INTRODUCTION

Asthma is a chronic disorder that can place considerable restrictions on the physical, emotional, and social aspects of the lives of patients. Inhaled glucocorticoids (GCs) are the most effective controller therapy. The purpose of this study was to evaluate the effect of inhaled GCs on quality of life in patients with moderate to severe asthma. Patients completed the asthma quality of life questionnaire (AQLQ) and pulmonary function test at baseline and after 4 wks treatment of GCs. We enrolled 60 patients who had reversibility in FEV₁ after 200 μg of albuterol of 15% or more and/or positive methacholine provocation test, and initial FEV₁% predicted less than 80%. All patients received inhaled GCs (fluticasone propionate 1,000 μg/day) for 4 wks. The score of AQLQ was significantly improved following inhaled GCs (overall 51.9 ± 14.3 vs. 67.5 ± 12.1, p<0.05). The change from day 1 to day 28 in FEV₁ following inhaled GCs was diversely ranged from -21.0% to 126.8%. The improvement of score of AQLQ was not different between at baseline and after treatment of GCs according to asthma severity and GCs responsiveness. Quality of life was improved after inhaled GCs regardless of asthma severity and GCs responsiveness in patients with moderate to severe asthma.

MATERIALS AND METHODS

Study design

On the first day of study, a clinical history was obtained inhaled GCs would be the best way to control and maintain asthma symptoms. Control of asthma (1) is monitored by asthma symptoms, the use of rescue inhaled β2-agonist, and measurement of diurnal variation of peak expiratory flow (PEF), FEV₁, and by non-invasive markers of inflammation such as exhaled nitric oxide and induced sputum and airway hyper-responsiveness. A wide variation of response to inhaled GCs is expected between patients, but there is little data about responsiveness to high dose inhaled GCs relation to change in FEV₁ and asthma symptoms such as asthma quality of life questionnaire (AQLQ). Therefore, the aims of this study were to examine the effect of maximally recommended dose of inhaled GCs (1,000 μg of fluticasone propionate, FP) for 4 wks on AQLQ of patients with moderate to severe asthma, and the correlation of AQLQ with asthma severity and GCs responsiveness.
using a physician-administered questionnaire. Chest PA radiography, the allergy skin prick test, and spirometry including bronchodilator response after inhalation of 2 puffs of 100 μg aerosolized albuterol were performed. Blood and sputum were sampled for differential cell counts. AQLQ was evaluated at baseline and 4 wks. On second day, airway hyperresponsiveness (AHR) was measured in case of 70% or more in FEV1% predicted. The patients were educated visually by the trained nurse how to use the inhaled GCs until the accuracy score reach 12 of 14 (maximal score) (7). The inhaled GCs was started and maintained for 4 wks. The dose of inhaled GCs used via a multi-dose dry powder inhaler was FP 1,000 μg/day (2 puff b.i.d, Diskhaler; GSK, U.S.A.). During the study period, the patients were asked to record their symptom score and medication usage. The patients used short acting bronchodilator as needed base. The switch to combination or add on therapy was done in exacerbation during study period; deterioration of greater than 12% in AQLQ or FEV1 on treatment was regarded as demonstrating greater response than 12% or more in AQLQ or FEV1 at any time with developing aggravating symptoms. The primary end points were the change in AQLQ, basal FEV1, FEF25-75%, and FEV1/FVC after treatment of inhaled GCs.

**Subjects**

The patients with chronic asthma were recruited from the outpatient clinics in Soonchunhyang University Hospital. All patients with asthma had currently one or more asthma symptoms and the findings of physical examination compatible with asthma definition by the American Thoracic Society (8). Each patient showed airway reversibility as documented by a positive bronchodilator response of more than 15% increase in FEV1 and/or an airway hyper-reactivity of less than 10 mg/mL methacholine (9). Asthma severity was classified with symptoms, pulmonary function before treatment. The exclusion criteria were as follows: duration of asthma less than one year, acute exacerbated asthma within 4 wks, history of brittle asthma, atopic individuals to pollens, parenchymal lung diseases on chest radiography, diffusing capacity less than 80%, previous inhaled steroid or systemic steroid usage with-in the past 4 wks, and maintaining theophylline or leukotriene antagonist therapy. The prospective controlled trial involved 60 patients of mean age 45 yr with moderate to severe persistent asthma. The clinical parameters are summarized in Table 1. 42.5% of asthmatics showed positive skin test to the common inhalant allergens. The change from day 1 to day 28 in FEV1 (AFEV1=(FEV1 at 4 wks-baseline FEV1)/ baseline FEV1) following inhaled GCs was measured. Response to inhaled GCs was regarded as demonstrating greater response than 12% or more in AFEV1. During this period, 5 patients of asthmatics moved to the combination or add on therapy according to the protocol due to decreases of greater than 12% in FEV1 or AQLQ with symptom aggravation. This study was performed with the approval of the Ethics Committee of the University Hospital and informed writ-

**Quality of life measurement**

AQLQ was evaluated at baseline and 4 wks by using the quality of life questionnaire for adult Korean asthmatics (10). Each question was answered by the patient on a 5-point scale, with a score of 1 representing the greatest impairment and a score of 5 representing no impairment (lower AQLQ scores therefore reflect increased impairment). Items were equally weighted and reported as the mean score for each domain (activity limitations, emotions, symptoms, and exposure to environmental stimuli) along with an overall score.

**Lung function tests**

Baseline measurements of FVC and FEV1 were selected according to American Thoracic Society criteria (8). Basal and post-bronchodilator FEV1, FVC, and FEF25-75% were measured. The measurement was made between 1 p.m. and 4 p.m. AHR was measured by a methacholine challenge test and expressed as the provocation concentration to cause a fall in FEV1 of 20% (PC20) in non-cumulative units (11).

**Sputum examination**

Sputum was induced using isotonic saline containing a short-acting bronchodilator as described by Norzila et al. (12). Samples were treated within 2 hr of collection using the method of Pizzichini et al. (13) with a minor modification. Briefly, all visible portions with more solidity were carefully selected and placed in a preweighed Eppendorf tube. Samples were treated by adding four volumes of 0.1% dithiothreitol (Sputolysin, Calbiochem Corp., San Diego, Calif., U.S.A.). One volume of protease inhibitors (0.1 M EDTA and 2 mg/mL

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**Table 1. Baseline characteristics of the patients**

|                         | Moderate asthma | Severe asthma |
|-------------------------|-----------------|---------------|
| Number                  | 40              | 20            |
| Age (yr)                | 46.2±14.7       | 42.2±13.4     |
| Sex, male/female        | 23/17           | 11/19         |
| FEV1, % predicted       | 70.5±4.8        | 51.5±5.43     |
| FEV1/FVC                | 70.8±9.0        | 65.1±15.3     |
| FEF25-75%               | 50.3±13.8       | 29.0±11.7     |
| AQLQ                    | 52.3±13.2       | 51.2±16.6     |
| Atopy (%)               | 42.5            | 40            |
| Duration of asthma (yr) | 6.3±8.3         | 6.8±8.5       |
| Pack years smoked       | 7.7±10.6        | 11.8±12.0     |
| Blood eosinophils (%)   | 5.4±4.1         | 7.9±6.4       |
| Sputum eosinophils (%)  | 4.3±11.3        | 8.0±14.9      |
| Total IgE, Unit         | 350.2±616.1     | 634.2±496.7   |

*Plus-minus values are mean±SD. FEV1, forced expiratory volume in one second. FVC, forced vital capacity; FEF, forced expiratory flow. *p<0.01 compared with moderate asthma patients. AQLQ score, asthma quality of life score.
phenylmethylsulfonylfluoride) was added to 100 volumes of the homogenized sputum, and the total cell count was determined with a hemocytometer. Homogenized sputum was spun in a cytocentrifuge and 500 cells were read on each sputum slide stained with Diff-quick solution (American Scientific Products, Chicago, Ill., U.S.A.).

**Allergy skin prick tests**

Allergy skin prick tests were performed using commercially available 55 inhalant allergens including dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*, Bencard co, Reinbek, Germany) and histamine (1 mg/mL, Bencard, U.K.). None of the subjects had received antihistamines orally in the three days preceding the study. All tests included positive (1 mg/mL histamine) and negative (diluent) controls. After 15 min, the mean diameter of any wheal formed by the allergen was compared with that formed by histamine. If the former was the same or larger than the latter (A/H ratio ≥ 1.0), the reaction was deemed positive. Atopy was determined by the presence of an immediate skin reaction to one or more aeroallergens as previously described (14).

**Statistical analysis**

Data were doubled entered onto SPSS (v 10.0; SPSS Inc, Chicago, Ill., U.S.A.). Data are expressed as mean ± SD. Comparison of continuous variables was made using independent samples t testing. Differences in proportions were analyzed by chi-square testing with Fisher exact test when low expected cell counts were encountered. Pearson's correlations and Spearman's correlations were used to assess relationships between variables. A *p*-value of <0.05 was considered significant.

### RESULTS

The scores of AQLQ were significantly increased after 4 wks of inhaled GCs (overall; 51.9±14.3 vs. 67.5±12.1, asthma symptoms; 13.5±4.5 vs. 18.4±4.2, limitation of activity; 19.9±5.4 vs. 24.8±4.3, emotional functioning; 8.6±4.0 vs. 12.1±3.2, environmentally induced symptom; 10.0±3.6 vs. 12.1±2.4, respectively *p*-0.01. Fig. 1). During the study period, 33 patients (55.0%) with asthma showed 12% or more increase in FEV1 after high dose inhaled GCs and 27 patients were non-responder. The change in FEV1 [ΔFEV1= (FEV1 at 4 wks-baseline FEV1)/baseline FEV1] following inhaled GCs was diverse from -21% to 126.8%. The change in FVC [ΔFVC= (FVC at 4 wks-baseline FVC)/baseline FVC] following inhaled GCs was diverse from -74% to 37%. The change in FEF [ΔFEF= (FEF at 4 wks-baseline FEF)/baseline FEF] following inhaled GCs was diverse from -27.0% to 100%. FEV1% predicted, FEF25-75%, FEV1/FVC were significantly increased at 4 wks of inhaled GCs in moderate to severe asthmatics (Table 2). The responder of greater than 12% in ΔFEV1 demonstrated significantly lower base-
line FEV1% predicted. The responder of greater than 12% in ΔFEV1 compared with non-responder had higher trend proportion of sputum and blood eosinophils prior to treatment (sputum; 6.17 ± 12.0 vs. 4.90 ± 8.52, blood 7.15 ± 5.18 vs. 4.88 ± 3.72). Although the scores of AQLQ were increased after 4 wks of inhaled GCs, there was no difference of the scores of AQLQ at baseline and after treatment between responder and non-responder (Fig. 2). Also there was no difference of the scores of AQLQ at baseline and after treatment in terms of asthma severity and atopy. Duration of asthma, age, sputum eosinophils, blood eosinophils, FEV1% predicted at baseline, and PC20 methacholine were not correlated with AQLQ.

**DISCUSSION**

Quality of life scores and FEV1% predicted were improved in patients with moderate to severe asthma after high dose inhaled GCs, indicating that AQLQ as well as pulmonary function test may be an additive clinical parameter for effectiveness of GCs treatment in patients with asthma.

Clinical trials in asthma have studied on physiological measures of outcome such as airway caliber (15) and responsiveness (16). Questionnaires on asthma symptoms and treatment requirements have been used to assess clinical severity, but they have tended to be restricted to conventional clinical symptoms and have not taken into the impact of the symptoms and other aspects of the disease on the patients' lives. Asthma is associated with significant impairments of quality of life. Specific quality of life scales include questions targeted to asthma; many studies have been employed in clinical trials (17-21).

GCs, usually administered by means of inhalation, are potent inhibitors of inflammatory responses and therefore are currently considered to be the standard therapeutic regimen for the treatment of persistent asthma (22). GCs treatment of asthmatic patient reduces the numbers of infiltrating eosinophils and lymphocytes in the airways and decreases production and release of pro-inflammatory mediators and cytokines. As a consequence, some of the structural abnormalities of asthmatic airways are normalized after GCs treatment (23). In our study, responder asthmatic patients had higher trend of blood and sputum eosinophils prior to inhaled GCs, indicating that asthma patients with eosinophilic airway inflammation may be more responsive to inhaled GCs.

It is now well documented (24, 25), in both adults and children, that long-term treatment with inhaled GCs suppresses the disease by affecting the underlying airway inflammation. As a result, symptoms disappeared and lung function improves. The outcome parameter responding most rapidly to the initiation of inhaled steroid therapy is symptoms, PEF values improve gradually, while improvements in AHR may continue over many months or even years. Inhaled GCs may also modify the disease outcome if prescribed early enough and long enough. In this study we evaluated effect of high dose inhaled GCs to exclude dose dependent effect of GCs. We found that significant increase in FEV1 was observed at 4 wks in patients with asthma received high dose inhaled GCs. The responsiveness to inhaled GCs was diverse among patients with asthma.

The scores of AQLQ were used as a tool to measure outcome of drug treatment. Measurement of AQLQ may show benefits of asthma treatments not revealed by objective monitoring and can complement clinical and physiological assessments of treatment outcome (16, 20, 21, 26-29). In this study, we found that the scores of AQLQ in terms of overall and each item were improved after treatment of inhaled GCs, indicating that the AQLQ is valuable as the conventional clinical variables considered important in measuring asthma control. The correlations between pulmonary function and AQLQ scores not observed in this study, which was in consistent with Marks et al. (30). In contrast with Juniper et al. (27, 29) correlations between severity and AQLQ scores not observed due to the smaller sample size. Also age, atopy, duration of asthma, PC20 methacholine was not correlated with AQLQ scores.

The scores of AQLQ in terms of overall and each item were improved after treatment of GCs for 4wks, suggesting that the AQLQ can be used as a measure of outcome in GCs responsiveness in asthma.

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