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Potential Masking of Airway Eosinophilic Inflammation by Combination Therapy in Asthma

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Purpose: Long-acting β_2 agonists (LABA) may mask ongoing bronchial inflammation, leaving asthmatic patients at greater risk of severe complications. The aim of this study was to compare the effect of combination therapy using low-dose inhaled corticosteroids (ICS) plus LABA on airway inflammation in asthma to the effect of medium-dose ICS alone. **Methods:** Twenty-four patients with asthma not controlled by low-dose (400 μg per day) budesonide alone were enrolled in this prospective crossover study. Patients were randomized into 2 treatment phases: one receiving medium-dose (800 μg per day) budesonide (ICS phase), and the other receiving a combination therapy of low-dose budesonide/formoterol (360 μg/9 μg per day) delivered by a single inhaler (LABA phase). Each treatment phase lasted for 6 week, after which patients were crossed over. Asthma symptoms, lung function, and airway inflammation were compared between the 2 phases. **Results:** Twenty-three patients completed the study; adequate sputum samples were collected from 17 patients. Asthma symptoms and lung function remained similar between the 2 phases. However, the mean sputum eosinophil percentage was higher in the LABA phase than in the ICS phase (5.07±3.82% vs 1.02±1.70%; $P<0.01$). Sputum eosinophilia (≥3%) was more frequently observed in the LABA phase than in the ICS phase (6 vs 2). **Conclusion:** Addition of LABA may mask airway eosinophilic inflammation in asthmatic patients whose symptoms are not controlled with low-dose ICS.

Key Words: Airway; inflammation; asthma; corticosteroids; beta2-agonists

INTRODUCTION

The goal of asthma treatment is to control and suppress clinical symptoms.[1] Two primary treatment options for patients with moderate asthma inadequately controlled by low dose inhaled corticosteroids (ICS) are addition of long-acting inhaled β_2 agonists (LABA), or increasing the dose of ICS administered.[1,2] Several studies have shown that LABA in combination with low dose ICS results in better asthma control than medium dose ICS alone with respect to asthma symptoms, lung function, and the need for short acting β_2 agonist rescue therapy.[2-5] However, concerns regarding the safety of regular LABA use in asthmatic patients remain. LABA has been associated with higher risk of adverse outcomes, including severe exacerbations and deaths,[6-11] although these events were relatively rare. These results suggest that LABA treatment may mask ongoing airway inflammation, leading to more severe asthmatic exacerbations, even with regular use of ICS. This study was designed to compare the effects of combination therapy (LABA plus low dose ICS) on airway inflammation in asthmatic patients to those of medium dose ICS therapy alone.

MATERIALS AND METHODS

Subjects

Eligible patients had a documented history of asthma treatment for more than 6 months at Samsung Medical Center. Patients at 16 to 70 years of age with a forced expiratory volume in one second (FEV1) of more than 60% of the predicted normal value were screened for enrollment. Each patient was assessed to establish his or her current treatment regimen, adherence to

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the current regimen, and level of asthma control. Asthma control was monitored using a simplified scheme, which included daytime symptoms, limitation of activity, nocturnal symptoms, need for reliever treatment, and lung function, as set forth by international guidelines.[1] Patients were enrolled if their asthma was either uncontrolled, or only partly controlled by administration of low dose ICS (budesonide 200 μg, twice per day) for at least 3 months.

Patients were excluded if they had received treatment for acute asthma exacerbation within the previous 12 weeks, if they were smokers, pregnant, or lactating. All patients provided written informed consent prior to the study, which was approved by the Institutional Review Board of Samsung Medical Center.

Study design (Fig. 1)

This randomized, prospective, crossover study was carried out in an outpatient setting. Following an initial run-in period of 2 weeks, patients were randomly assigned to either of 2 treatment phases: one received medium-dose budesonide (400 μg twice per day; ICS phase), and the other received a combination therapy of budesonide/formoterol delivered by a single inhaler (160 μg budesonide plus 4.5 μg formoterol twice per day; LABA phase). Each treatment phase lasted for 6 weeks, followed by a 1-week washout period, after which patients were crossed over.

All patients completed asthma control test (ACT) questionnaires for their symptoms at the end of each treatment phase. The ACT contained 5 questions, each scored on a 5-point scale, with higher scores reflecting better asthma control.[12] FEV1, peak expiratory flow rate (PEFR), and induced sputum eosinophil percentile were measured following completion of each treatment phase.

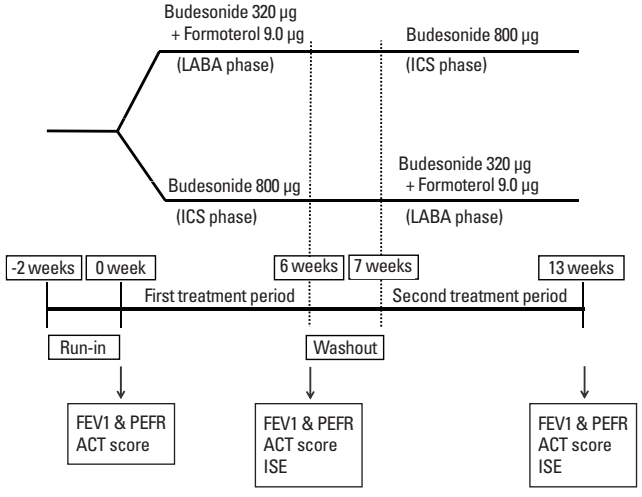

Fig. 1. Study design. Following completion of the run-in period, patients began receiving either 800 μg budesonide per day (ICS phase) or 320 μg budesonide plus 9 μg formoterol per day (LABA phase) for 6 weeks, followed by a 1 week washout period, after which patients were crossed over.
FEV1, forced expiratory volume in one second; PEFR, peak expiratory flow rate; ACT, asthma control test; ISE, induced sputum eosinophil.

Induced sputum examination

Sputum induction and processing were performed as described previously.[13] Differential cell counts from sputum samples were recorded as the average of counts performed by 2 examiners on separate occasions in a blinded manner. Eosinophilic inflammation of airways was defined as an eosinophil percentage of ≥3% in the sputum.

Endpoints

The primary outcome was mean sputum eosinophil percentile following completion of each treatment phase. Secondary variables included FEV1, morning PEFR, and ACT scores.

Sample size was determined by assuming a standard deviation for repeated induced sputum eosinophil percentile of 0.69% for each patient. Thirty participants would therefore provide 90% power to detect a change of 2% or greater in sputum eosinophil levels. Due to recruitment difficulties, only 24 subjects were recruited, which reduced the power to 70%.

Statistical analysis

Statistical analyses were performed using the SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Individual parameters including FEV1, PEFR, ACT score, and eosinophil percentage in the induced sputum were compared using the Wilcoxon signed-rank test. All values are presented as means±standard deviation [SD]. Statistical significance was defined as $P<0.05$.

RESULTS

Twenty-four asthmatic patients were enrolled, with 23 patients (12 males and 11 females; mean age, 57.9 years; range, 34-68 years) initially randomized into either the LABA phase (12 subjects) or ICS phase (11 subjects); following completion of the initial study phase patients were crossed over into the alternative study phase. All subjects completed the study; however, adequate sputum for downstream analyses was obtained from only 17 patients (9 males and 8 females; mean age 54.5 years; range 35-68 years). No adverse events were reported during the study period.

Comparison of lung function and asthma symptoms between study phases

Baseline measurements were collected following completion of the initial run-in period; mean FEV1 was 86.8±16.2% of the predicted value, morning PEFR was 371.0±75.5 L/min, and mean ACT score was 23.2±1.2 in the 23 subjects.

No differences in the 2 secondary outcomes, FEV1 and PEFR, were seen between the LABA and ICS phases. ACT scores were also similar in both phases (Table).

Table. Comparison of lung function and asthma symptoms between two phases

Variables	ICS phase	LABA phase
FEV1 (% predicted)	88.2±17.0	89.3±15.6
PEFR (L/min)	400.7±78.6	410.8±35.2
ACT score	24.36±0.81	24.45±0.69

No differences were observed between the ICS and LABA phases for FEV1, PEFR, and ACT score ($P>0.05$). Values are presented as means±SD.
ICS phase, 800 μg budesonide per day; LABA phase, 320 μg budesonide plus 9 μg formoterol per day; FEV1, forced expiratory volume in one second; PEFR, peak expiratory flow rate; ACT, asthma control test.

Comparison of airway eosinophilic inflammation between study phases

After 6 weeks of treatment, the mean sputum eosinophil percentage was 5.07±3.82% in the LABA phase, significantly higher than that seen in the ICS phase (1.02±1.70%, $P=0.007$). Sputum eosinophilia (≥3%) was present in 6 subjects during the LABA phase, compared to only 2 during the ICS phase (Fig. 2). Two patients showed a substantial increase in sputum eosinophil during the LABA phase (22.6% and 14.0%), which was decreased following completion of the ICS phase (0% and 3.66%).

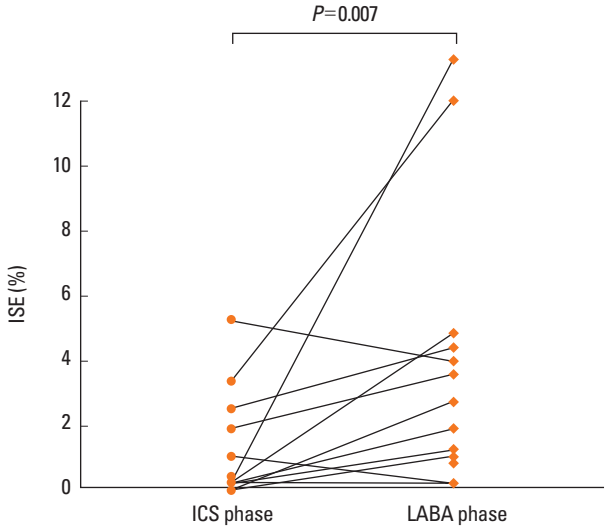

Fig. 2. Comparison of induced sputum eosinophil percentile between two phases. ICS phase, 800 μg budesonide per day; LABA phase, 320 μg budesonide plus 9 μg formoterol per day; ISE, induced sputum eosinophil.

DISCUSSION

When control of asthma is not achieved with low-dose ICS, the addition of a LABA is recommended, according to the Global Initiative for Asthma guidelines.[1] However, our results suggest that increasing the dosage of ICS provides better control of airway inflammation than addition of LABA, although asthma symptoms and lung function were comparable between the 2 strategies. Six of the 17 asthmatic patients had persistent airway eosinophilia during the LABA phase. Two patients showed a substantial increase in sputum eosinophil (more than 10%) using a combination of LABA plus low-dose ICS, which was decreased following treatment with medium-dose ICS alone. However, these changes in eosinophilic airway inflammation did not translate into differences in either lung function or asthma symptom scores between the ICS and LABA phases.

Traditional asthma management guidelines focus on symptoms, lung function, and the use of short acting β_2 agonists rescue therapy.[14] However, these features do not address underlying airway inflammation.[15] Several studies have demonstrated that asthma treatment decisions which focus on reducing eosinophilic airway inflammation can reduce the risk of acute exacerbations.[16,17]

A recent meta-analysis of clinical trials found that use of LABA increased the likelihood of life-threatening asthma exacerbations and death, leading the United States Food and Drug Administration to issue warnings regarding regular use of LABA.[18] Although the risk of adverse events is reduced with concomitant use of ICS, the overall safety of LABA remains controversial. A large-scale cohort study demonstrated a higher risk of severe exacerbations and hospitalization after combination therapy with LABA and ICS compared to increased dosage of ICS alone.[11]

LABA may worsen asthma symptoms as a result of continuous stimulation of β adrenergic receptors, leading to uncoupling and internalization of receptors, followed by a decrease in receptor density and receptor gene expression.[7-9,19] In patients with uncontrolled asthma, the addition of LABA may also mask progression of inflammatory processes, allowing the disease to worsen before symptoms appear.[6,7]

To date, few studies have compared the anti-inflammatory effects of addition of LABA to those of medium-dose ICS alone. In this study, neither treatment strategy resulted in measurable clinical deterioration, despite differences in airway inflammation. However, it is uncertain whether these findings are the result of limitations of the present study, such as the short duration or the small number of patients enrolled.

In conclusion, a combination of LABA and low-dose ICS could result in masking of eosinophilic inflammation in some patients, compared to medium-dose ICS alone. These results suggest that before or during the step-up with LABA add-on therapy, an evaluation of airway inflammation may be necessary to prevent persistent airway inflammation. Further studies of the effects of airway inflammation on clinical outcomes are required.

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