

# Analysis of Inhaled Corticosteroid Selection in Patients with Bronchial Asthma Using a Questionnaire Survey—Effects of Age, Gender, and Disease Severity—

Kyuma Ota<sup>1</sup>, Takashi Hasegawa<sup>2</sup>, Toshiyuki Koya<sup>1</sup>, Takuro Sakagami<sup>1</sup>, Takashi Sekikawa<sup>1</sup>, Shinichi Toyabe<sup>3</sup>, Kohei Akazawa<sup>4</sup>, Masaaki Arakawa<sup>1</sup>, Fumitake Gejyo<sup>1</sup> and Eiichi Suzuki<sup>2</sup>

## ABSTRACT

**Background:** Inhaled corticosteroid (ICS) has played an important role in the management of asthma. Although several kinds of ICSs are currently available, there is no established strategy for ICS selection.

**Methods:** Using the data from the 2004 questionnaire surveys by the Niigata Asthma Treatment Study Group, we analyzed relationships between each patient and the ICS employed on the basis of patient background, asthma control and treatment, and indicated characteristics of ICS selection by the physician.

**Results:** Of 2852 cases, 2279 (79.9%) were ICS users, and 1513 (66.4% of ICS users) were classified as being in the fluticasone propionate (FP) group, 438 (19.2%) in the budesonide (BUD) group, and 240 (10.5%) in the hydrofluoroalkane-beclometasone (HFA-BDP) group, indicating that FP was a standard ICS in this study. The mean age was significantly lower in the BUD group (52.3+/-18.2 years) and was significantly higher in the HFA-BDP group (59.9+/-17.0 years) than that in the FP group (55.8+/-16.6 years). The proportion of female patients was significantly higher not in the HFA-BDP (46.5%) but in the BUD group (59.0%) than in the FP group (51.1%). These results indicated that BUD was frequently prescribed to young female and HFA-BDP was employed in the elderly patients irrespective of gender compared with FP.

**Conclusions:** Our study indicates that ICS selection is reasonably adapted to each patient's background at least in the surveyed area. We need to elucidate the characteristics of ICS selection further in the future as new ICS and devices are developed.

## KEY WORDS

bronchial asthma, inhaled corticosteroid, Japan, selection strategy, therapy

## ABBREVIATIONS

AIA, aspirin intolerant asthma; BUD, budesonide; DPI, dry powder inhaler; FP, fluticasone propionate; HFA-BDP, hydrofluoroalkane-beclometasone; ICS, inhaled corticosteroid

## INTRODUCTION

The management of bronchial asthma has changed since it has been recognized as a chronic airway inflammation.<sup>1,2</sup> Guidelines for bronchial asthma in

many countries<sup>3-5</sup> recommend inhaled corticosteroids (ICS) as the main treatment. Therefore, ICS plays an essential and important role in the management of bronchial asthma. In the clinical setting, the prevalence of ICS has resulted in excellent asthma con-

<sup>1</sup>Division of Respiratory Medicine, Niigata University Graduate School of Medical and Dental Sciences, <sup>2</sup>Department of General Medicine, <sup>3</sup>Department of Patient Safety and <sup>4</sup>Division of Medical Information Science, Niigata University Medical and Dental Hospital, Niigata, Japan.

Correspondence: Takashi Hasegawa, Department of General

Medicine, Niigata University Medical and Dental Hospital, 1-754 Asahimachi-dori, Chuo-ku, Niigata, 951-8510, Japan.

Email: htaka@med.niigata-u.ac.jp

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trol.<sup>6</sup>

The treatment of asthma by ICS involves the serious problem of ICS selection for individual patients. Although the efficacy of ICS is one of the most important factors for ICS selection, it can be influenced by various factors, including distribution and metabolism of ICS to bronchi, drug compliance of the patients, and inhalation proficiency of each ICS device employed.<sup>7</sup> In fact, we previously reported the effect of ICS compliance on the control of asthma.<sup>8</sup> It was also reported that ICS devices could affect not only asthma control but also asthma death.<sup>9</sup> These factors indicate that the differences among various ICSs, including efficacy, depend on the differences not only of inhaled medicine itself but also the relationship between individual patients and the employed ICS. Considering this characteristic of ICS, physicians must select the most adequate ICS for each asthmatic patient. However, there have been few reports focusing on ICS selection.

In a clinical setting, many patients actually use the ICS recommended by their physician. Their election may be based on the efficacy of ICS that can be influenced by factors as mentioned above. Therefore, the use of ICS in each patient can be related to certain characteristics for ICS selection. Starting in 1998 a regular questionnaire survey by the Niigata Asthma Treatment Study Group was administered; the survey considered problems concerning asthma management. The subjects in this survey were adult patients with bronchial asthma who visited medical institutions in the Niigata prefecture. The attending physicians of these patients were included in the survey. On the basis of these surveys, we reported the clinical characteristics of adult bronchial asthma patients,<sup>10</sup> the characteristics of elderly bronchial asthma<sup>11</sup> and near fatal asthma,<sup>12</sup> the relationship between smoking and gender in asthmatics,<sup>13</sup> and changes in asthma management.<sup>14,15</sup> These surveys clearly indicated which ICS was being employed for asthmatic patients. Using the data from 2004 surveys, when there were 3 major available ICSs, including hydrofluoroalkane-beclometasone (HFA-BDP) pressurized metered-dose inhaler (pMDI), fluticasone propionate (FP) dry powder inhaler (DPI), and budesonide (BUD) DIP in Japan, we analyzed the relationship between individual patients and the employed ICS focusing on patient background, asthma control and treatment, and indicated characteristics of ICS selection in accordance with each asthma patient by the physician.

## METHODS

Each institute in the Niigata prefecture participated in this study with the intention of joining the Niigata Asthma Treatment Study Group. This study was performed with the approval of the Ethics Committees at the School of Medicine of Niigata University in the

Niigata prefecture, Japan, or at each attending institution under the Ethical Principles for Medical Research Involving Human Subjects, Declaration of Helsinki. The study involved 28 large hospitals (200 beds or more), 15 small hospitals (less than 200 beds), and 35 clinics (no beds). A total of 3650 questionnaires were prepared, and 2865 were answered (response rate, 78.5%). Table 1 presents the contents of the questionnaire (originally in Japanese). The questionnaire study was performed over 2 months from September to October 2004. Subjects were adult patients (aged 16 years and more) with bronchial asthma who regularly visited the participating institutes for asthma management (typically once or twice per month). The recruited patients were asked to complete the questionnaire by themselves. Therefore, the understanding of technical terms such as "attack" or "unconsciousness" in the questionnaire (Table 1) depended upon the individual patients.

For an evaluation of asthma control, patients were asked about their mean expiratory peak flow value and the incidence of asthma attacks during the 2 weeks prior to answering the questionnaire. During the year prior to the performance of the questionnaire, the patients were also asked to provide information about the asthma affecting them by choosing 1 of the following 3 answers: "few attacks," "seasonal attacks," and "frequent attacks." Furthermore, they were asked about asthma-related work or school absences. The questionnaires included questions on asthma-related symptoms in the 2 weeks prior to the questionnaire, including those regarding cough and sputum in the morning and at night, and sleep disturbances. The questionnaire also inquired about asthma-related emergencies, including ambulance use, emergency department visits, and hospitalization, and life-threatening events such as unconsciousness during asthma attacks, attacks requiring respirator management, and asthma attacks induced by an anti-inflammatory agents (aspirin intolerant asthma, AIA). The subjects were required to answer with a "yes" or "no" to the following 5 questions: "Have you ever been hospitalized due to asthma?"; "Have you ever been taken by ambulance or visited an emergency room due to an attack?"; "Have you ever been placed on a respirator due to an asthma attack?"; "Have you ever been unconscious due to an asthma attack?"; and "Have you ever had an attack induced by anti-inflammatory drugs including painkillers, antipyretics, or cold medicine?" To evaluate problems in asthma management and treatment related to normal activity levels, the questionnaires asked patients about their satisfaction in daily life. The subjects answered by choosing 1 of 5 answers: "very satisfied"; "fairly satisfied"; "mediocre"; "slightly dissatisfied"; and "dissatisfied."

In addition to monitoring the completion of the questionnaire by the patients, physicians were asked



**Table 2** Patient background

	FP	BUD	HFA-BDP
Age (year)	55.8 +/- 16.6	52.3 +/- 18.2***	59.9 +/- 17.0***
Gender: male/female (%)	723/755 (48.9/51.1)	174/250 (41.0/59.0)***	120/113 (53.5/46.5)
Duration (year)	14.0 +/- 13.1	11.8 +/- 12.9***	13.6 +/- 13.1
Type: atopic/nonatopic (%)	1000/466 (68.2/31.8)	306/115 (72.7/27.3)	162/73 (68.9/31.1)
Severity: Step1/2/3/4 (%)	404/408/520/119 (27.8/28.1/35.8/8.2)	120/150/142/17** (28.8/35.0/33.1/4.0)	58/64/82/22 (25.7/28.3/36.3/9.7)
Smoking status: Non/Ex/Cu (%)	673/565/220 (46.2/38.8/15.1)	200/154/151*** (39.6/30.5/29.9)	103/102/28 (44.2/43.8/12.0)
PEF use: use/non-use (%)	672/628	142/219***	93/120*

\*:  $p < 0.05$ , \*\*:  $p < 0.01$ , \*\*\*:  $p < 0.001$  v.s. FP, FP: fluticasone dry powder inhaler, BUD: budesonide dry powder inhaler, HFA-BDP: hydrofluoroalkane-beclomethasone pressurized metered-dose inhaler, Non: non-smoker, Ex: exsmoker, Cu: current smoker, PEF: peak flow meter.

to supply details on current treatment, primarily identifying control medication, the type of asthma (atopic or nonatopic) in accordance with the elevation in serum total IgE or detection of specific IgE for allergens, and the severity of asthma in accordance with the Japanese Society of Allergology guideline for the diagnosis and management of bronchial asthma. The definition of severity of asthma is essentially the same as that used by the Global Initiative for Asthma.

The representative results for continuous variables were expressed as arithmetic means and standard deviations. The differences between groups regarding continuous variables were evaluated with Kruskal-Wallis test and Wilcoxon's rank sum test. Chi-square test was used to assess the significance of differences in proportions among groups. In all statistical analyses, a  $p$ -value less than 0.05 was considered statistically significant. All analyses were performed using SPSS Statistics 17.0 (SPSS, Chicago, IL, USA) software.

## RESULTS

### PATIENT BACKGROUND

Of the patients who completed this questionnaire, 2279 (79.9%) were ICS users, and 1513 (66.4% of ICS users) were classified as being in the FP group, 438 (19.2% of ICS users) were classified as being in the BUD group, 240 (10.5% of ICS users) were classified as being in the HFA-BDP group, and 88 (3.8% of ICS users) were not classified as being in any of these 3 groups (chlorofluorocarbon beclomethasone pressurized metered-dose inhaler [CFC-BDP], 78; the lack of the used ICS trade-name, 10). Table 2 summarizes the backgrounds of patients in the FP, BUD, and HFA-BDP groups. The mean age was significantly lower in the BUD group and was significantly higher in the HFA-BDP group than that in the FP group. The proportion of female patients was significantly higher not in the HFA-BDP but in the BUD group than in the FP group. The duration of the disease was significantly less in the BUD group than that in the FP

group. The proportion of patients with step 4-disease severity was significantly lower in the BUD group than that in the FP group. The proportion of current smokers was also significantly higher in the BUD group than that in the FP group. The number of peak-flow meter (PEF) users was significantly higher in the BUD and HFA-BDP group than those in the FP group. There were no significant differences in type of asthma between the FP and BUD groups. There were no significant differences in age, disease duration, type of asthma, disease severity, or smoking state between the FP and HFA-BDP groups.

### DRUG/MEDICATION

In terms of medication (Table 3), the used dose of ICS was significantly greater in the BUD group and was significantly less in the HFA-BDP group than that in the FP group. There was a significantly lower usage of oral corticosteroids and salmeterol (SML) among patients in the BUD group and a significantly lower usage of SML among patients in HFA-BDP group, compared to the FP group. Further, there was a higher usage of tulobuterol patch (p-TBL) and oral sustained-released theophylline (OSRT) in the HFA-BDP group compared to the FP group. The used doses of oral corticosteroid, calculated as prednisolone, in the BUD group were significantly less than those in the FP group.

### ASTHMA CONTROL AND SYMPTOMS

There was a higher rate of asthma attacks during the 2 weeks prior to answering the questionnaire in the BUD group than that in the FP group. Except for this, there were no significant differences between the FP and BUD groups in asthma control and symptoms during the 2 weeks prior to answering the survey (Table 4A). During the 1 year period prior to answering the survey, the proportion of respondents who reported "few" asthma attacks was significantly lower; further, the proportion of respondents who reported "seasonal" asthma attacks was significantly higher in

**Table 3** Drug/Medication

	FP	BUD	HFA-BDP
ICS doses (µg/day)	407 +/- 206	534 +/- 274***	345 +/- 202***
LTRA use: use/non-use (%)	707/806 (46.7/53.3)	183/255 (41.8/58.2)	108/132 (45.0/55.0)
OCS use: use/non-use (%)	115/1398 (7.6/92.4)	18/420 (4.1/95.9)*	21/219 (8.8/91.3)
OCS dose (mg/day: calculated as PSL)	6.2 +/- 3.6	4.6 +/- 2.4*	6.1 +/- 3.8
SML use: use/non-use (%)	360/1153 (23.8/76.2)	68/370 (15.5/84.5)***	34/206 (14.2/85.8)***
p-TBL use: use/non-use (%)	153/1360 (10.1/89.9)	46/392 (10.5/89.5)	37/203 (15.4/84.6)*
OSRT use: use/non-use (%)	877/634 (58.3/41.7)	248/190 (56.6/43.4)	154/86 (64.2/35.8)***

\*:  $p < 0.05$ , \*\*\*:  $p < 0.001$  v.s. FP, FP: fluticasone dry powder inhaler, BUD: budesonide dry powder inhaler, HFA-BDP: hydrofluoroalkane-beclometasone pressurized metered-dose inhaler, ICS: inhaled corticosteroid, LTRA: leukotriene receptor antagonist, OCS: oral corticosteroid, PSL: prednisolone, SML: salmeterol, p-TBL: tulobuterol patch, OSRT: oral sustained-released theophylline.

**Table 4A** Incidence of asthma attacks, percentages of predicted peak flow values, asthma-related symptoms and sleep disturbances during the two weeks prior to answering the questionnaire

	FP	BUD	HFA-BDP
Asthma attacks: present/absent (%)	314/879 (26.3/73.7)	112/239 (31.9/68.1)*	44/140 (23.9/76.1)
PEFV (morning)	394 +/- 161	383 +/- 120	365 +/- 161
PEFV (night)	406 +/- 221	394 +/- 122	377 +/- 140
ARS in morning: present/absent (%)	599/914 (39.6/60.4)	188/250 (42.9/57.1)	97/143 (40.4/59.6)
ARS in night: present/absent (%)	396/1117 (26.2/73.8)	127/311 (29.0/71.0)	60/180 (25.0/75.0)
Sleep disturbance: present/absent (%)	174/1339 (11.5/88.5)	62/376 (14.2/85.8)	30/210 (12.5/87.5)

\*:  $p < 0.05$  v.s. FP, FP: fluticasone dry powder inhaler, BUD: budesonide dry powder inhaler, HFA-BDP: hydrofluoroalkane-beclometasone pressurized metered-dose inhaler, PEFV: peak flow value, ARS: asthma-related symptoms.

**Table 4B** Asthma attacks and asthma-related work absences during the one year period prior to answering the questionnaire

	FP	BUD	HFA-BDP
AA: frequent/seasonal/few (%)	163/396/719 (12.8/31.0/56.3)	45/149***/164*** (12.6/41.6/45.8)	19/65/120 (9.3/31.9/58.8)
ARWA: present/absent (%)	153/1045 (12.8/87.2)	52/310 (14.4/85.6)	15/152 (9.0/91.0)

\*\*\*:  $p < 0.001$  v.s. FP, FP: fluticasone dry powder inhaler, BUD: budesonide dry powder inhaler, HFA-BDP: hydrofluoroalkane-beclometasone pressurized metered-dose inhaler, AA: asthma attacks, ARWA: asthma-related work or school absences.

**Table 5** Satisfaction in daily life

	Very satisfied/ fairly satisfied/ mediocre/ slightly dissatisfied/dissatisfied (%)
FP	277/820/216/125/18 (19.0/56.3/14.8/8.6/1.2)
BUD	72/231/84*/32/5 (17.0/54.5/19.8/7.5/1.2)
HFA-BDP	48/139/31/17/0 (20.4/59.1/13.2/7.2/0.0)

\*:  $p < 0.05$  v.s. FP, FP: fluticasone dry powder inhaler, BUD: budesonide dry powder inhaler, HFA-BDP: hydrofluoroalkane-beclometasone pressurized metered-dose inhaler.

the BUD group than that in the FP group, despite no significant differences in asthma-related work or school absences (Table 4B). There was no significant difference in asthma-related work or school absences between the HFA-BDP and FP groups (Table 4A, B).

**SATISFACTION IN DAILY LIFE AND ASTHMA-RELATED EMERGENCY EPISODES**

The proportion of respondents who reported “mediocre” for the satisfaction in daily life was significantly higher in the BUD group than that in the FP group, despite no significant differences between the FP and BUD groups (Table 5). There was no significant difference in satisfaction in daily life between the FP and HFA-BDP groups (Table 5). Table 6 summarizes the results regarding asthma-related emergency episodes. Lower rates of hospitalization, and ambulance or emergency department visits were reported by patients in the BUD group compared with those in the FP group. The rates of asthma attacks with unconsciousness and AIA episodes were also significantly lower in the BUD than in the PF group. There were no significant differences between the FP and HFA-BDP groups except the significantly higher rate of respirator management history in the HFA-BDP

**Table 6** Hospitalization, ambulance use or ED visits, attacks with unconsciousness, respirator management and AIA attacks

	FP	BUD	HFA-BDP
Hospitalization: present/absent (%)	687/723 (48.7/51.3)	152/257 (37.5/62.5)***	114/103 (52.5/47.5)
Ambulance use or ED visits: present/absent (%)	592/821 (41.9/58.1)	140/269 (34.2/65.8)**	88/126 (41.1/58.9)
Attacks with unconsciousness: present/absent (%)	103/1269 (7.5/92.5)	16/380 (4.0/96.0)*	15/190 (7.3/92.7)
Respirator management: present/absent (%)	92/1275 (6.7/93.3)	19/376 (4.8/95.2)	22/184 (10.7/89.3)*
AIA attacks: present/absent (%)	130/1277 (9.2/90.8)	24/378 (6.0/94.0)*	17/202 (7.8/92.2)

\*:  $p < 0.05$ , \*\*:  $p < 0.01$ , \*\*\*:  $p < 0.001$  v.s. FP, FP: fluticasone dry powder inhaler, BUD: budesonide dry powder inhaler, HFA-BDP: hydrofluoroalkane-beclometasone pressurized metered-dose inhaler, ED: emergency department, AIA: aspirin induced asthma.

group.

## DISCUSSION

The aim of this study was to compare the various asthmatic patients classified on the basis of the kind of employed ICS with their associated clinical features, and to find characteristics of ICS selection by physicians suitable for each asthma patient. As more than two decades after the introduction of ICS have passed, the characteristics of ICS selection can be included in the data of the questionnaire survey. When chlorofluorocarbon beclometasone was available, there were no problems of ICS selection in accordance with the patient characteristics because there were no other ICSs with little systemic adverse effects due to corticosteroids. Later, new ICSs, including their improved pharmacological properties and progressive devices, have become available. In Japan, FP, BUD, and HFA-BDP were offered in 1998, 2001, and 2003, respectively. Further, the questionnaire survey employed in this study was performed 6, 3, and 1 years following FP, BUD, and HFA-BDP introduction, respectively. It is very clear that FP played a major role in the ICS asthma treatment, indicating that FP is the standard ICS in Japan. However, considering the background of ICS introduction mentioned above, the earlier recognition of FP than BUD and HFA-BDP had a certain influence on the FP majority. In other words, the already accepted perception of FP as a major second generation ICS by the physicians might be advantageous to its use.

For the prescription of ICSs to asthmatic patients, a comparison of BUD and HFA-BDP with FP will be the first step in the selection of ICS by each physician, and the accumulation of this step would reflect a certain characteristic of ICS selection in our data from the questionnaire survey. Therefore, in this study, we compared BUD and HFA-BDP group with FP group. Table 2 clearly showed that there were apparent differences in age, gender, and disease duration between FP and BUD, or FP and HFA-BDP. Regarding for BUD group, it was used in younger age patients and predominantly in female. These results indicate that both age and gender were considered in the selection of BUD. Recently, the safety of ICS during pregnancy was established,<sup>16</sup> and BUD was rec-

ognized as a safe ICS option for the first time.<sup>17</sup> This was likely reflected in our results. In other words, physicians can safely opt for BUD in potentially pregnant patients. Other characteristics in the BUD group were found in disease severity and ICS dose. Except for asthma attacks during the 2 weeks prior to answering the questionnaire, there were no differences in the indicators of asthma control in this study between FP and BUD groups (Table 4). However, milder patients tended to employ BUD than FP (Table 2) and the users of BUD less frequently employed SML than FP. Although the doses of BUD were greater than those of FP, it was less than double the amount of FP. It was reported that the clinical efficacy of BUD was approximately equal to half of that of FP.<sup>18</sup> Furthermore, the Ministry of Health, Labour and Welfare in Japan have decided that the allowable maximum dose of BUD is 2 times that of FP and HFA-BDP. Therefore, the actual doses of ICS in the BUD group could be considered to be less than those in the P group, indicating that the physicians tended to select BUD for somewhat mild asthmatic patients. Lower rates of hospitalization, ambulance, or emergency department visits in the BUD group was likely to be related with this BUD property. However, this BUD feature might be uncertain, because the comparison among dose efficacy responses of each ICS has not been completely established yet. The causes of the low rates of asthma attacks with unconsciousness and AIA episodes in the BUD group remain unknown.

HFA-BDP was employed in older patients without gender differences, compared to FP (Table 2). In Japan, FP was used almost like a DPI. Although DPI removes the need for inhalation-actuation synchrony, it usually requires a certain inspiratory flow rate. It was reported to be difficult for patients with impaired lung function, including low forced expiratory volume 1 second and vital capacity, to adequately inhale FP powder.<sup>19</sup> Moreover, there is a problem in loading and priming for DPI use, and medical personnel are required to possess knowledge on accurate usage of DPI.<sup>20</sup> In cases of the elderly, the same situation as mentioned above can be frequently anticipated. In contrast, the use of pMDI, including HFA-BDP, does not require either adequate inspiratory flow rate or

correct loading/priming for DPI use, although the handling pMDI requires inhalation-actuation synchrony. These factors might be the causes of high usage rates of HFA-BDP in elderly patients. The patients in HFA-BDP were older and employed PEF to a lesser extent than those in FP; which corresponded with the results of our previous report.<sup>11</sup> The reasons for the lower doses of ICS, the lower usage rate of SML, the higher usage rate of OSRT, and the higher usage rate of p-TBL in the HFA-BDP group than those in FP group also might be related to the fact that the patient age in HFA-BDP group was greater than that in FP group. The causes of the high rate of respirator management in the HFA-BDP group are still unknown, as in the case of the BUD group. On the basis of the data on HFA-BDP selection by physicians, HFA-BDP can be considered to be suitable for elderly patients with asthma.

In summary, we attempted to elucidate characteristics of the ICS selection in each patient by comparison with the characteristics of each ICS user in the data obtained from questionnaire surveys. FP was likely to be a standard ICS in Japan. BUD was prescribed to young and female patients; it is affected by both age and gender. HFA-BDP was used in the elderly patients irrespective of gender. As we retrospectively showed characteristics of ICS selection, this was a limitation in our study, and more prospective studies will be required. In the future, new ICSs and devices will be developed, and the principles of ICS selection will also be altered. However, we should try to elucidate the characteristic of ICS selection adapted to the circumstance of ICS development and apply them in clinical settings.

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