Allergology International. 2012;61:625-627
DOI: 10.2332/allergolint.12-LE-0430

LETTER TO THE EDITOR

Dear Editor

Efficacy of Budesonide in Combination with Formoterol in Patients with Inadequately Controlled Asthma on Fluticasone in Combination with Salmeterol

Global Initiative for Asthma (GINA) guidelines (GINA 2010) advocate the use of inhaled corticosteroids combined with a long-acting inhaled β2-agonist in a single inhaler (ICS/LABA) in Treatment Steps 3 through 5 for bronchial asthma.[1] Fluticasone in combination with salmeterol (FP/SM) is effective in patients with moderate to severe asthma,[2] but some patients do not resolve the persistent symptoms and require step up treatments. Therefore, the efficacy of budesonide in combination with formoterol (BUD/FM) was assessed in patients with inadequately controlled asthma on FP/SM.

Methods

224 patients with asthma received FP/SM 250/50 μg bid more than 3 months between May and December 2010 in Respiratory Center of Takatsuki Red Cross Hospital, Osaka, Japan. 29 patients were judged as "not controlled" from the following questionnaire defined by GINA 2010; daytime and nocturnal symptoms, limitation of activities, and the frequency of need for reliever. After inhalation guidance instruction, peak expiratory flow (PEF) measured with a Mini-Wright® peak flow meter, routine usage of FP/SM, and need for short-acting inhaled β2-agonists (SABA) were recorded in the asthma diary twice daily. PEF measurements were repeated three times every morning and evening before FP/SM was taken and the best of three attempts was recorded on each occasion. As 26 of the patients did not improve symptoms after 1 month of inhalation guidance instruction (Visit 1), they chose between increase dose of FP or other ICS and/or add-on of other controllers, or switch to BUD/FM 320/9 μg bid. All 26 patients selected to switch from FP/SM to BUD/FM and continued to note their diary. The lowest morning PEF over a week, expressed as a percent of the recent best (Min%Max), which has been suggested as correlating with airway hyperresponsiveness (AHR)[3] was calculated every 4 weeks. The lowest morning PEF over a week defined the lowest daily mPEF in the previous week before each visit. The recent best was defined as the highest PEF over all of asthma diary. All data from the diary at Visit 1 were compared with switching therapy after 4, 8 and 12 weeks (Visits 2-4) respectively. At Visits 1 and 4, the Asthma Control Questionnaire (ACQ-5) which consists of five questions; night-time waking, symptoms on waking, activity limitation, shortness of breath and wheezing, was also completed.[4]

Table 1 Patient characteristics

	mean ± SE	range
Duration of asthma (years)	8.62 ± 1.31	1-22
Age (years)	57.0 ± 3.75	29-80
Number of patients (Male/Female)	8/13	
Smoking history (Never/Ex-smoking)	15/6	
Concomitant drugs other than SFC (None/Use)	7/14	

Fourteen were additionally on concomitant drugs: nine were on leukotriene antagonist (LTRA), one was on theophylline (Theo), and one each was on LTRA plus Theo and LTRA plus oral anti-allergic compound respectively.

Results

A summary of the demographic and baseline characteristics of the study subjects and asthma daily data are shown in Table 1 and Figure 1 respectively. Since 4 of patients required step up treatments and the remaining 21 patients were analyzed. At Visit 1, all subjects were classified according to GINA 2010 as moderate persistent asthma and not well controlled (18 subjects were classified as partly controlled and 3 as uncontrolled). None of the study subjects were current smokers, but six were ex-smokers with a median smoking history of 5.78 ± 2.31 pack-years. ACQ-5 scores significantly decreased from 1.3 at Visit 1 to 1.0 at Visit 4 (Fig. 1A). PEF showed significant improvements at the all Visits in the morning and evening from Visit 1 (Fig. 1B). Although no significant differences were observed in any of the data with need for SABA in the evening, morning requirement of SABA on Visits 3 and 4 were improved from those on Visit 1 (Fig. 1C). Min%Max obtained through Visits 2 to 4 were also significantly increased from Visit 1 (Fig. 1D). Although adherence to therapy and pulmonary spirometry were similar with no significant difference throughout the study periods, a 10% decline was shown in Visit 4 relative to Visit 1 (data not shown).

Discussion

This study confirmed that when inadequately uncontrolled asthmatic patients by FP/FM were switched to BUD/FM, they exhibited significant improvements in ACQ-5, PEF, Min%Max, and requirement of morning SABA, suggesting good asthma control. Many articles have reported the efficacy of BUD/FM, particularly the improvement in lung function and asthma control in comparison with other ICS and ICS/LABA.[4-10] Although, we did not confirm the as-

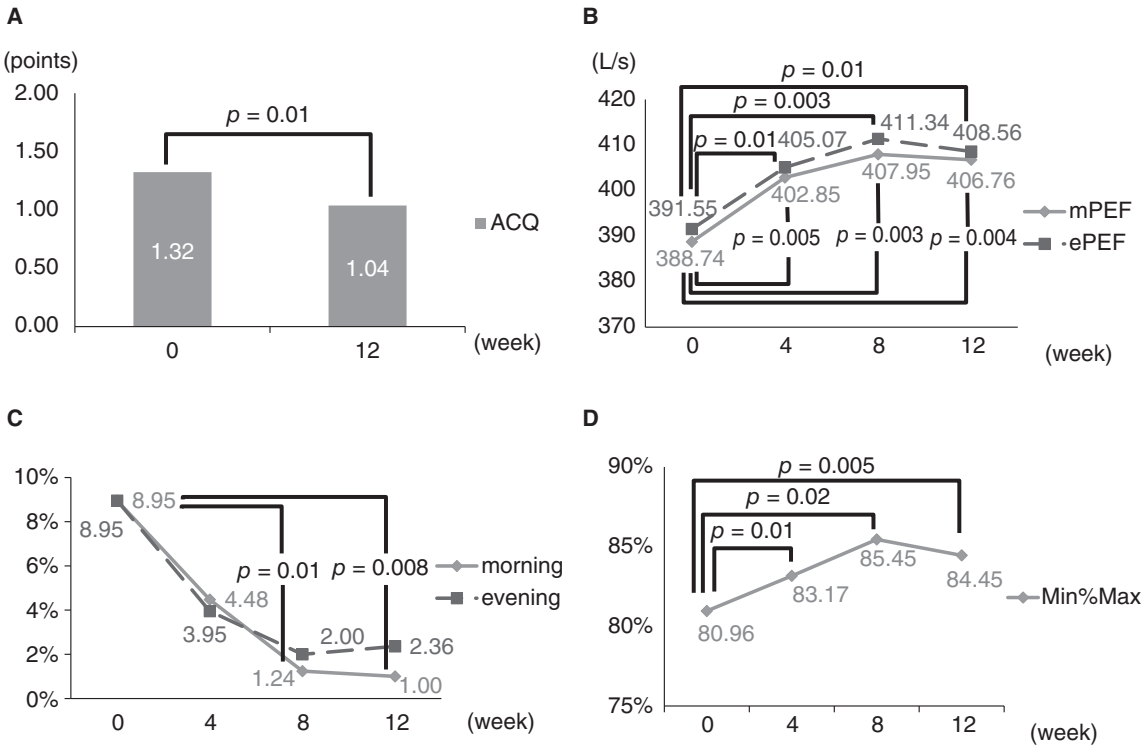

Fig. 1 Change from baseline in the average of Asthma Control Questionnaire (**A**), PEF (**B**). The frequency of need for SABA (**C**) and Min%Max (**D**).

sessment of airway inflammation by methods such as methacholine inhalation challenge, our result suggests that AHR improvement might be responsible for their asthma control because GINA 2010 notes that Min%Max correlates with AHR. On the other hand, we could not provide the improvement in spirometry. PEF were measured everyday on time and calculated the average, meanwhile, spirometry measurement represented the state at the examination and ranged in different time among patients. This is the possible reason for discrepancy between PEF and spirometry findings. There are several limitations to this study. First, it is possible that the observed Min%Max improvement might have been due to the influence of seasonal bias and differences between SM and FM. In fact, no studies have shown that FM 18 μg and SM 100 μg are the same titer. Second, we could not assess the efficacy of FP/SM in patients who were not well controlled on BUD/FM. When patients whose asthma is inadequately controlled by BUD/FM are switched to FP/FM, they might experience similar findings as observed in our result. Third, we should have also evaluated the demographic data between patients who were well controlled on FP/SM and those who were not. As a result, we could not find the characteristics of patients with no effect of FP/SM and answer the question of which subgroup of patients should be recommended BUD/FM. Finally, switching to the other ICS/LABA which is situated at the same treatment dosage might not be effective basically because four patients required the step up. However, in clinical practice, it has been often performed an exchange from one ICS or ICS/LABA to another ICS or ICS/LABA at the same treatment recommendation dose.

In conclusion, though our result is not applicable all of patients with inadequately controlled asthma on FP/SM, the switching from FP/SM 500/100 μg daily to BUD/FM 640/18 μg daily is effective in subset of patients. Additional studies to evaluate the clinical difference between validity and invalidity case for each BUD/FM and FP/SM are needed.

ACKNOWLEDGEMENTS

The authors thank Dr. Elizabeth Juniper for giving the permission to use ACQ-5.

Authors' contributions: YKan contributed to the recruitment of patients; the conception of the whole study; the acquisition and interpretation of data, and drafting of the manuscript. HK contributed to the recruitment of patients; the conception of the whole study; the design, acquisition, and interpretation of data; and revision of the manuscript. AN contributed to supervision of the study and revision of the manuscript. YF, KT, YKat, TT, YH, YN and TS contributed to the interpretation of data.

Yoshihiro Kanemitsu[1,2], Hideo Kita[1], Akio Niimi[3], Yoshinori Fuseya[1,2], Kazuya Tanimura[1], Yuko Katayama[1], Tamaki Takahashi[1,2], Yukimasa Hatachi[1], Yumi Nishihara[1] and Toshikatsu Sado[1]
[1]Takatsuki Red Cross Hospital Respiratory Center, Osaka, [2]Department of Respiratory Medicine, Kyoto University, Kyoto and [3]Medical Oncology and Immunology, Nagoya City University School of Medical Sciences, Aichi, Japan
Email: kaney32@kuhp.kyoto-u.ac.jp
Conflict of interest: No potential conflict of interest was disclosed.

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