Pulmonary Pharmacology & Therapeutics 27 (2014) 190–196

Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

Comparison of the effects of budesonide/formoterol maintenance and reliever therapy with fluticasone/salmeterol fixed-dose treatment on airway inflammation and small airway impairment in patients who need to step-up from inhaled corticosteroid monotherapy

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ARTICLE INFO

Article history:
Received 27 September 2013
Received in revised form
20 December 2013
Accepted 23 December 2013

Keywords:
Symbicort maintenance and reliever therapy (SMART)
Budesonide/formoterol
Fluticasone propionate/salmeterol
Fractional exhaled nitric oxide
Impulse oscillometry
Small airways

ABSTRACT

Background: If asthma patients fail to achieve symptom control using a medium dose of inhaled corticosteroid (ICS) alone, adding a long-acting β_2 agonist (LABA) is the preferred treatment. We aimed to compare the effect of two widely available ICS/LABA combinations in these patients in real-life conditions: budesonide/formoterol (BUD/FM; Symbicort®) for maintenance and reliever therapy (SMART) and a fixed dose of fluticasone propionate/salmeterol (FP/SM).

Methods: Inadequately controlled asthma patients treated with a medium dose of ICS alone, with an Asthma Control Questionnaire (ACQ) score >0.75 and using a short-acting β_2-agonist (SABA) 2–6 occasions/week, were enrolled. Patients were randomized into two groups and treated with two inhalation twice-daily BUD/FM 160/4.5 μg plus as-needed BUD/FM (SMART group, $n = 15$) or one inhalation twice-daily FP/SM 250/50 μg plus as-needed procaterol (FP/SM group, $n = 15$) for 8 weeks.

Results: Both groups showed significant improvement in airway inflammation, pulmonary functions and symptoms from baseline. The SMART group showed significant improvement in the fraction of nitric oxide, ACQ score, rescue medication use and small airway parameter R5–R20 measured by impulse oscillometry compared with the FP/SM group.

Conclusion: For stepping up treatment from ICS alone to an ICS/LABA combination, SMART is preferable for controlling asthma symptoms by suppressing airway inflammation and improving small airway impairment compared with a fixed dose of FP/SM. It may be achieved by the property of BUD/FM itself and as-needed use, but the degree of each contribution must be investigated further.

1. Introduction

The main feature of asthma is episodic airway obstruction caused mainly by airway inflammation. Anti-inflammation therapy with an inhaled corticosteroid (ICS) is the first-line treatment, with the addition of a long-acting β_2 agonist (LABA) as a bronchodilator if the ICS cannot control symptoms. ICS/LABA combinations such as budesonide/formoterol (BUD/FM) and fluticasone propionate/salmeterol (FP/SM) are employed widely because of evidence of efficacy for individuals whose asthma is not controlled using ICS without LABA [1,2]. In addition to a fixed dose of maintenance therapy, BUD/FM can be used as reliever therapy. This treatment, BUD/FM (Symbicort®) maintenance and reliever therapy (SMART), is endorsed in asthma guidelines [3,4], showing reduced exacerbation compared with the same maintenance dose of BUD/FM plus as-needed short-acting β_2 agonist (SABA) [5] or fixed dose of FP/SM plus as-needed SABA [6].

Inflammation in asthma is not confined to the large central airways; it extends to the small peripheral airways. Inflammation of the small airways is responsible for airway hyper-responsiveness and exacerbations, and is an important target of asthma treatment [7]. Green et al. reported that using the eosinophil count in induced sputum as an inflammation marker for treatment reduced asthma exacerbations compared with symptom-based treatment [8]. In general, it is thought that asthma treatment should be adjusted according to the intensity of airway inflammation and small airway impairment. However, measurement of airway inflammation or distinguishing between impairment of the large and small airways in everyday practice is difficult.

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http://dx.doi.org/10.1016/j.pupt.2013.12.003

Fractional exhaled nitric oxide (FeNO) is associated with eosinophil counts in sputum [9]. FeNO can be used for the accurate diagnosis of asthma, and can be measured using hand-held devices [10]. In one study, the time-course of FeNO change showed rapid improvement and reached a *plateau* within 8 weeks after the controller medication was stepped up [11]. Hence, it is useful as a quick check to ascertain the effect of treatment change. Impulse oscillometry (IOS) can be used to assess function in large and small airways separately, and is more sensitive than conventional spirometric methods [12–14]. These new measurement methods are now available in daily clinical practice, and can be used to detect slight differences in treatment effects between medications. For example, Akamatsu et al. showed recently that BUD/FM improves small airway obstruction and alveolar inflammation even though there is no improvement in pulmonary function as measured by conventional spirometric methods [15]. Using these new measurement methods, previously we compared the fixed-dose treatments of BUD/FM and FP/SM in a patient whose asthma seemed well-controlled but who had small airway impairment and airway inflammation, and reported that BUD/FM improves both of these signs [16].

If asthma patients fail to achieve symptom control using a medium dose of ICS alone, adding LABA is the preferred treatment. A study comparing the efficacy of fixed-dose BUD/FM and FP/SM directly in patients treated with ICS alone concluded that both drugs improved asthma symptoms and lung function, and the rate of exacerbations was also reduced over time with both treatments; however, FP/SM was superior in reducing the rate of moderate/severe exacerbations [17]. Conversely, another research team conducted a similar study with SMART in place of fixed-dose BUD/FM: they concluded that SMART reduced exacerbations compared with FP/SM [18]. Several other studies have also compared FP/SM with fixed-dose BUD/FM and/or SMART, but the results have been inconsistent.

If inflammation of the small airways is the main treatment target of asthma patients, it is better to measure airway inflammation and small airway function. However, there is little evidence for the treatment effect on inflammation in the large and small airways. In addition, over half of the patients in most of the direct-comparison studies between SMART and fixed-dose FP/SM were treated with LABA before study treatment. Thus, the treatment effect, especially for airway inflammation in patients who need to step-up their treatment from ICS alone to an ICS/LABA combination, is not clear.

Here, we compared the treatment effects on airway inflammation and small airway impairment in real-life conditions between two widely available ICS/LABA combinations in Japan. These were BUD/FM by Turbuhaler® (BUD/FM-TH) as maintenance and reliever therapy (SMART group), and a fixed dose of FP/SM by Diskus® (FP/SM-DK) plus SABA (FP/SM group) for patients whose asthma was not controlled well with ICS alone. The primary objective was reduction of FeNO, which is thought to represent airway inflammation.

2. Materials and methods

This was an 8-week, single-center, randomized, open-label study to compare the effect of BUD/FM-TH maintenance and reliever therapy (SMART) and FP/SM-DK fixed-dose controller plus as-needed procaterol. It was conducted between July 2012 and June 2013 at Hiroshima Allergy and Respiratory Clinic (Hiroshima, Japan). The study (UMIN000011241) was conducted in accordance with the principles of the Declaration of Helsinki, and was approved by the Ethical Review Board of the Hiroshima Allergy and Respiratory Clinic. All subjects provided written informed consent before participating in this study.

2.1. Subjects

Outpatients diagnosed with asthma as defined by the American Thoracic Society [19] were enrolled if they satisfied the following inclusion criteria: age ≥20 years; prior treatment for ≥12 consecutive weeks with a medium dose of ICS (BUD, 800 μg/day; or FP and mometasone furoate, 400 μg/day) without another controller or concomitant asthma medication except SABA; Asthma Control Questionnaire (ACQ5; five-item Japanese version) score >0.75 [20,21]; SABA use 2–6 times per week; FeNO >35 ppb; IOS parameter for small airways R5–R20 (respiratory resistance at 5 Hz (R5) − respiratory resistance at 20 Hz (R20)) >0.05 kPa/L/s; no history of smoking; and using an asthma diary before study entry with good adherence rate for controller medication.

Patients were excluded from the study if they had any respiratory infection, tuberculosis and/or other respiratory diseases in the previous 8 weeks, used beta-adrenoceptor antagonists (including eye drops), had used systemic corticosteroids in the previous 30 days, or had allergic rhinitis necessitating pharmacological treatment.

2.2. Study design

Subjects were randomized into two groups and underwent treatment for 8 weeks (Fig. 1). For the SMART group, BUD/FM-TH (AstraZeneca, Osaka, Japan) containing 160 μg BUD and 4.5 μg FM (delivered dose) in each dose was used: two inhalations twice daily for controller medications (i.e., four inhalations per day) and one inhalation for as-needed reliever use. For the FP/SM group, FP/SM-DK (GlaxoSmithKline, Tokyo, Japan) containing 250 μg FP and 50 μg SM in each dose was used: one inhalation twice daily (i.e., two inhalations per day) and 10 μg procaterol (Otsuka Pharmaceutical, Tokyo, Japan) was used (two inhalations each time for as-needed reliever use).

2.3. Measurements

The primary objective of the present study was the change in FeNO values from baseline to after 8 weeks of treatment. FeNO values, ACQ5 scores, spirometry parameters, and IOS parameters were observed 0, 4, and 8 weeks after randomization. Each

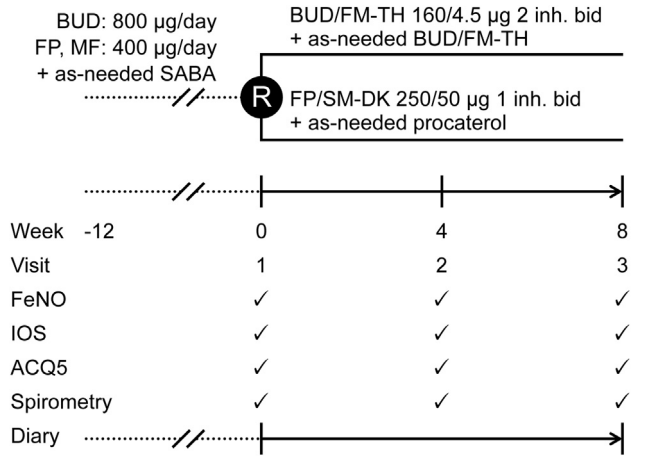

Fig. 1. Study design. BUD, budesonide; FP, fluticasone propionate; MF, mometasone furoate; SABA, short-acting β_2 agonist; BUD/FM-TH, BUD/formoterol-Turbuhaler®; FP/SM-DK, FP/salmeterol-Diskus®; R, randomization; IOS, impulse oscillometry; FeNO, fractional exhaled nitric oxide; ACQ5, Asthma Control Questionnaire, five-item version. Diary was used for recording reliever use by patients.