Role of budesonide/formoterol maintenance and reliever therapy: a pragmatic study

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Summary

***Background*: Many studies have demonstrated the efficacy of budesonide/formoterol (BUD/FORM) for Maintenance and Reliever Therapy (SMART®) for asthma control. However, there are concerns regarding its over-use and effectiveness.**

***Objective*: To examine asthma control and over-use of BUD/FORM in real-life situations.**

***Methods*: This study was a hospital-based cross-sectional and multi-center design. Patients were enrolled if they were >12 years old, had persistent asthma, had received BUD/FORM SMART for 3 months or longer, and smoked less than 10 pack-year.**

***Results*: Of the 792 patients who used BUD/FORM for a mean of 28.2 months, all used BUD/FORM as maintenance and only 22.2% of the patients required BUD/FORM to relieve symptoms. The average inhaled corticosteroid dose used was 355.3±154.9µg/ day (95% CI: 344.5 to 366.1). In 792 patients, constituting 2,376 person-months of observations, there was only one patient who used more than 12 puffs/ day of BUD/FORM for 3 days, with a rate of 0.015 days per patient per year (95%CI: 0.003 to 0.044), without reporting any adverse events.**

The percentage of asthma control according to the Asthma Control Test score of 20 or greater was 86.5% (95% CI: 84.1 to 88.9). Overall, the rates per patient per year of emergency room (ER) visits and hospital admissions were 0.18 and 0.21, respectively.

Conclusions*: BUD/FORM SMART is effective in real-life clinical practice. On average, patients who received a low dose steroid in the form of BUD/FORM, had a satisfactorily high proportion of asthma control and had a low rate of ER visits and hospitalization. BUD/FORM maintenance and reliever therapy seems to be promising as a treatment approach for persistent asthma in every day clinical practice. *(Asian Pac J Allergy Immunol 2014;32:160-5)

Key words: Budesonide/formoterol, over-use, under-use, asthma control, real clinical practice

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Introduction

A fixed dose combination of budesonide/ formoterol (BUD/FOM) is an effective treatment for asthma.[1-5] There are several advantages of using this combination. In particular, it can be used as both maintenance and reliever therapy (SMART®) in a single inhaler.[1] The US FDA approved BUD/FOM as maintenance therapy in asthma patients with an age over 12 years. The Global Initiative for Asthma (GINA) also stated that it provides a high level of asthma control and reduces exacerbations requiring systemic glucocorticosteroids and hospitalization.[1, 5] Asthma control in both adults and adolescents can be achieved even with relatively low doses of treatment.[4] SMART® treatment therefore is a beneficial asthma therapy for treatment of acute exacerbations, disease control, exacerbation prevention, and effectiveness as a low dose treatment with no serious side effects.

Several concerns have been raised concerning SMART® therapy, a single combination of agents which functions as both controller and reliever. Patients may use it as needed and receive very high doses of corticosteroid due to its ease of use. The effectiveness of SMART® therapy in real clinical practice has not been previously demonstrated. The aim of this study was to evaluate the incidence of over-use of BUD/FORM as needed in actual clinical practice, as well as the percentage achievement of asthma control among patients who received

BUD/FORM maintenance and reliever therapy for 3 months or longer.

Methods

This study was a multi-center, hospital-based, cross-sectional, epidemiological survey conducted in provincial hospitals across Thailand between May and November, 2009. The provincial hospitals were invited to participate in the study if BUD/FORM was available for use in their hospital. Patients were enrolled if they were 12 years or older, had asthma and had received BUD/FORM SMART for 3 months or longer. The maximum number of enrolled patients per hospital was 100.

A face-to-face interview was conducted with eligible patients by the researchers, who were independent of the responsible physicians. All interviewers were research associates from a single organization and trained in asthma control, asthma outcomes, medical history, and prescribed medications. BUD/FORM over-use was defined as the use of more than 12 puffs/day. For asthma control, the Asthma Control Test (ACT) score was used and obtained from the patients at the survey date when the patients visited the hospital for routine out patient appointments. Numbers of hospitalizations for asthma-related visits and overall health status were also recorded.

This study was conducted in full conformity with Good Clinical Practice (GCPs), including the International Conference on Harmonization (ICH) Guidelines and was consistent with the Declaration of Helsinki (October 2008).

Statistical Methods

The incidence of over-use of BUD/FORM per patient per year along with its 95% confidence intervals (95%CI) was estimated based on the exact Poisson distribution. This method of estimation was also used to estimate the incidence of ER visits and hospitalization. The ER visit incidence was the ER visits for asthma exacerbations, excluding those in which the patient required admission. The percentage of asthma control and its 95% CI was estimated based on the normal approximation of binomial distribution. For exploratory purposes the proportion of hospitalizations was compared to patients with and without controlled asthma using the chi-square test. All analyses were performed using STATA version 10 (StataCorp, College Station, TX). A p-value of less than 0.05 was considered to be statistically significant. All statistical tests were two-sided.

Table 1. Characteristics of the patients (n = 792)

Characteristics	Percent
Age (years), mean (SD)	52.3 (15.0)
Sex, % female	73.5%
Smoking status, % smokers	10.6%
Age at onset of asthma symptoms (years), mean (SD)	37.6 (17.9)
Duration of illness (years), median (min:max)	10.3 (0.3 : 75.5)
Duration under BUD/FORM treatment (months), median (min:max)	28.2 (0.3 : 571.6)

SD=standard deviation; min=minimum; max=maximum

Results

Characteristics of patients and treatments on the date they started budesonide/formoterol

A total of 1,030 asthma patients from 23 hospitals were screened; 792 of these used budesonide/formoterol maintenance and reliever therapy. Of the 792 patients included in this study, three quarters (73.5%) were female. The mean and standard deviation of age were 52.3±15.0 years old (Table 1). On average, patients had asthma symptoms beginning at age 37.6±17.9 years, an asthma duration of 10.3 years, and had been on budesonide/formoterol maintenance and reliever therapy for 28.2 months. Medications prescribed in combination with budesonide/formoterol were mainly theophylline, 43%, followed by β2-agonist tablets, 19% (Figure 1).

Use of budesonide/formoterol

Of the 792 patients, who represented 2,376 person-months of observations, there was only one patient who used more than 12 inhalations of budesonide/formoterol(160/45) per day for 3 days (Table 2). This patient reported no adverse events.

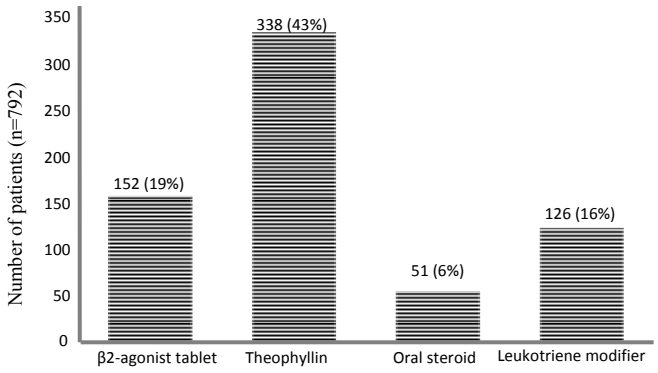

Figure 1. Number of patients according to medications prescribed in combination with budesonide/formoterol

Table 2. Use of bedesonide/formoterol during a period of 3 months before the most recent visit. Figures represent number and percent unless indicated otherwise.

Type	Number	Percent
Incidence of over-use		
In persons (patient per year)	1/2,376	0.0051
95%CI		0.0001 to 0.0281
In occasions (days per patient per year)	3/2,376	0.015
95%CI		0.003 to 0.044
Ever used in addition to the usual dose due to the occurrence of symptoms since started the treatment (i.e., BUD/FORM used as needed)	175	22.2
Average quantity of budesonide used (μg per day)		
a) Summary of all usages (n = 790)		
Mean (SD)		355.3 (154.9)
95%CI		344.5 to 366.1
b) Used as controller exclusively (n = 613)		
Mean (SD)		348.8 (153.1)
95%CI		336.7 to 361.0
c) Used as controller and reliever (n = 175)		
Mean (SD)		378.0 (159.6)
95%CI		354.2 to 401.8
Mean difference (μg per day) between prescribed and used		
Mean (SD) prescribed		361.3 (147.3)
Mean (SD) used		355.3 (154.9)
Mean difference (prescribed – used)		6.0
95%CI		0.3 to 11.8
p-value		0.041

The rate of over-use was 0.015 days per patient per year (95%CI: 0.003 to 0.044). There were 175 patients who used BUD/FORM as needed in addition (22.2%) to maintenance. Among this extra-use group, the mean dose of budesonide was 378.0±159.6 μg per day (95% CI: 354.2 to 401.8). The mean dose for all patients was 355.3±154.9 (95% CI: 344.5 to 366.1) μg per day.

Asthma control profiles

The mean ACT score was 22.5±3.0 (Table 3). Among a total of 792 subjects, 685 had an ACT score of 20 or above. Thus, the percentage of asthma control based on ACT scores was 86.5% (95% CI: 84.1 to 88.9). The proportion of patients with an ACT ≥ 20 and peak expiratory flow (PEF) ≥ 80% predicted was 72.0% (95% CI: 68.6 – 75.3).

Table 3. Asthma controlled according to various measurements

Measurements	Percent
Mean (SD) ACT score	22.5 (3.0)
ACT ≥ 20	685/792 (86.5%)
95% CI	84.1 to 88.9
PEF ≥ 80% predicted	548/685 (80.0%)
95% CI	76.8 to 82.9
ACT ≥ 20 and PEF ≥ 80% predicted	493/685 (72.0%)
95%CI	68.6 to75.3

SD = standard deviation; ACT = Asthma control test; CI = confidence interval; PEF = peak expiratory flow

Hospital admissions due to asthma

For the 2,376 person-months of observations, the emergency room (ER) visits were 0.18 per patient per year (95%CI: 0.12 to 0.26). In other words, it would be expected that there were 18 ER visits per 100 patients in a year. Twenty-five (3.16%) patients had at least one hospital admission as an inpatient, thus the admission rate was 0.21 per patient per year (95%CI: 0.15 to 0.29) (Table 4). Overall, the rate of all type of hospital admissions due to asthma was 0.39 per patient per year (95%CI: 0.31 to 0.49). In other words, it would be expected that there would be about 39 hospital admissions per 100 patients in a year.

Comparison of hospitalizations between asthma controlled and uncontrolled groups

Overall, the percentage of hospitalizations was statistically higher in patients with uncontrolled than controlled asthma, based on ACT scores (Table 5). The proportions of patients with at least one hospital admission of any types were 26.17% in the uncontrolled group and 2.77% in the controlled group, with the difference of 23.39% (95% CI: 14.98 to 31.81, p -value < 0.001). The corresponding magnitude of the difference in ER visits was 9.76% (95% CI: 3.71 to 15.80, p -value < 0.001).

Discussion

This study showed that in every day clinical practice, only one patient out of 792 patients or 2,376 person-months of observations used more than 12 puffs/day of BUD/FORM and this individual did not have any adverse reactions. If patients used BUD/FORM for more than 3 months,

Table 4. Hospitalizations due to asthma

Characteristics	Number	Percent
Emergency room visits		
Prevalence (%)	22/792	2.78 (95%CI:1.75 to 4.18)
Rate (occasions per patient per year)	35/2,376	0.18 (95%CI: 0.12 to 0.26)
Hospital admissions as inpatients		
Prevalence (%)	25/792	3.16 (95%CI:2.05 to 4.62)
Rate (occasions per patient per year)	42/2,376	0.21 (95%CI:0.15 to 0.29)
Any type of hospitalizations		
Prevalence (%)	47/792	5.93 (95%4.39 to 7.81)
Rate (occasions per patient per year)	77/2,376	0.39 (95%CI: 0.31 to 0.49)

the asthma control rate identified by an ACT score of more than 19 was 86.5%, with a low ER and admission rate. The average dose of BUD was low at 353.3 micrograms/day.

This study confirms that BUD/FORM is an effective treatment for asthma control in the everyday clinical practice. Using BUD/FORM, in a single inhaler, did not increase its use as a rescuer and the control rate was quite high at 86.5%. When asthma is under control, the use of BUD/FORM as a reliever will also be lower. In addition, the average corticosteroid use was lower than standard recommendations (353 vs 1,200 microgram/day) and lower than previously reported.[6,7] Studies from Malaysia and Spain showed that the average BUD/FORM dose was between 1,400 and 779 microgram/day. Even among the over-users, the average dose of BUD/FORM actually being used was 652.3±334.7 µg per day, which is within the recommended dose limit.

Many studies suggest the use of a long acting beta2 agonist (LABA) with inhaled corticosteroid (ICS).[8-11] The results of using a low dose of BUD/FORM in this study indicate that the patients may only require a low dose of inhaled corticosteroid to control their asthma.[6] A systematic review suggested that ICS/LABA combination therapy is effective in reducing the risk of exacerbations than ICS alone.[12] BUD/FORM also increased the probability of well-controlled asthma, compared to a substantial increase in the dose of an ICS.[12-15] The BUD/FORM study in Sweden has shown that the percentage of patients with well controlled asthma increased with BUD/FORM maintenance and reliever therapy compared with the conventional best standard treatment (45% vs 40% ; p-value < 0.01).[16] This indicated that the ICS/LABA combination is more effective than the ICS alone. Even though BUD/FORM has a very high control rate, some patients may not respond to this treatment. In addition, long term use of LABA therapy is still not warranted.[17] Clinicians may need to stop LABA after asthma is under control.

Using BUD/FORM treatment had a much lower hospitalization rate compared to the national asthma survey in Thailand.[18] This indicates a much lower health burden in patients who were treated with BUD/FORM. A similar difference was also found in the rate per patient per year of ER visits, 0.98 and 0.18 in the ICS study and the BUD/FORM study, approximately an 82% reduction. ICS therapy without LABA relies on short-acting β2-agonist medication for quick relief of symptoms but not long term control, thus lowering anti-inflammatory protection and increasing the risk of exacerbations. This is unlikely to occur in patients with simplified treatment strategies such as the combination of ICS and LABA as both maintenance and reliever.[19] Not surprisingly, patients with uncontrolled asthma had higher ER admission rates than those with controlled asthma. The ER visits in patients with controlled asthma in the present study was 1.46%, while the rate was 5.89% in the study using ICS alone. The ER visit rate was 75% less if patients

Table 5. Percentage of hospitalizations during a period of 3 months comparing between asthma controlled and uncontrolled group

Hospitalizations	Uncontrolled Group (n = 107)	Controlled Group (n= 685)	Difference	95%CI	*p*-value
Admissions (%)	14.95	1.31	13.64	6.83 to 20.45	< 0.001
Emergency room (ER) visits (%)	11.21	1.46	9.76	3.71 to 15.80	< 0.001
Any type of hospitalizations either Admission or ER) (%)	26.17	2.77	23.39	14.98 to 31.81	< 0.001

were treated with BUD/FORM and had good asthma control.

There are several strengths in this study. Sample selection was implemented by well-trained research associates that were from a single research organization and were independent of the attending physicians at the study hospitals. It was done consecutively, without any follow-up arrangements, and under uncontrolled conditions. Assessments of asthma control using the ACT scores were also done by these well trained personnel. This design reduced the likelyhoodof either selection or information bias. It also reflected every day clinical practice.

This study had a study design called 'a pragmatic study'. It has been shown that pragmatic studies may have different results from the randomized controlled trials but they are more realistic and practical.[20] The variations in populations in every day clinical practice require 'real world' studies to confirm the results of randomized controlled trials that enrol only patients who meet particular criteria.[21] Another advantage of this study is that the study was done in 23 hospitals around Thailand. The results therefore may be applied to other hospitals all across the country. The cost effectiveness of this treatment regimen makes it easier to implement guidelines and government policies for asthma treatment, particularly when recent studies throughout Asia show that the rate of asthma is increasing.[22,23]

Although most of the data were collected by face-to-face interviews with the patients, information at the date of starting BUD/FORM use was based on what was recorded in the medical records. This included weight, height, lung function, and prescriptions of the medications. In addition, prescriptions of the medications at the most recent visit might not be assumed to be unchanged throughout the period until the survey date. Thus the results that involved this information need to be viewed with caution. This limitation may also have affect the low average dose use of corticosteroid reported. Another limitation is that information regarding hospitalization and BUD/FORM use were obtained by interviewing the patients on the survey date. This required the patients to recall what happened during the three month period prior to the survey date. Although recollection of remarkable events, such as hospitalizations, can be reliable, recalling the number of the hospitalizations within a period of 3 months might be difficult to determine for some patients. In addition to establishing the efficacy of BUD/FORM in every day practice, further study of the misuse or failure rate of BUD/FORM is needed.

In conclusion, asthma patients tended to use BUD/FORM at a significantly lower dose than was prescribed in a real-life setting. On average, patients used a low steroid dose, had satisfactory high asthma control, and had a low rate of hospitalizations. Using BUD/FORM for maintenance and reliever therapy seems to be promising as a treatment approach in every day clinical practice.

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Both Drs Boonsawat and Thinkhamrop provided overall guidance and were fully involved in inception, data collection, and data analysis. Their work was coordinated by Wilaiporn Thinkhamrop and Utis Chaichaya, who were involved in site management, data collection and data management. They conducted the research independent of AstraZeneca and are responsible for the independent data review and analysis. They had full access to all of the data.

Conflict of interest

Dr. Boonsawat has received consultant's fees from AstraZeneca. Dr. Thinkhamrop has received fees to conduct this research from AstraZeneca. The authors have indicated that they have no other conflicts of interest with regard to the content of this article.

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