

EXPERT
REVIEWS

Combination ICS/fast-onset LABA inhaler as maintenance and reliever therapy: the future for uncontrolled adult asthma?

Expert Rev. Respir. Med. 7(5), 451–454 (2013)

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In the Single combination inhaler as Maintenance And Reliever Therapy (SMART) regimen, asthma patients use a corticosteroid/fast-onset long-acting beta-agonist inhaler as both regular maintenance and reliever therapy. In this multicenter, double-blind randomized controlled trial, Papi *et al.* have demonstrated that treatment with the combination beclometasone/formoterol hydrofluoroalkane (HFA)-MDI when used as both maintenance and reliever therapy significantly prolongs the time to the first severe asthma exacerbation and reduces severe exacerbations compared with the same fixed dose of maintenance beclometasone/formoterol HFA-MDI with salbutamol MDI for relief. These findings are consistent with those of the prior studies of the SMART regimen with the budesonide/formoterol DPI and extend the evidence for use of the SMART regimen to the extrafine beclometasone/formoterol HFA-MDI, to patients with high baseline reliever use, and to patients in whom the SMART regimen results in a step up, step down or no change in baseline inhaled corticosteroid dose.

KEYWORDS: asthma • beclometasone • budesonide • formoterol • inhaled corticosteroid • long-acting beta-agonist • maintenance • reliever • SMART

Combination inhaled corticosteroid (ICS)/long-acting beta-agonist (LABA) treatment delivered via a single inhaler is the preferred option for adult patients with poorly controlled or severe asthma [101]. The usual approach is to prescribe this treatment as regular maintenance ‘preventer’ therapy, with an additional short-acting beta-agonist (SABA) inhaler for ‘reliever’ therapy. If using a combination ICS/fast-onset LABA inhaler, another option is the Single combination inhaler as Maintenance And Reliever Therapy (SMART) regimen, in which patients use a single ICS/LABA inhaler as regular maintenance therapy and use additional doses of the same inhaler for reliever therapy. The use of a combination inhaler for both maintenance and reliever therapy has previously been tested with the budesonide/formoterol dry powder inhaler (DPI) and was

found to reduce severe exacerbations of asthma when compared with the same dose of fixed maintenance therapy with SABA for relief [1,2], in adult patients with poorly controlled asthma.

Current asthma guidelines suggest that the SMART regimen may be considered for use with the budesonide/formoterol combination inhaler in selected patients who remain uncontrolled on ICS or ICS/LABA treatment [101,102]. In a recently published article by Papi *et al.* the authors sought to investigate the efficacy and safety of an extrafine combination beclometasone/formoterol hydrofluoroalkane (HFA)-metered dose inhaler (MDI) when used as maintenance and reliever therapy, compared with the same fixed dose of maintenance beclometasone/formoterol HFA-MDI with salbutamol MDI for relief [3].

Methods

This study was a 48-week, double-blind, randomized parallel group, active-controlled trial undertaken at 183 centers in 14 European countries between 2009 and 2010. Adult patients with asthma were eligible if they had a clinical diagnosis of asthma for 6 months or more, a forced expiratory volume in 1 second (FEV₁) of $\geq 60\%$ predicted, significant bronchodilator reversibility, a severe asthma exacerbation in the preceding 12 months and were not fully controlled in the past month. Patients established on ICS (≥ 1000 $\mu\text{g/day}$ of beclometasone equivalent) or ICS/LABA (≥ 500 $\mu\text{g/day}$ of beclometasone equivalent) treatment were also eligible to participate. The key exclusion criteria were the presence of other significant respiratory disease or recently unstable asthma.

Potentially eligible participants entered a 2-week run-in period, during which they were treated with 100/6 μg of extrafine beclometasone/formoterol via HFA-MDI one inhalation twice daily as maintenance treatment, with 100 μg salbutamol via MDI as reliever treatment. Participants who remained not fully controlled at the end of this run-in period continued with their maintenance treatment as above, and were randomized to one of two double-blind reliever treatments for 48 weeks: 100/6 μg beclometasone/formoterol HFA-MDI ('as-needed beclometasone/formoterol' group) or 100 μg salbutamol MDI ('as-needed salbutamol' group). Participants were instructed to continue with their two inhalations per day of maintenance beclometasone/formoterol treatment throughout the study and to take one inhalation of their reliever inhaler as guided by their asthma symptoms, up to a maximum of six reliever inhalations per day. Participants were required to contact the study investigators if six reliever inhalations per day were taken for two consecutive days.

The primary outcome variable was the time to the first severe asthma exacerbation, defined as worsening asthma requiring hospital admission or a visit to the emergency department (ED), or requiring systemic corticosteroids for at least 3 days. Key secondary outcomes were the rate of severe exacerbations, rate of hospitalizations or ED attendances for asthma, asthma control (as measured by the Asthma Control Questionnaire-7 [4] and symptom scores) and lung function (FEV₁). A *post hoc* analysis was undertaken to assess the impact of pre-study ICS dose on severe asthma exacerbations within the study; in this analysis, a dose equivalence of 1:2.5 between beclometasone extrafine to non-extrafine was used, and a cut-off of 500 $\mu\text{g/day}$ of pre-study (non-extrafine) beclometasone or equivalent was used to categorize patients into an ICS dose increase group (pre-study < 500 $\mu\text{g/day}$) or an ICS dose reduction/dose neutral group (pre-study ≥ 500 $\mu\text{g/day}$).

Results

There were 852 and 849 participants included in the intention-to-treat analysis in the as-needed beclometasone/formoterol and as-needed salbutamol groups, respectively. Approximately 60% of participants were female, mean FEV₁ was 75% of predicted and mean ACQ-7 score was around 1.9. Mean baseline ICS dose (non-extrafine beclometasone equivalent) was around 1130 μg and approximately 80% of participants were on a LABA at baseline.

Treatment with the as-needed beclometasone/formoterol regimen significantly prolonged the time to the first severe asthma exacerbation by 75 days and reduced the risk of a severe exacerbation by 36% (hazard ratio: 0.49–0.82 [95% CI: 0.64]; $p = 0.0005$). The rate of severe asthma exacerbations (hazard ratio: 0.66 [0.55–0.80]; $p < 0.0001$) and asthma exacerbations resulting in hospitalization or ED visits (hazard ratio: 0.67 [0.54–0.84]; $p = 0.0003$) were also significantly reduced in the as-needed beclometasone/formoterol group. The *post hoc* analyses showed that the time to the first severe exacerbation and the rates of severe exacerbations were improved by treatment with the as-needed beclometasone/formoterol regimen, in the subgroups with ICS dose increase (< 500 $\mu\text{g/day}$ prior to study enrolment) and ICS dose reduction/dose neutral (≥ 500 $\mu\text{g/day}$ prior to study enrolment).

Mean ACQ-7 scores improved (reduced) to a similar extent in both groups (mean 0.48 and 0.42 point reductions in the as-needed beclometasone/formoterol group and as-needed salbutamol groups, respectively; between group difference: -0.06 [95% CI: -0.13 to 0.02]; $p = 0.137$). Improvements in asthma symptom scores, asthma control days and FEV₁ were also similar between groups.

Expert commentary

This study has demonstrated the efficacy of the extrafine beclometasone/formoterol HFA-MDI when used according to the maintenance and reliever therapy regimen in reducing severe exacerbations of asthma, compared with the same fixed dose of beclometasone/formoterol for maintenance treatment with salbutamol for relief. The 34% reduction in severe exacerbations with beclometasone/formoterol MDI when used for maintenance and relief was similar in magnitude to the 46–48% reduction with budesonide/formoterol via DPI or MDI when used according to this regimen [1,2,5]. In keeping with the previous findings relating to budesonide/formoterol, use of beclometasone/formoterol for maintenance and reliever therapy was also associated with a significant reduction in severe asthma exacerbations resulting in hospitalization or ED attendance [6] but did not lead to a clinically important improvement in lung function or symptom control compared with the same fixed dose of maintenance beclometasone/formoterol with salbutamol for relief.

As a result, the evidence-base for the efficacy of the SMART regimen from combination budesonide/formoterol therapy is extended to the use of combination beclometasone/formoterol in an extrafine HFA-MDI formulation. This means that clinicians now have alternatives in terms of the particular ICS/fast-onset LABA combination and/or inhaler device that they can prescribe according to the SMART regimen.

The study also extends the generalizability of the efficacy of the SMART regimen to poorly controlled patients who have high reliever use at baseline, a group which had been excluded from some of the previous key trials [1,2]. These patients represent a high-risk population at greatest need of effective long-term asthma treatment.

The study also resolved one of the concerns raised with previous trials of the SMART regimen in that some patients with current

asthma symptoms were randomized to receive a lower maintenance ICS dose than their pre-study treatments [7]. It has been proposed that this effectively represented a dose reduction which favoured 'as-required' use of a product containing an ICS. To specifically address this concern, *post hoc* analyses were undertaken which confirmed the superiority of this regimen in reducing the risk of severe exacerbations, irrespective of whether the dose of ICS administered before entry was stepped up, stepped down or was left unchanged. Indeed, data on these *post hoc* analyses presented in the online supplement show that a greater benefit in reducing the risk of severe exacerbations with the beclometasone/formoterol maintenance and reliever therapy regimen occurred in patients with a step up in maintenance ICS dosing. This observation not only suggests that the greatest efficacy of the SMART regimen may be obtained in patients who receive an accompanying step up in maintenance ICS therapy, but also that the findings from previous studies of the SMART regimen may have underestimated rather than overestimated the potential benefit with the SMART regimen by stepping down the ICS dose at randomization.

Similar to two of the key trials involving budesonide/formoterol [1,2], the authors chose a double-blind design for the study, which would have resulted in participants in the 'as-needed beclometasone/formoterol' group receiving one combination beclometasone/formoterol inhaler for maintenance and another inhaler for symptom relief. In the clinical setting, the use of the combined beclometasone/formoterol inhaler for maintenance and reliever therapy would involve use of a single inhaler (the SMART regimen), which may result in increased adherence to medication [8] and even greater improvements in patient outcomes.

Five-year view

In the next 5 years, the SMART regimen is likely to be increasingly used in clinical practice with a wide range of combination ICS/fast-onset LABA MDI and DPI formulations. Its evidence-

based use will extend from poorly controlled severe asthma [1-3,5] to mild and moderate asthma [9].

In terms of ICS/fast-onset LABA therapy, there is a need to determine its efficacy/safety profile in patients with poorly controlled intermittent or mild persistent asthma, currently treated with regular ICS together with a SABA as required for symptom relief [10,11]. The potential efficacy of regular ICS therapy is limited by low ICS prescription rates [12] and poor adherence to ICS in clinical practice [13], leaving patients at risk of severe exacerbations. There is evidence to suggest that sole treatment with a combination ICS/fast-onset LABA inhaler used for relief of symptoms may have significant advantages over regular ICS therapy and SABA for relief of symptoms, and represent an effective, safe and novel regimen for the treatment of mild asthma [10,11]. Randomized controlled trials are needed to compare the efficacy and safety of 'ICS/fast-onset LABA reliever therapy' versus 'ICS maintenance and SABA reliever therapy' regimens in mild asthma. We suggest that such randomized controlled trials represent a priority for the next 5 years.

Financial & competing interests disclosure

M Patel, J Pilcher and R Beasley have been involved in clinical research of the budesonide/formoterol SMART regimen, funded by the Health Research Council of New Zealand (a government funding organization). R Beasley has been a member of the GlaxoSmithKline (NZ) advisory board, consulted for Cytos Biotechnology and Pharmaxis, received research grants from AstraZeneca, Cephalon, Chiesi, Genentech, GlaxoSmithKline and Novartis, payment for lectures or support to attend meetings from Boehringer Ingelheim, GlaxoSmithKline, Novartis, Nycomed and Otsuka Pharmaceuticals. J Pilcher is a Health Research Council of New Zealand Clinical Research Training Fellow. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Key issues

- The conventional treatment for adult patients with moderate to severe asthma or poor asthma control is a combination inhaled corticosteroid (ICS)/long-acting beta-agonist inhaler for maintenance treatment with a short-acting beta-agonist for relief.
- Prior studies have demonstrated that the budesonide/formoterol Single combination inhaler as Maintenance And Reliever Therapy regimen has greater efficacy in reducing severe asthma exacerbations, including those requiring hospitalization or emergency department attendance, than the same fixed dose of maintenance budesonide/formoterol with short-acting beta-agonist for relief, in adult patients with poor control.
- This current study demonstrates that the use of the extrafine beclometasone/formoterol hydrofluoroalkane-metered dose inhaler (MDI) as maintenance and reliever therapy has greater efficacy in reducing severe exacerbations than the same fixed dose of beclometasone/formoterol hydrofluoroalkane-MDI with salbutamol for relief.
- Severe asthma exacerbations, including those requiring hospitalization or emergency department visits, were reduced by approximately a third by treatment with beclometasone/formoterol as maintenance and reliever therapy.
- The Single combination inhaler as Maintenance And Reliever Therapy regimen, used with either budesonide/formoterol dry powder inhaler or MDI or beclometasone/formoterol MDI, provides an alternative treatment option for use in adult patients at risk of severe exacerbations or patients with poor asthma control.
- Investigation of the use of an ICS/fast-onset long-acting beta-agonist inhaler solely as reliever therapy in intermittent or persistent mild asthma is a research priority.

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