ORIGINAL ARTICLE

Budesonide/Formoterol Combination Therapy as Both Maintenance and Reliever Medication in Moderate-to-Severe Asthma: A Real-Life Effectiveness Study of Malaysian Patients

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SUMMARY

Budesonide/Formoterol (Symbicort®) combination therapy as both maintenance and reliever treatment (SMART) is a novel approach in asthma management. We examined its 'real-life effectiveness' in treating Malaysian patients with moderate-to-severe asthma in whom despite on combined inhaled corticosteroids and long-acting β2-agonist, were still inadequately controlled. In a retrospective study, 22 eligible adult patients on SMART [mean (range) age: 49 (36-65) years; FEV1: 41 (21-74)% predicted] were identified from medical records of an urban-based university hospital chest clinic, and their clinical outcomes studied at three months. Another 16 patients [50 (14-66) years; 48 (20-91)% predicted] of similar severity and treatment (i.e. Symbicort® maintenance treatment plus short-acting β2-agonist as reliever), but not on SMART, were used as comparator over the same assessment period. In addition, the patients were separately interviewed with standard questionnaire on their satisfaction and compliance to the SMART approach. In SMART group, rescue treatment requirement (p<0.001) and FEV_1 [median difference = 2.5%, p=0.015; mean difference: 90 ml, p=0.013] showed significant improvement while in comparator, there was significant improvement only in the requirement for rescue treatment (p=0.023). Hospital admission rates were significantly reduced in SMART group compared to the other (p=0.039), but not in emergency treatment. Five patients asked to discontinue SMART while all others were satisfied, compliant and perceived improvement of their asthma with SMART. The maximum daily doses of inhaled budesonide and formoterol were 1400μg and 31.5μg respectively. Our preliminary findings suggest that SMART approach can be attempted as an effective and safe treatment option for patients with inadequately controlled moderate-to-severe asthma in Malaysian setting.

KEY WORDS:
Asthma, Symbicort, Budesonide/formoterol, Rescue medication, Malaysia

INTRODUCTION

Budesonide/formoterol (Symbicort®) combination therapy is recently shown to be safe and efficacious as both maintenance and reliever medication in both adult and paediatric patients with asthma[1,2]. This novel approach is made possible because of the pharmacological properties of formoterol that allow for safe multiple and flexible dosing[3]. Such an approach of using Symbicort® as maintenance and relief treatment (SMART) appears to be superior to using Symbicort® or fluticasone/salmeterol (Seretide®) as maintenance treatment alone and short-acting β2-agonist as relief treatment, from the perspective of reducing asthma exacerbations and improving asthma symptoms and lung function, in adults[4] and children[5]. Although not invariably, the patients that had been evaluated for this treatment were predominantly those with moderate-to-severe asthma, since combination treatment with inhaled corticosteroids and long-acting β2-agonist is generally indicated for asthma from moderate severity onwards[6]. Currently, the obvious clinical pursuit is to ask how best to implement the SMART approach and to do so safely [7] outside the well supervised environment of clinical trials.

'Real-life effectiveness' study answers the question whether the results of clinical research trials that focus on 'efficacy' can be adequately translated to day-to-day clinical practice. The criticism has always been of whether the patient populations studied in clinical trials are sufficiently representative of those in clinical practice[8]. It provides another facet of clinical evidence for our on-going attempt to practice sound evidence-based medicine. To this end, we undertook a retrospective study examining the 'real life effectiveness' of SMART approach in Malaysian multi-ethnic patients based on a recent cohort of moderate-to-severe asthmatics who were such treated in a specialist chest clinic in an urban-based university teaching hospital. These were patients who despite on standard Step 3 or 4 asthma treatment [6], were still inadequately controlled. The primary outcomes, assessed at three months in follow-up visits, were changes in (a) requirement for reliever medication, (b) Forced Expiratory Volume in One Second (FEV_1) and (c) frequency in unscheduled visits to doctors for emergency treatment and hospital admissions for asthma exacerbations. All these patients were also interviewed for their perception on SMART approach. As a comparator group, another cohort of asthmatic patients with similar severity and treatments (i.e. Symbicort® maintenance treatment plus short-acting β2-agonist as reliever) that were being followed up in the clinic over the same period of time, were selected.

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MATERIALS AND METHODS

Data collection

Medical case notes of all patients with physician-diagnosed asthma from a tertiary-referral chest clinic of an urban-based teaching hospital (Tuanku Jaafar Hospital, Seremban, a teaching hospital of International Medical University, Kuala Lumpur) were reviewed for eligibility for study. Patients were non-smokers and if previously did, had smoked fewer than 10 pack-years. The particular chest clinic was conducted by a single chest physician. Included were adult patients with moderate-to-severe asthma requiring Step 3 treatment or higher, as defined by international guidelines [6], in whom SMART approach was commenced and followed up for three months, between 2005 and 2006. Another cohort of patients, with similar asthma severity but not on SMART, who were treated by standard approach over the same period, was included as comparator. The rationale for having a comparator group is to allow better assessment of whether "treatment over time" alone could have an effect on clinical outcomes. Relevant clinico-demographic data and clinical outcome measures were collected using a standard data collection form. This 'real-life' effectiveness study was entirely clinician-initiated and independent from any influence of pharmaceutical industry.

Questionnaire study

A separate interview study using a standard questionnaire was conducted by a single research nurse on all recruited patients who underwent SMART and was carried out at a single time point in December 2006 either by telephone or clinic encounters. While the questionnaire was written in English, the interview was conducted according to the common language best understood by both the research nurse and the patients. This usually involved the use of Malay language for the Malay and Indian patients, and the use of Cantonese or English for Chinese patients. The questionnaire enquired about the various levels of satisfaction and compliance as reported by patients, primarily based on three or four-point scale in Likert format.

Outcome measures

Clinical outcomes comparing baseline and those from follow-up visits at three month, were (a) requirement of rescue medication (quick relief) graded into five categories i.e. Grade 1 = none required in a week; Grade 2= few times a week but not daily; Grade 3 = daily requirement between 1 and 2 times; Grade 4 = daily requirement between 3 and 4 times; and Grade 5 = daily requirement of 5 times or more; (b) Forced Expiratory Volume in One Second (FEV_1); (c) Frequency of emergency treatment in terms of requiring nebulized bronchodilators +/- corticosteroids; and (d) Frequency of hospital admissions for asthma exacerbation. The final two parameters were based on comparison with a three-month period prior.

Statistical analysis

Descriptive analysis is used for clinico-demographic characteristics of patients and the interview study. Non-parametric analysis is used in view of the small number of patients and their distribution for all analysis including the outcomes measures. Mann Whitney test is used for assessing significance of difference between continuous variables and Chi Square test for categorical variables. Statistical significance is defined at 5% level at both directions (two-tailed). All computation was made using statistical package SPSS version 11.5 for Windows (Chicago, Illinois, USA).

RESULTS

The SMART group and its comparator were matched in most clinical and demographic characteristics (Table I). However, SMART group had proportionately more females and more patients with Step 4 asthma severity, while the comparator group had more males and those with Step 3 asthma severity. There were also significantly more patients taking leukotriene receptor antagonists in SMART group compared to the other. The discrepancy reflects the practice of introducing SMART approach in patients with more difficult asthma. The gender difference between the two groups was probably coincidental. For inhaled corticosteroids and inhaled long-acting β_2-agonists, all patients used the dry-powdered device (turbohaler). For inhaled short-acting β_2-agonists (SABA) used for rescue medication, some were using aerosolized meter-dosed inhalers (MDI) while others used dry-powdered device (easyhaler). These differences were due to the availability of SABA is either MDI or easyhaler only (not turbohaler) in Ministry of Health hospitals.

Four patients (18.1%) in SMART group stopped using the SMART approach by themselves within this period and consequently, their outcomes were not analyzed. In both groups, the requirement for rescue medication was significantly reduced for the period assessed, but the reduction in SMART group more significant than that in the comparator [$p<0.001$ vs. 0.023](Figure 1). FEV_1 was significantly improved in the SMART group [median difference: 90ml, $p=0.013$; 2.5%, $p=0.015$], but not in the comparator (Figure 2). There was a significant difference in hospital admission rates between SMART and its comparator ($p=0.039$), with a clear reduction reported in the SMART group (Figure 3). There was no significant difference in emergency treatment rates between the two groups.

Among the 22 patients started on SMART, the majority had secondary education (n=13, 61.9%), while 5 (23.8%) had primary and 3 (14.3%) had tertiary education. Except for two, all earned under RM2000 per month (n=19, 90.5%). The median (range) duration of using SMART approach was 5 (1-13) months. On patients' perception on efficacy of SMART approach (n=22), the majority reported improvement of their asthma (86.4%) while three patients (13.6%) reported no change. None had worsened in their asthma. Of those who reported improvement, one third (31.6%) were 'a lot', another one third (31.6%) were moderate, and last one third (36.8%) reported 'only a little'. The majority of patient described their current asthma as 'partly controlled' (76.2%) while the rest as 'well controlled' (23.8%). None were 'uncontrolled'.

On patients' satisfaction on SMART as a treatment approach, the majority reported that their expectations were generally met (Table II). Overall, the majority was satisfied (77.3%) with such treatment approach. Three patients (13.6%) were very satisfied but two patients (9.1%) were unsatisfied with SMART.

DISCUSSION

Our 'real-life study' findings showed that SMART approach in Malaysian adult patients with inadequately controlled moderate-to-severe asthma can be effective and safe, based on three months' treatment alone. Most patients appeared satisfied with the approach and were compliant. There were no reported unduly high doses of Symbicort® used by any of the patients on any single day (≤1400 μg budesonide; ≤31.5 μg formoterol).

Our preliminary findings lend support to the increasing optimism of SMART treatment approach[1,2]. Latest recommendation from Global Initiative for Asthma (GINA) welcomes the use of budesonide/formoterol as rescue medication in addition to maintenance use as they "contribute to enhanced protection from severe exacerbations" and "provide improvement in asthma control at relatively low doses of treatment", graded at evidence A level[9]. It is interesting to note that at three months, the requirement for rescue medication was reduced in both SMART and comparator groups, consistent with observations that with patience, asthmatics treated on combined inhaled corticosteroids and long-acting β2-agonists do continue to improve with time[10]. Nevertheless the reduction in SMART group was greater than that in comparator group, indicating at the additional benefit achievable with Symbicort® as reliever. Although statistically significant, the small improvement in FEV_1 observed in SMART group is probably not clinically important. However it is likely that the trend of improvement will continue with longer treatment period. Putting in perspective, this can be significant because of potential of such treatment to further arrest the accelerated decline in lung function in patients with moderate-to-severe asthma[11]. The findings of significantly fewer hospital admissions in SMART group compared to the comparator group within three months are interesting. It indicates that additional inhaled corticosteroids derived from rescue use in SMART group can contribute to preventing serious asthma exacerbations within such a short time. The reason why difference was not found in frequency of emergency

Table I: Clinical and demographic characteristics of asthmatic patients treated with SMART§ approach and the comparator group

	Treatment approach			p
	Entire group	SMART§ group	Comparator	
n	38	22	16	-
Age, years	50 (14-66)	49 (36-65)	50 (14-66)	0.505
Gender				
Male	26.3	13.6	43.8	-
Female	73.7	86.4	56.3	0.037
Ethnicity				
Malay	42.1	50.0	31.3	-
Chinese	21.1	27.3	12.5	-
Indians	36.8	22.7	56.3	0.102
Asthma severity*				
Step 3	52.6	27.3	87.5	-
Step 4	47.4	72.7	12.5	<0.001
ICS** dose, μg	800 (400-1200)	800 (400-1200)	800 (400-800)	0.355
On theophyllin	21.1	31.8	6.3	0.56
On LTRA¶	39.5	59.1	12.5	0.004
FEV_1, litres	1.30 (0.52-2.79)	1.16 (0.71-2.35)	1.41 (0.52-2.79)	0.092
FEV1,% predicted	42 (20-91)	41 (21-74)	48 (20-91)	0.167
FVC, litres	1.77 (0.84-3.52)	1.68 (0.84-3.09)	1.82 (0.94-3.52)	0.836
FVC, % predicted	50 (23-88)	54 (23-74)	48 (23-88)	0.544

§ SMART= Symbicort® maintenance and relief therapy
Values are percentages or median (range) unless otherwise specified.
* Asthma severity classified according to Global Initiative for Asthma (ref)
**ICS= inhaled corticosteroids
¶ LTRA= leukotriene receptor antagonist

Table II: Patients' perception on SMART§ treatment approach

	"Meet my expectations"			
	Highly don't	Generally don't	Generally do	Highly do
"SMART is easy to understand and use"	0	2 (9.1)	16 (72.7)	4 (18.2)
"SMART simplifies my life as an asthmatic"	0	3 (13.6)	13 (59.1)	6 (27.3)
"My asthma is generally better controlled"	0	1 (4.5)	15 (68.2)	6 (27.3)
"More convenient to use: just one inhaler"	0	1 (4.5)	16 (72.7)	5 (22.7)
"I get quick relieve from attacks"	1 (4.5)	3 (13.6)	15 (68.2)	3 (13.6)
"I need fewer times of rescue medication now"	1 (4.5)	3 (13.6)	15 (68.2)	3 (13.6)
"The device is easy to use"	1 (4.5)	1 (4.5)	13 (59.1)	7 (31.8)

Values indicate number (percentage)
§ SMART= Symbicort® maintenance and relief therapy

Table III: Reasons reported by patients for not wishing to continue SMART§ approach

Reasons
• Experiences headache
• "Can't feel the medicine going into the lungs"
• Experience "bad taste" after inhalation
• Prefer Seretide®*
• Prefer Asthalin®** as quick reliever
• Develop mouth ulcers
• Does not experience immediate relief of acute symptoms
• During attack, does not have "strength to inhale"

§ SMART= Symbicort® maintenance and rescue therapy
* Seretide®= Fluticason/salmeterol combination inhaler
** Asthalin®= salbutamol inhaler

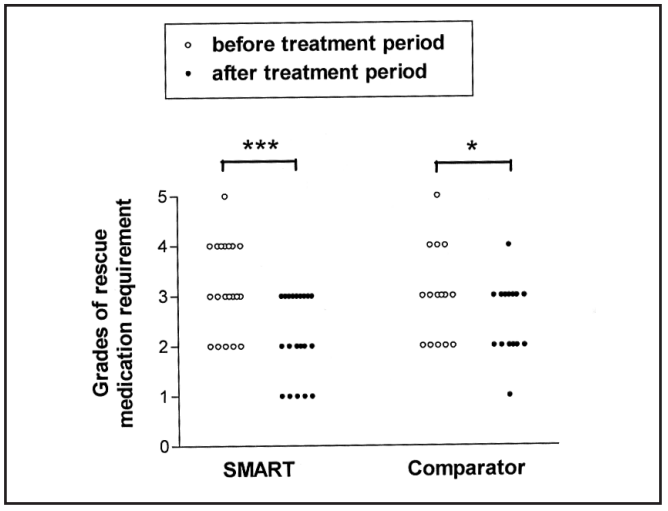

Fig. 1: The effect on requirement for day-to-day rescue medication (graded from 1 to 5) by SMART (n=18) and conventional treatment (n=16) approaches. Grade 1 = none required in a week; Grade 2= few times a week but not daily; Grade 3 = daily requirement between 1 and 2 times; Grade 4 = daily requirement between 3 and 4 times; Grade 5 = daily requirement of 5 times or more. Symbols = individual patients. * = p<0.05. *** = p<0.001.

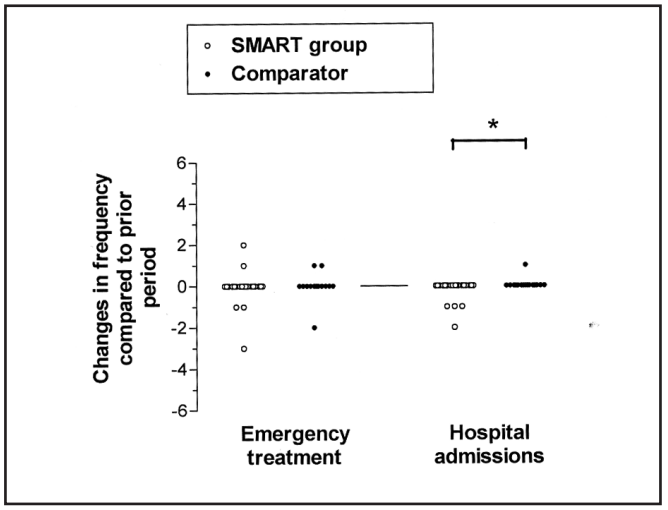

Fig. 3: Changes in frequencies of emergency treatment and hospital admissions in patients treated with SMART approach (n=18) and their comparator (n=16), compared to period prior to treatment. * = p<0.05

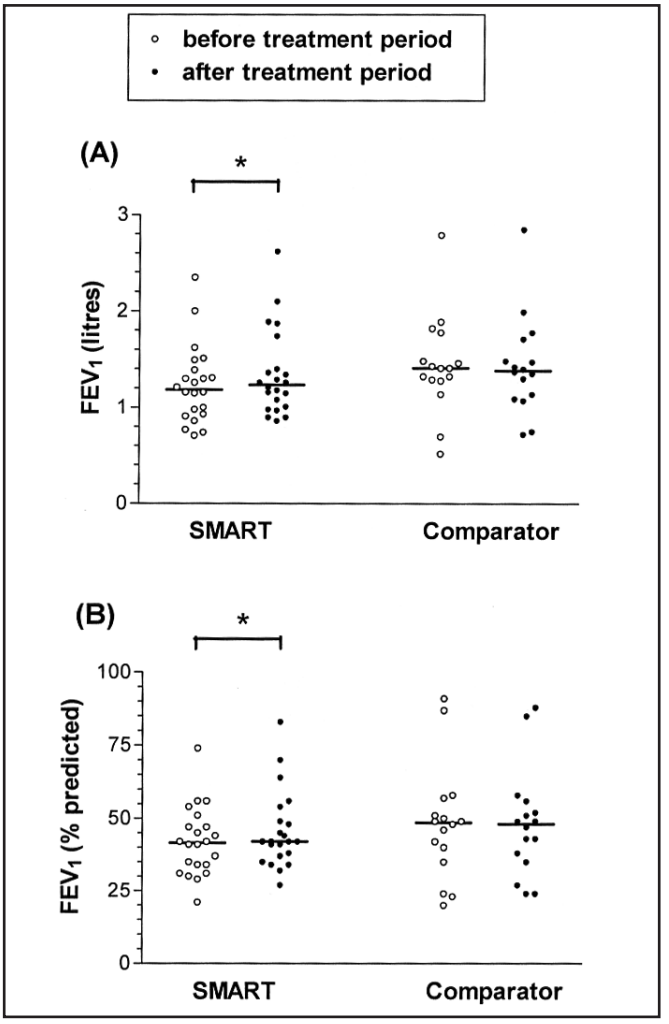

Fig. 2: Changes in Forced Expiratory Volume in One Second (FEV1) before and after treatment with SMART (n=18) and conventional approaches (n=16). Horizontal bar = median. Symbols = individual patients. * = p<0.05

The majority (86.4%) were 'always' compliant to the approach. Three patients (13.6%) however were only 'sometimes' compliant or finding it easy to understand. None reported total non-compliance or incomprehensibility. Except for five patients (22.7%), all patients wish to continue with the SMART approach. The reasons quoted by these five patients for discontinuing SMART approach were listed in Table III.

With regards to ICS doses used for daily maintenance treatment, 18 patients (81.8%) had 800 μg, two patients (9.1%) had 400 μg, and 1 patient each had 200 Ìg and 600 μg budesonide. For rescue use, seven patients (31.8%) had 600 μg, 6 (27.3%) had 200 μg, 5 (22.7%) had 400 μg budesonide, and 4 (18.2%) hardly needed rescue Symbicort®. Taken together, the median budesonide daily dose was 1200 μg with the lowest dose at 200 and the highest dose at 1400 μg. The lowest and highest dose of formoterol used daily was 4.5 and 31.5 μg respectively.

treatment is unclear. It may be due to the fact that the majority of patients did not experience any emergency treatments three months before and after the treatment under study, and the data therefore do not have sufficient changes to assess the treatment effect.

To the best of our knowledge, there is no published data on patients' perception on SMART approach. Clinical research trials generally could not adequately answer this question because of the nature of recruitment that normally involves motivated and compliant patients. Most of the patients perceived improvement of their asthma and agreed to the purported advantages of SMART over the conventional approach. However, five out of 22 patients indicated unwillingness to continue the approach. From most of the reasons quoted, it appears that relief from acute symptoms with Symbicort® may be a problem to some. While this is largely an issue of perception, it may be related to individual patient's acceptance of the inhaler devices [12] and their underlying disease severity. This reiterates the importance of tailoring appropriate treatment to individual patients.

Our study is noble in that this is the first study to demonstrate the feasibility and effectiveness of SMART approach in Malaysian multi-ethnic patients. This is important because of the concern of how much SMART approach can be understood and followed by Malaysian patients and how practical it is in the setting of a busy hospital outpatient consultation. However, our study is subjected to weaknesses inherent to any retrospective study and biases created from being open-label and non-randomized. Also, importantly, the sample size was small and the study period was short. Regardless, we have sought to minimize these biases by reviewing patients managed only by a single chest physician and conducting a survey that was interviewed by only one research nurse. How SMART approach can be better implemented should continue to be an important topic to explore in near future since its potential to benefit the difficult-to-treat asthmatics is promising. Our small Malaysian study provides a preliminary but important first-look data at how SMART can improve asthma management in this country.

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