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Efficacy of single inhaler Budesonide/Formoterol in Asthma maintenance and relief therapy

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Abstract: *The goal of the trial was to determine the efficacy and safety of a single inhaler containing budesonide [corticosteroid] and formoterol [long acting β2 agonist] for asthma exacerbation maintenance and symptom alleviation. For 65 patients who were using inhaled corticosteroids before evaluation and symptomatic on budesonide/formoterol [160g and 4.5g respectively] single inhalation twice day for 4 weeks, a ten-month, randomised, double-blind, parallel groups investigation was conducted. Patients were randomly randomised to budesonide/formoterol maintenance treatment after four weeks. In terms of the time it took for the first severe exacerbation, there was no difference between the groups. The rate of severe exacerbations was found to be lower in the budesonide/formoterol maintenance and relief therapy groups. The risk of having severe exacerbation was 34 percent lower with budesonide/formoterol single inhaler therapy compared with corticosteroid therapy and the treatment was well tolerated. As a result, the budesonide/formoterol single inhaler is efficacious and minimises severe asthma exacerbation when compared to alternative therapies.*

Key Words: *Budesonide, formoterol, asthma, corticosteroid, exacerbation.*

1. INTRODUCTION:

Asthma is a recurrent respiratory ailment caused by a chronic inflammatory condition of the airways. It is characterised by airway hyper responsiveness. [1] The major goals of asthma treatment are to prevent severe asthma exacerbations, control symptoms, and preserve normal lung function while using the smallest effective amount of medicine possible to avoid unwanted side effects.[2,3] Patients with persistent asthma who are not well controlled by low-to-medium doses of inhaled corticosteroids (ICS) alone are given a low, and if necessary, a medium or high dose of ICS in combination with a long-acting b2-adrenoceptor agonist (LABA)[3]. Maintenance therapy with a low-dose ICS/long-acting 2-agonist (ICS/LABA) as a reliever was more effective than two- or four-week treatment with a two- or four-week treatment with a two- or four-week treatment with a two- or four-week treatment with a two- or four-week treatment[4,5]. Asthma control is suboptimal despite such therapies. Exacerbations can range from moderate elevations in symptoms to occurrences requiring medical intervention or hospitalisation, even in patients who are taking regular ICS or ICS/LABA maintenance medication.[5,6] Budesonide is a strong corticosteroid with immediate anti-inflammatory and anti-respiratory actions[3]. Formoterol is a short- and long-acting bronchodilator that can be taken as a relief or as maintenance therapy[7]. The use of budesonide/formoterol as a maintenance and relief medication is well established and recommended[8]. Its great appeal is in lowering severe exacerbations, without compromising any measure of asthma control, when compared to other higher fixed-dose steroid-containing regimens[9-12]. This effect's mechanism is yet unknown[10].

One explanation is that events initiating unstable asthma, and potentially an exacerbation, occur less frequently or are promptly aborted and thus not recognisably different from the usual asthma state[13,11.]This approach should, therefore, further reduce asthma exacerbations and improve asthma control compared with the improvements seen with traditional fixed-dose combination therapy.[12] Using a double-blind approach, we hypothesised that SMART (budesonide/formoterol 160/4.5µg one inhalation bid plus additional as-needed inhalations for relief) would prevent exacerbations more effectively than large dose of corticosteroid, and that this important benefit would not be achieved at the expense of daily asthma control.[16] In this study, severe asthma exacerbations were selected as the primary outcome variable, as these are a sensitive clinical measure of control, responding to higher maintenance doses of budesonide, and thus are less likely to respond to low-dose combination therapy.[15]

2. METHODS AND MATERIALS:

Exacerbation prevention patients come from two double-blind, parallel-group investigations (Study A & Study B). Severe exacerbations were defined as a decrease in asthma control that required hospitalisation, ER treatment, or the use of oral corticosteroids for more than three days. [Fig. 1]

During a 2-week run-in period and throughout the 12-month randomised treatment period, participants in Study A received budesonide/formoterol 160/4.5 g bid. Patients in Study B were randomly assigned to one of three 6-month regimens after a 2-week run-in on ICS with terbutaline without LABA.

2.1 Study design:

The Declaration of Helsinki and Good Clinical Practice principles were followed in this 6-month, randomised, double-blind, and parallel-group trial. The study protocol, patient information, and permission forms were all approved by independent ethics boards. All patients, as well as the parents or guardians of minors, signed a written informed consent form. Patients came to the clinic at the start and conclusion of their run-in (visits 1–2), as well as after 8, 16, and 24 weeks of therapy (visits 3–5). Patients were randomly assigned to one of three therapy groups: bud/form 80/4.5 g twice daily plus 80/4.5 g as needed, bud/form 80/4.5 g twice daily plus terbutaline 0.4 mg as needed, or budesonide 320 g twice daily plus terbutaline 0.4 mg as needed. All patients were taught how to use the Turbuhaler and Evohaler devices correctly at the start of the research. Any patient who required more than 10 inhalations of relief medication in a single day was advised to contact the investigator for reassessment.

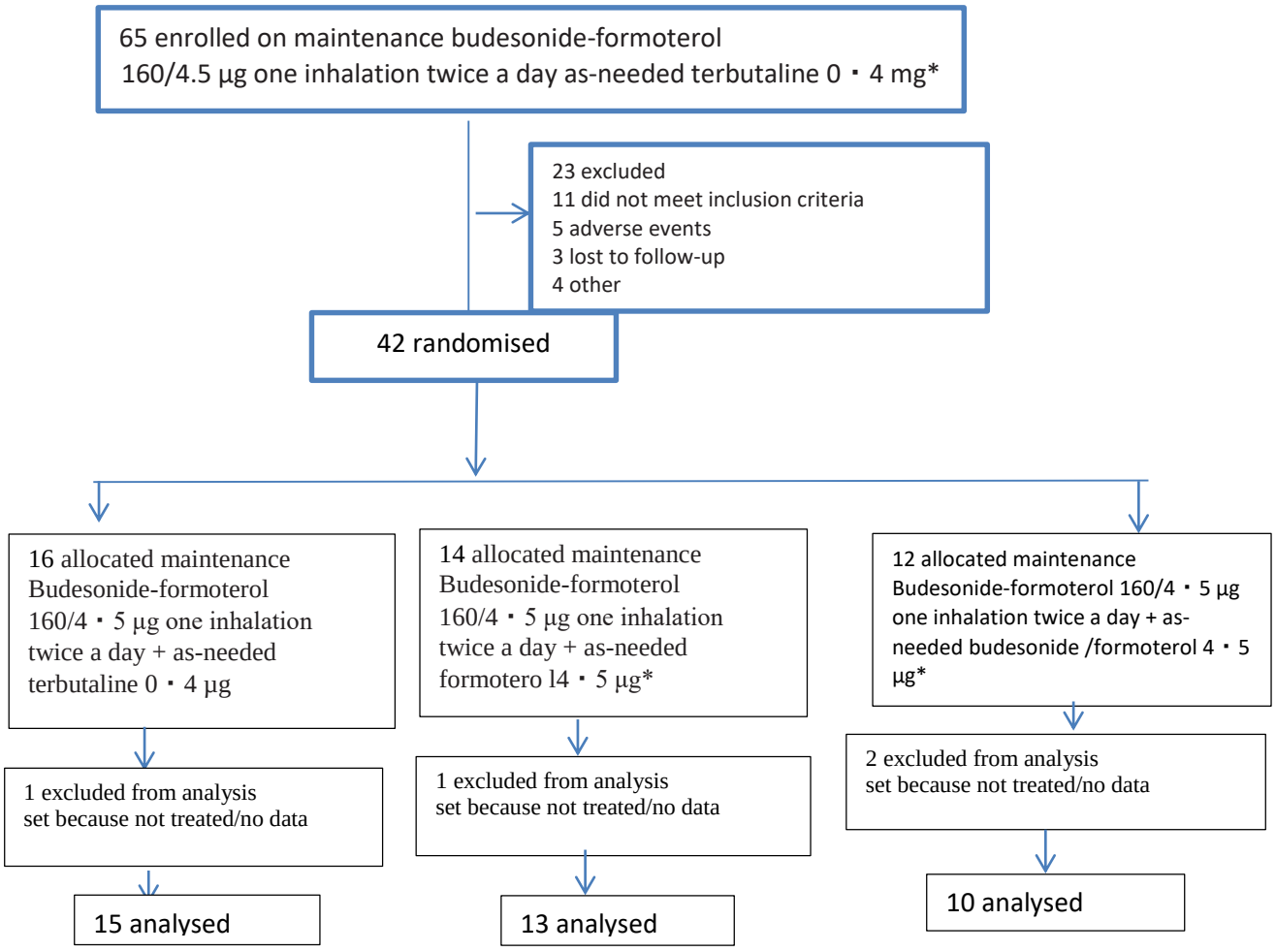


Figure 1: Chart of Study Design

2.2 Randomisation and blinding:

Patients were randomly assigned to each centre in strict order when they became eligible. Individual treatment codes and code envelopes (identifying each randomised patient's treatment allocation) were issued, however code envelopes were only to be opened in the event of a medical emergency. Patients were instructed to take one inhalation from the red grip inhaler (budesonide/formoterol or placebo Turbuhaler) and two inhalations from the pMDI (salmeterol/fluticasone or placebo Evohaler) upon rising and before going to bed to maintain blindness; as-needed inhalations from the white grip inhaler (salmeterol/fluticasone or placebo Evohaler) were to be taken for symptom.

2.3 Statistical analysis:

The study's major goal was to evaluate budesonide formoterol maintenance against budesonide-formoterol with formoterol as needed. A secondary goal was to see how budesonide/formoterol compared to budesonide-formoterol with terbutaline for maintenance and as needed. The time from randomization to the first severe asthma

exacerbation was the major outcome variable. A log-rank test had a 90% chance of finding a difference with 1000 patients in each group, assuming a genuine difference of 25% versus 19% in the proportion of patients with severe exacerbation. The full analysis set, which was used for all efficacy analyses, includes all patients for whom data were recorded after randomization. All patients who received one or more doses of the randomised study medicine and had data recorded after randomisation was included in the safety analysis.

Other daily diary card variables were examined using analysis of variance as a change from baseline, with the baseline value (last 10 days of run-in) as a covariate. Individual growth was measured as the difference in height between enrolment and the end of the 12-month treatment period. Analysis of variance was used to compare growth between treatments, with height at enrolling as a covariate.

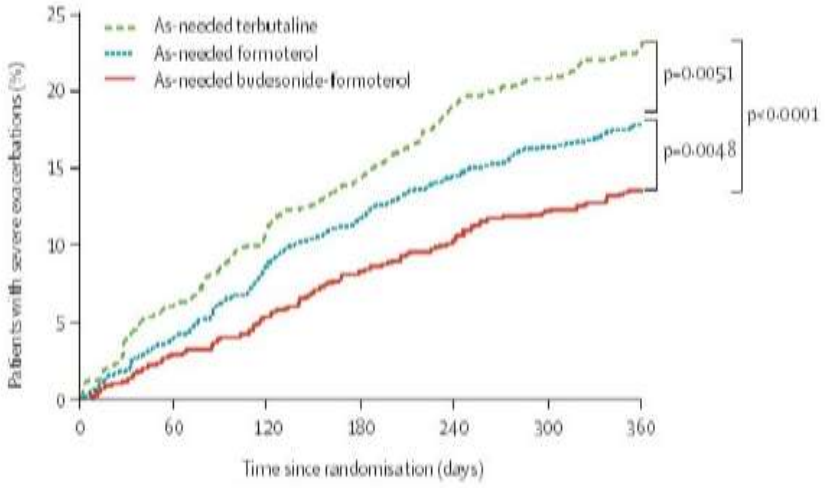
3. RESULT:

The study's first participant was enrolled. 42 patients were randomly assigned out of the 65 that were recruited in the trial. 11 patients (11%) were not randomly assigned because they did not meet the eligibility criteria, 5 had an adverse event, 3 were lost to follow-up, and 4 were dropped for other reasons. All randomised patients who provided any data following randomisation were included in the entire analysis set. Before they quit the research, two randomly assigned patients' data were not obtained. As a result, the efficacy and safety evaluations covered 40 patients. Seven patients had one or more protocol deviations, with a similar distribution across groups. The average number of protocol deviations per patient was 02 (range 1–10), and none of the deviations warranted the data being excluded from the study.

3.1 Time to first severe exacerbation:

The primary efficacy variable, time to first severe exacerbation, is shown in figure 2. There was no significant difference between the two treatments.

Kaplan-Meier curves of time to first severe asthma exacerbation



Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG.
***Lancet* 368:744-753, 2006**

Figure 2

3.2 Severe exacerbations:

SMART prolonged the time to first severe exacerbation compared with fixed-dose salmeterol/fluticasone and budesonide/formoterol. There was a 33% reduction in the hazard ratio (HR) for a first severe exacerbation with SMART compared with salmeterol/fluticasone and a 26% reduction compared with fixed-dose budesonide/formoterol. In terms of time to first severe exacerbation, the two fixed-dose groups did not vary. When compared to fixed-dose salmeterol/fluticasone and fixed-dose budesonide/formoterol, the total number of severe asthma exacerbations was reduced by 39 percent in the SMART group and by 28 percent in the fixed-dose budesonide/formoterol group. In both fixed-dose groups, the total number of exacerbations was similar.

When compared to the fixed-dose salmeterol/fluticasone group, the total number of hospitalizations/ER treatments was reduced in both budesonide/formoterol groups: the SMART group had a 39 percent rate reduction and the fixed-dose budesonide/formoterol group had a 32 percent rate reduction. There was no statistically significant difference between the two budesonide/formoterol groups.

3.3 Mild exacerbations:

There were no significant changes in the number of mild exacerbation days or the time to a mild exacerbation between the SMART group and the two fixed-dose regimens (two consecutive mild exacerbations days). In the salmeterol/fluticasone group, there were an average of 27 mild exacerbations days per patient/6 months, 29 in the fixed-dose budesonide/formoterol group, and 27 in the SMART group.

3.4 Safety:

All three therapies were well tolerated, with no significant differences in the frequency or severity of adverse events between groups. Upper respiratory tract infection, pharyngitis, and nasopharyngitis were the most commonly reported side effects. In all treatment groups, the incidence of pharmacologically predicted side events due to ICS and LABA use was low and comparable.

3.5 Hospitalisations/ER visits:

During the 21-day period of Study A, the necessity for hospitalization/ER visits was not substantially different between regimens. In contrast to the ITT population, this was not the case. Nonetheless, budesonide/formoterol was associated with fewer hospitalizations and emergency room visits than terbutaline. The risk of hospitalisation/ER visits in Study B during the 21-day period was significantly lower for both budesonide/formoterol regimens compared with fixed-dose salmeterol/fluticasone. This mirrored previous findings in the ITT population.

4. DISCUSSION:

4.1 Main findings:

Despite a 59 percent reduction in ICS dose compared to UC treatment, BHR remained stable with SMART management in patients with mild-to-moderate asthma in primary care. In addition, morning and evening PEF levels improved, and patients were happier with the SMART concept's ease of use. For all other efficacy measures, the two management approaches were comparable. Patients in this primary care trial have significantly different baseline characteristics than those in prior SMART studies13–18, which drew outpatients from secondary care patient record files. SMART therapy was also helpful in our primary care population, despite the fact that they had milder disease in almost every element of clinical characterization. Furthermore, unlike previous trials, there was no necessity for symptoms/poor control at recruitment, reducing the risk of regression to the mean and making the inclusion of UC as a control simpler to explain. In addition to the clinical efficacy of SMART, ratings on the domain ‘ease of use’ of the questionnaire on treatment satisfaction (SATQ) were significantly higher in the SMART group.

Despite a lower dose of ICS, the frequency of severe asthma exacerbations in the SMART group was low. The occurrence of severe exacerbations was too infrequent in both treatment groups to analyse statistically. This is an important finding because severe exacerbations have been related to excess lung function decline in asthma, hence worse disease prognosis. Three of the total of four exacerbations was caused by one patient in the SMART group. Although his symptom scores and PEF values in his diary plainly showed that an exacerbation was coming, this patient did not take more inhalations for comfort.

5. CONCULSION

In summary, we conclude that budesonide/formoterol maintenance and reliever therapy appears to be a well-tolerated and beneficial concept for the management of patients with mild-to-moderate asthma in primary care. It reduces the dose of inhaled corticosteroids needed and can be considered as a good alternative for guideline-based treatment.[1]

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