both $P < 0.01$). When the patients were divided into ICS treated and untreated groups, none of the parameters analyzed differed significantly between the two groups, although all parameters tended to be lower in the ICS treated group.

Conclusions: Adult asthma patients undergoing treatment with LTRAs exhibit lower incidence rates of common cold-like symptoms than those not receiving LTRAs. LTRAs play an important role in reducing the incidence of common cold-like symptoms among asthma patients and in suppressing exacerbation of asthma symptoms possibly associated with these symptoms.

KEY WORDS

acute exacerbation, asthma, common cold-like symptoms, ICS, LTRAs

INTRODUCTION

When managing patients with bronchial asthma (hereinafter simply called asthma) in clinical practice, physicians often encounter cases in which symptoms of cold or flu trigger exacerbation of asthma symptoms. These experiences suggest that flu symptoms (*i.e.* viral infections) have some impact on eosinophilic inflammation of the airway, which is a basic feature of asthma. Involvement of viral infection in exacerbation of asthma has been reported in children as well as in adults.[1-3] However, although viral infection is known as a noteworthy factor when predicting asthma prognosis in children,[4,5] less is known about the corresponding relationship between these factors in adult patients.[6,7]

Regarding the mechanism for exacerbation of asthma following viral infection, it was recently disclosed that leukotrienes (LTs) produced in the airway in response to infection play important roles in this process.[8] Thereafter, several reports were published concerning suppression of exacerbation of asthma in-

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duced by viral infection of the airway using LT receptor antagonists (LTRAs).[9,10] Although there have been reports of the possibility of preventing onset of cold or flu in asthmatic children by LTRAs,[11] our literature search identified no such reports in adults with this disease.

Under these circumstances, we retrospectively investigated adult asthma patients attending our outpatient clinic as to whether LTRAs are effective in preventing common cold-like symptoms in these patients. Furthermore, the use of inhaled corticosteroid (ICS) was also studied in this respect.

METHODS

This retrospective cohort study examined whether LTRAs are useful in preventing common cold-like symptoms in adult asthma patients. Subjects were all 279 asthma patients who were referred to our institution between June and December 2004. The study duration was 12 months. Patients were divided into LTRA treated and untreated groups. Of the 183 LTRA treated patients, 68 took montelukast and 115 pranlukast. At the start of the study, the following parameters were analyzed and compared: peak expiratory flow (PEF), percentage of eosinophils in peripheral blood, serum and sputum eosinophil cationic protein (ECP), forced expiratory volume in 1 s ($FEV_{1.0}$), airway hyperresponsiveness (Dmin), and expired NO. Expired NO level was measured by NO Analyzer (280NOAi, Sievers, Boulder, CO, USA). PEF (L/min) was measured by Mini-Wright peak flow meter (Clement Clarke, Essex, UK) and $FEV_{1.0}$ (L) by spirometer, CHESTAC-8800 (CHEST, Tokyo, Japan).

Frequency of infections and indicators of asthmatic exacerbation including frequency of acute exacerbations, number of visits to emergency rooms, and number of hospital admissions over the 12 month period were checked by viewing medical records of individual patients and analyzed in relation to use of LTRAs and ICS. Based on the classification of the Global Initiative for Asthma (GINA) 2002[12] a judgment of acute exacerbation of asthma was made if at least one of the following requirements was satisfied: 1) persistence of asthma symptoms for $\geq$3 days; 2) prescription of short acting β agonist (SABA) twice daily or more frequently; and 3) prescription of oral steroids. Common cold-like symptoms were defined as a condition in which at least one symptom of acute rhinitis (rhinorrhea, nasal congestion, and sneeze) is accompanied by symptoms of pharyngitis and lower airway inflammation. Presence or absence of lower airway inflammation was judged on the basis of presence or absence of sputum. Use of other anti asthmatic drugs was not taken into account in the present study. Written informed consent was obtained from all patients before their medical data were accessed.

Total frequency of each event during the 12 month period was divided by total number of patients so as to yield annual frequency/person. Background variables in the LTRA treated and untreated groups were compared by chi square test and unpaired *t* test. The Mann Whitney test was employed for intergroup comparison of the frequency of each event, *i.e.* comparison between the LTRA treated and untreated groups subdivided by use or non use of ICS and between the ICS treated and untreated groups subdivided by use or non use of LTRAs.

RESULTS

When background variables before treatment were compared between the LTRA treated and untreated groups, no significant difference was noted in age, duration of sickness, smoking history, severity of disease, and disease type (Table 1). Moreover, no significant difference was noted in disease severity parameters (PEF, percentage of eosinophils in peripheral blood, serum and sputum ECP, $FEV_{1.0}$, Dmin, and expired NO) between these two groups (Table 2).

ICS was administered as the primary treatment for asthma and LTRAs were added when ICS was not enough to control the symptoms. Overall, the frequency of infection during the 12 month period was significantly lower in the LTRA treated than in the LTRA untreated group (0.3 ± 0.7 versus 1.6 ± 4.2 times/year, $P < 0.05$) (Fig. 1). Furthermore, when the same parameter was analyzed among subgroups of patients treated with and without ICS, it was significantly lower in those receiving versus those not receiving LTRAs (0.3 ± 0.7 versus 1.3 ± 3.5 and 0.3 ± 0.6 versus 2.3 ± 6.0 times/year, respectively; both $P <$ 0.05) (Fig. 1).

As shown in Figure 2, frequency of acute exacerbation and number of hospital admissions were significantly lower in the LTRA treated than in the untreated group (acute exacerbation: 0.4 ± 0.8 versus 2.7 ± 4.3 times/year; hospital admissions: 0.0 ± 0.2 versus 0.4 ± 0.7 times/year; both $P < 0.01$). Number of visits to emergency rooms tended to be lower in the LTRA treated versus untreated group, although this difference was not statistically significant (0.3 ± 0.8 versus 0.7 ± 1.6 times/year; P = NS) (Fig. 2). When the frequency of each of these events was analyzed in patients subdivided by use or non use of ICS, frequency of acute exacerbation and number of hospital admissions were significantly lower and number of visits to emergency rooms tended to be lower (*i.e.*, P = NS) in the LTRA treated than untreated group irrespective of taking ICS (data not shown). When the frequency of each of these events was analyzed in patients subdivided by use or non use of LTRAs, it tended to be lower in the ICS treated than in the untreated group irrespective of the use or non use of LTRAs, although this difference was not statistically significant (data not shown).

Table 1 Patient characteristics.

	LTRA (+)	LTRA (−)	Total
Total number of cases	183	96	279
Sex (M/F)	85/98	34/62	119/160
Age (years)	53.3 ± 19.2	49.5 ± 18.9	52.0 ± 19.1
Duration of asthma (years)	6.9 ± 8.8	7.6 ± 7.3	7.1 ± 8.3
Smoking history (*n*)			
Current smoker	56	30	86
Ex smoker	33	18	51
Never smoker	94	48	142
Severity (*n*)			
Step 1	88	44	132
Step 2	47	27	74
Step 3	21	13	34
Step 4	27	12	39
Disease type (*n*)			
Atopic	101	61	162
Non atopic	82	35	117

Table 2 Baseline parameters of patients in the LTRA (+) and (−) groups.

	LTRA (+)	LTRA (−)	*P* value
PEF (L/min)	369 ± 141	345 ± 162	NS
Peripheral blood eosinophils (%)	5.71 ± 3.34	5.86 ± 4.01	NS
IgE RIST (IU/mL)	529 ± 590	915 ± 1789	NS
Serum ECP (μg/L)	27.8 ± 10.1	19.6 ± 18.6	NS
Sputum ECP (μg/L)	1395 ± 2489	914 ± 1190	NS
$FEV_{1.0}$ (L)	2.41 ± 1.44	2.18 ± 0.88	NS
Dmin (units)	2.32 ± 2.77	3.04 ± 4.58	NS
NO value (ppb)	57.9 ± 45.1	68.4 ± 66.7	NS

RIST, radioimmunosorbent test; ECP, eosinophil cationic protein; $FEV_{1.0}$, forced expiratory volume in 1 second.

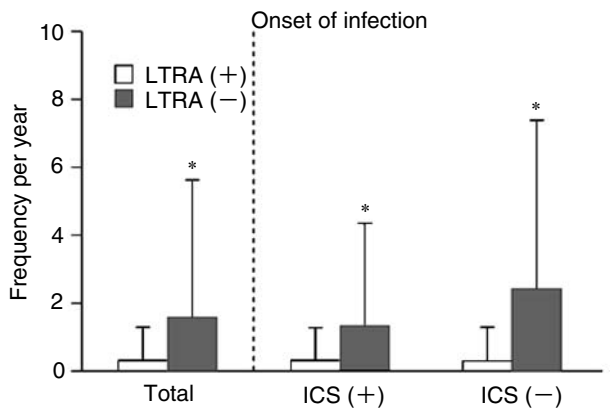

Fig. 1 Frequency of infections during the 12 month study period in 279 adult asthma patients divided into LTRA treated and untreated groups and ICS treated and untreated groups. LTRA (−) ICS (+): 24 patients, LTRA (−) ICS (−): 72 patients, LTRA (+) ICS (+): 109 patients, LTRA (+) ICS (−): 74 patients. The Mann Whitney test was employed for intergroup comparison of the frequency of onset of infection. *$P < 0.05$.

DISCUSSION

Both psychological and environmental factors have been shown to influence the onset of asthma attacks.[13] Among all causes, viral infection of the airway is the most frequent precipitating factor for asthma episodes. In particular, many data have been accumulated concerning the relationship between viral infection and exacerbation of asthma in infants and children.[4,5,14] Regarding the mechanism for exacerbation of asthma due to viruses, it was recently revealed that LTs produced in the airway under stimulation with infection play an important role. It therefore seems reasonable to suppose that LTRAs, which block the LT pathway, may be useful in suppressing exacerbation of asthma following viral infection, and several reports endorsing this view have been published. Among animal studies, Wedde-Beer *et al.*[9] reported that treatment with montelukast suppresses vascular permeability of airway mucosa in a rat model of respiratory syncytial (RS) virus infection. Clinically, Bisgaard *et al.*[10] reported that montelukast delays and

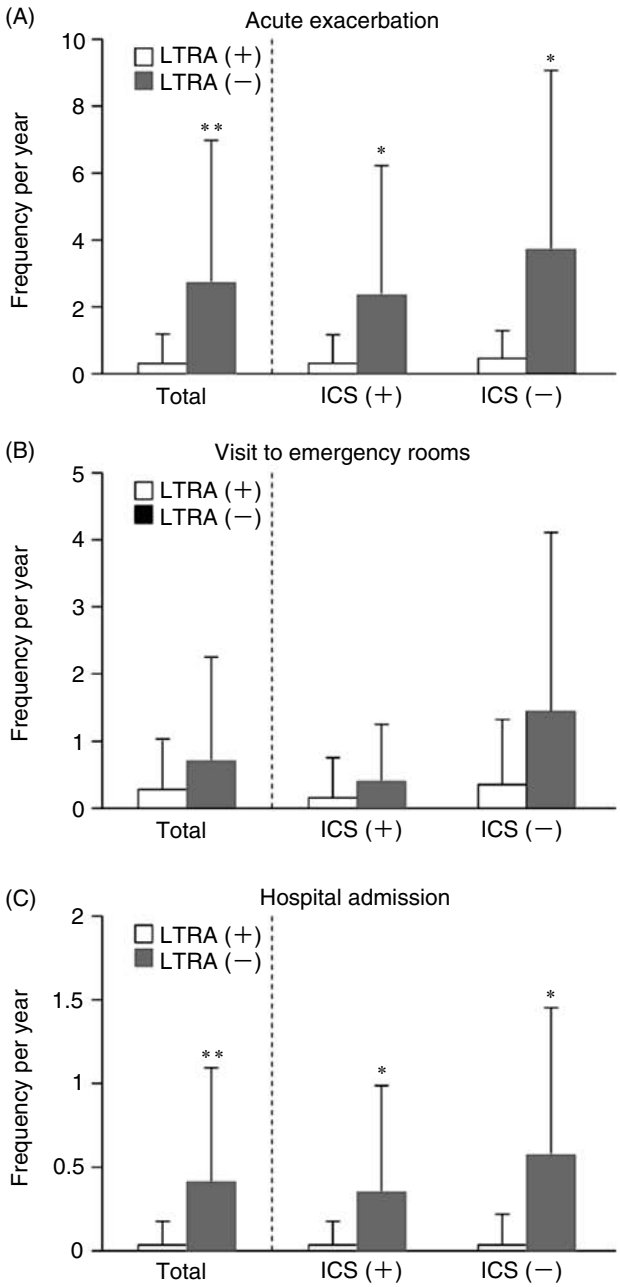

Fig. 2 Frequency of acute exacerbation of asthma symptoms (**A**), visit to emergency rooms (**B**), and hospital admission (**C**) in 279 adult asthma patients divided into LTRA treated and untreated groups and ICS treated and untreated groups. LTRA (−) ICS (+): 24 patients, LTRA (−) ICS (−): 72 patients, LTRA (+) ICS(+): 109 patients, LTRA (+) ICS (−): 74 patients. The Mann Whitney test was employed for intergroup comparison of the frequency of onset of infection. *$P < 0.05$, **$P < 0.01$.

reduces the onset of asthmatic symptoms in children following RS virus infection. They additionally reported that in children aged 2–5 years intermittent asthma treatment with montelukast significantly suppresses the incidence of acute exacerbation of asthma following viral infection in comparison with placebo.[11] It has been suggested that viral infection in infants and children, particularly those with severe bronchiolitis requiring hospitalization, serves not only as a factor precipitating attacks of asthma immediately after infection but also as a risk factor for persistence of asthma or recurrent wheeze lasting >10 years.[4,5,14] Hence it seems natural that the results of montelukast therapy in children are attracting close attention. To date, however, very few reports have been published concerning the effects of this drug in adult asthma patients. Regarding LTRAs, discussions have been made not only on their effects against exacerbation of asthma following viral infection but also in preventing viral infection itself. Concerning the latter possibility, Bisgaard *et al*.[11] reported that the incidence of cold or flu among children with intermittent asthma was reduced by 29% following montelukast therapy. On the other hand, van Adelsberg *et al*.[15] reported that in a study designed to evaluate the safety of montelukast in infants with asthma aged 6–24 months and in patients presenting with asthma-like symptoms, the incidence of upper airway infection was 32% in the montelukast treatment group and 21% in the placebo group. Thus no clear cut results have been obtained concerning the effect of LTRAs in preventing viral infection. Moreover, in some reports that have suggested the possibility of preventing viral infection by LTRAs, the mechanism of action was not clearly demonstrated.

In the present study, emphasis was placed on assessing the possibility of preventing common cold-like symptoms in adults using LTRAs. Retrospectively assessing the medical records of patients managed at our facility, we observed that the frequency of infection was significantly lower in those taking versus not taking LTRAs irrespective of whether they concomitantly used ICS. Possible mechanisms explaining this effect of LTRAs include: 1) direct effect on cells by suppressing infection; 2) indirect effect such as normalization of airway function and reduction of receptor expression needed for viral infection of airway epithelium. On the basis of our results, it is plausible to estimate that treatment with LTRAs reduces the frequency of asthmatic attacks over long time periods, stimulating normalization of airway epithelium and resumption of foreign body eliminating function (ciliary movement etc.) and thus indirectly suppressing common cold-like symptoms. It was recently reported that LTRAs act on dendrocytes and suppress Th2 reactions in mice.[16] It seems likely that normalization of airway epithelium is mediated not only by suppression of LTs' action in inflammatory reaction but also by control of more upstream immune reactions. Another possible mechanism for indirect suppression of infection by LTRAs is lowering expression of cellular receptors for infecting viruses. For in-

stance, intercellular adhesion molecule (ICAM)-1, which is upregulated following major rhinovirus infection, acts as a receptor for this pathogen and serves as adhesion molecule for inflammatory cell infiltration.[17-19] Although there are no reports on the effect of montelukast in suppressing upregulation of ICAM-1 after rhinovirus infection, it is known that this agent significantly reduces expression of soluble ICAM-1 in asthma patients.[20] It seems probable that these actions of LTRAs reduce the susceptibility of asthma patients to viral infections. Regarding direct action of LTRAs in suppressing viral infection, the present study yielded no results in support of such action. This issue remains open for future research.

In the present study, many events (acute exacerbation, visit to emergency rooms, and hospital admission) took place within 1 week after common cold-like symptoms (data not shown). These events therefore seem associated with infection. As stated above, most previous reports on exacerbation of asthmatic symptoms following infection pertain to children. In this respect, our results obtained in adults (particularly the results of drug therapy) can be deemed valuable. Considering that LTRAs may reduce onset of infection and suppress postinfection exacerbation of asthmatic symptoms, it seems possible that LTRAs may be indicated for the prevention and suppression of common cold-like symptoms and post infection exacerbation of asthma as well as suppression of the loop of exacerbation (increased susceptibility to infection due to deterioration of airway condition).

We have shown that treatment with ICS alone has a tendency to suppress asthmatic events, but this is nonsignificant. It seems likely that for prevention of common cold-like symptoms and suppression of exacerbation of asthma following viral infection, combined use of ICS and LTRAs may be more useful than use of either drug alone.

CONCLUSION

The present study confirms that LTRAs can prevent common cold-like symptoms and suppress infection-associated exacerbation of asthma in adult patients with this disease. ICS are currently used as anti-inflammatory agents of first choice when dealing with chronic airway inflammation. The results of the present study suggest that LTRAs, by preventing common cold-like symptoms in adult asthma patients, could provide a very useful means of controlling asthma.

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