



Perspectives

Asthma maintenance and reliever therapy

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Introduction

The objectives of asthma management are to achieve optimal asthma control, which consists of current (day-to-day) control, defined by absence of daytime symptoms, nighttime waking, reliever use, functional limitation, and lung function stability, and to reduce the future risks of asthma exacerbations, deterioration in lung function, and medication adverse effects. However, achieving optimal asthma control can be difficult in many patients, despite maximum therapy. The cause of uncontrolled asthma is multifactorial, but poor adherence to treatment is one of the main factors that leads to treatment failure.

Asthma medications have traditionally been classified as relievers, which are recommended to be used infrequently, when needed, to treat symptoms (most commonly rapid-onset inhaled β_2 -agonists), and controllers (maintenance), which are taken regularly to control asthma.¹ The most widely used maintenance therapy is inhaled corticosteroids (ICSs). Other maintenance treatment options include ICSs in combination with long-acting inhaled β_2 -agonists (LABAs) in a single inhaler, leukotriene modifiers, and anti-IgE monoclonal antibodies.¹

This perspective considers the evidence that the combination of an ICS and a rapid-onset LABA provides additional clinical benefit, particularly in reducing the future risk of severe asthma exacerbations, when used not only as a maintenance treatment for asthma not controlled by an ICS alone but also as a reliever medication for asthma.

Maintenance ICS therapy for asthma

ICSs have been the cornerstone of asthma management for more than 30 years. ICSs have been demonstrated to improve all the symptoms and physiologic abnormalities that characterize asthma and to markedly reduce the risk of severe asthma exacerbations.^{2,3}

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The physiologic changes that benefit from ICSs include airflow obstruction and airway hyperresponsiveness. The improvements in these characteristics of asthma occur because of the anti-inflammatory effects of ICSs and in particular their ability to resolve eosinophilic airway inflammation.⁴ In addition, ICSs improve many of the pathologic abnormalities that characterize asthma, including structural changes that occur within the airway epithelium, increased deposition of subepithelial collagen, and reduction in the airway neovascularization.

Combination ICS and LABA therapy

A shift in thinking about the management of asthma occurred when the combination of a moderate-dose ICS and an LABA was found to be superior in improving asthma control than a high-dose ICS alone,⁵ particularly for the reduction of severe asthma exacerbations.^{2,6} Thus, all current asthma treatment guidelines recommend changing treatment to ICS-LABA combinations, delivered in a single inhaler, if a moderate-dose ICS fails to control asthma.^{1,7,8} The only study that has prospectively evaluated the effects of low compared with moderate maintenance doses of an ICS alone and these same doses combined with an LABA is the Formoterol and Corticosteroids Establishing Therapy (FACET) study.⁶ A post hoc analysis of this study demonstrated that increasing doses of the ICS budesonide alone had little added benefit in improving asthma control⁹ but were effective in reducing severe asthma exacerbations by approximately 50%;⁶ however, when added to the LABA formoterol, increasing doses of the ICS had a marked benefit in improving asthma control⁹ and provided a further reduction in asthma exacerbations. These results suggest that there is a synergistic benefit when combinations of ICSs and LABAs are used, when ICSs alone are not providing optimal asthma control.

LABA monotherapy has been found to increase the risk of asthma-related hospitalization and mortality in asthmatic patients.^{10,11} This finding has raised concerns that LABA-ICS combinations may also pose risk to some patients. Several meta-analyses of all the available clinical trial data have reported that ICS-LABA combinations in a single inhaler reduce asthma exacerbation risk without a significant increase in asthma mortality.^{12,13} Given the fact that patients with asthma often use β -agonists in

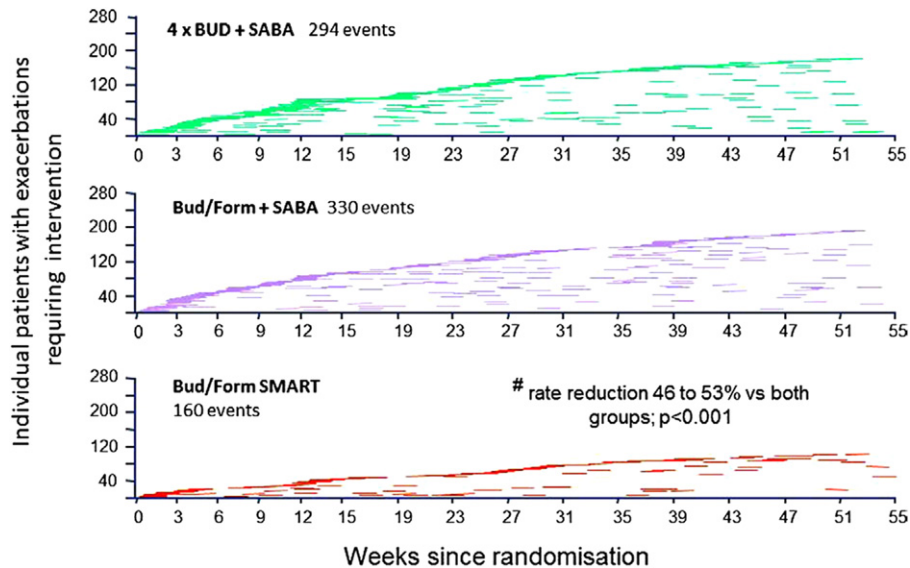


Figure 1. All severe asthma exacerbations requiring medical intervention in the STAY study. Each exacerbation is represented by a line, and the length of the line represents the duration of the exacerbation. Patients receiving budesonide, 800 $\mu\text{g}/\text{d}$, with terbutaline as reliever are in the upper panel; patients receiving budesonide-formoterol, 200/6 $\mu\text{g}/\text{d}$, with terbutaline as reliever are in the middle panel; and patients receiving budesonide-formoterol, 200/6 $\mu\text{g}/\text{d}$, with budesonide-formoterol as reliever are in the lower panel. Budesonide-formoterol as maintenance and reliever therapy significantly reduced the number of severe exacerbations when compared with the other 2 groups. Figure is adapted from data in O'Byrne et al.¹⁴

preference to ICSs when provided in separate inhalers, the practical recommendation is that LABAs should be provided as combination products in a single inhaler in which every dose of LABA is accompanied by an ICS.

ICS-LABA combinations as maintenance and reliever therapy

Two LABAs have been approved for use in asthma: salmeterol and formoterol. These LABAs differ in that formoterol is almost a full agonist on the β_2 -receptor, whereas salmeterol is a partial agonist. Formoterol has a similar onset of bronchodilation as all the short-acting inhaled β_2 -agonists (SABAs),¹⁴ provides increasing bronchodilation with increasing doses, and has been approved as a rescue bronchodilator in many countries.¹⁵ An hypothesis was developed that postulated that using a combination inhaler containing both an ICS and a LABA for regular maintenance and reliever therapy would be advantageous when compared with using an SABA as needed. This hypothesis implied that the ICS, when used in a combination for symptom relief, would provide additional clinical benefit, particularly in reducing the risks of severe asthma exacerbations, which are known to be associated with worsening airway inflammation and increasing symptoms.

An evaluation of this hypothesis was possible with the combination inhaler containing budesonide and formoterol because of the rapid onset of bronchodilator action of formoterol.¹⁶ The initial studies of the added value of using budesonide-formoterol combination as maintenance and reliever treatment in asthma were a comparison of moderate-dose budesonide and the SABA terbutaline.^{17,18} These studies demonstrated a significant reduction of severe asthma exacerbations when the combination was used as maintenance and reliever therapy. A limitation of these studies, however, was the fact that the comparator (ICS plus inhaled β_2 -agonists as reliever) is not accepted as the ideal maintenance treatment for patients with moderate-to-severe asthma, which were most of the patients enrolled.

Another study (the Symbicort Treatment as Maintenance and Reliever Therapy [STAY] study)¹⁹ overcame this limitation because it compared budesonide-formoterol as both maintenance and reliever

therapy with fixed dosing of either budesonide-formoterol or a 4-fold higher dose of budesonide alone, both with short-acting inhaled β_2 -agonists as reliever. On the basis of the results of the FACET study,⁶ the expectation was that the higher-dose budesonide treatment with terbutaline as reliever would be significantly better in reducing the risks of severe exacerbations than the lower fixed-dose budesonide-formoterol combination with terbutaline as reliever. The question being asked was whether using budesonide-formoterol as reliever instead of terbutaline would provide a benefit in reducing severe exacerbations similar to the higher-dose budesonide. The study demonstrated that budesonide-formoterol given both as maintenance and reliever therapy significantly prolonged the time to the first severe exacerbation when compared with both budesonide-formoterol as maintenance and terbutaline as reliever and higher-dose budesonide and terbutaline as reliever (Fig 1). The risk of experiencing a severe asthma exacerbation was 45% lower when budesonide-formoterol was used for maintenance and reliever when compared with budesonide-formoterol and terbutaline as reliever and 47% lower than a 4-fold higher dose of budesonide and terbutaline as reliever. This magnitude of the reduction in severe exacerbations was consistent in children, adolescents, and adults. The use of budesonide-formoterol as maintenance and reliever therapy was also found to significantly prolong the time to repeat exacerbations. This study has been the only study, to date, that has included children younger than 12 years. More studies are needed in this patient population.

A concern that has been raised about this treatment approach is that patients would overuse the budesonide-formoterol reliever and receive inappropriately high doses of ICSs. In fact, the mean number of reliever medications used was significantly lower for patients using budesonide-formoterol as maintenance and reliever therapy than for either comparator using SABA for relief.¹⁹

Another important issue that needs to be addressed is whether the use of formoterol alone or the combination of budesonide and formoterol provides this clinical benefit in reducing asthma exacerbations. Tattersfield et al²⁰ had previously shown that formoterol was significantly more effective than the SABA terbutaline, when used as a reliever medication, in reducing severe asthma

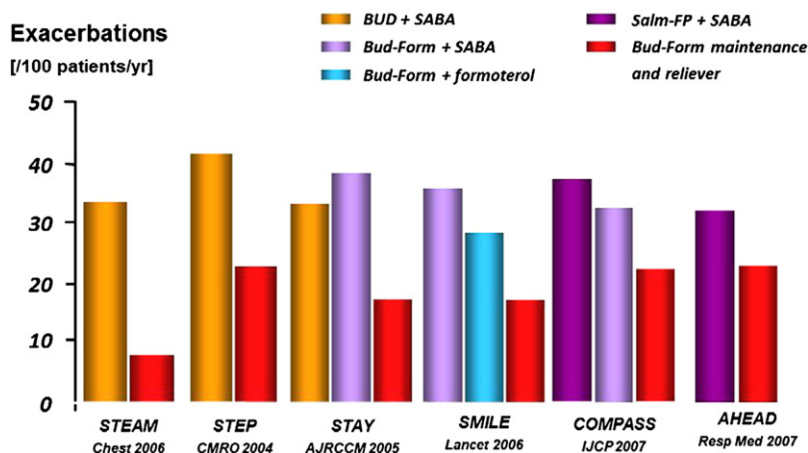


Figure 2. Summary of the effects of using budesonide-formoterol as maintenance and reliever therapy (red bars) when compared with a high-dose inhaled corticosteroid (ICS) alone as maintenance plus a short-acting β_2 -agonist (SABA) as reliever (orange bars), low-to-moderate ICS-LABA combination as maintenance plus an SABA as reliever (mauve bars), low-to-moderate ICS-LABA combination as maintenance plus an LABA as reliever (blue bars), or high-dose ICS-LABA as maintenance plus an SABA as reliever (purple bars) on the risk of severe asthma exacerbations, expressed as number per patient per year. In all studies, budesonide-formoterol used as both maintenance and reliever therapy reduced the risks of severe asthma exacerbations.

exacerbations. For this reason, a study was conducted in which a fixed maintenance dose of budesonide-formoterol (160 μ g/4.5 μ g twice daily) was administered to more than 3,000 symptomatic patients.²¹ There were 3 treatment groups. Each group had a different reliever medication: formoterol alone, terbutaline alone, or the combination of budesonide and formoterol. The study confirmed the previous observation that formoterol was significantly better than terbutaline at prolonging the time to the first exacerbation; however, the combination of budesonide and formoterol was significantly better than both of the other reliever medications. This study identified that most of the benefit achieved with this treatment approach is due to the additional ICS delivered to the airways when patients are more symptomatic as an asthma exacerbation develops.

The approach of using budesonide-formoterol as maintenance and reliever therapy has been studied using maintenance ICS-LABA doses lower than those used to treat patients at the time of recruitment into the studies. The treatment approach has been compared with much higher maintenance doses of ICS-LABA combinations with an SABA as reliever.^{22,23} Both studies identified that a lower maintenance dose of the combination as reliever was superior in reducing asthma exacerbations. A concern has been raised, however, that using lower maintenance doses of the combination would not provide as effective current (day-to-day) control of asthma.²⁴ This concern was evaluated in a retrospective analysis of all of the studies that have compared this treatment approach to a variety of maintenance doses of ICS-LABA combinations.²⁵ The percentage of patients achieving asthma control with budesonide-formoterol maintenance and reliever therapy increased with time, irrespective of treatment; the percentage of controlled or partly controlled asthma was similar to that controlled with higher-dose ICS alone (56% vs 45%), same-dose ICS-LABA combination (56% vs 53%), and higher-dose ICS-LABA combination (54% vs 54%). However, in every instance the risk of severe asthma exacerbations was lower with budesonide-formoterol maintenance and reliever therapy (Fig 2). The conclusion that there is still room for improvement in achieving asthma control, no matter which treatment approach is used in difficult-to-treat asthma, also confirmed the findings of other studies.²⁶

Airway inflammation in patients with asthma with high-fixed or low-fixed plus as-needed budesonide-formoterol has been previously studied.²⁷ The study compared budesonide-formoterol,

160 μ g/4.5 μ g twice daily, plus budesonide-formoterol, 640 μ g/9 μ g twice daily, as reliever on airway eosinophilia. During treatment for 1 year with budesonide-formoterol maintenance and reliever therapy, the geometric mean percentage of sputum eosinophils remained unchanged (1.6%–1.9%), whereas biopsy specimen sub-epithelial eosinophils increased (6.2–12.3/mm²). By contrast, the sputum and biopsy eosinophil counts decreased with high fixed-dose treatment (2.2%–1.2% and 7.7–4.8/mm²), which resulted in a significant treatment difference. No between-treatment differences were found in reticular basement membrane thickness, exhaled nitric oxide, exacerbation frequency, or forced expiratory volume in 1 second. Thus, when compared with a 4-fold higher maintenance dose of budesonide, budesonide-formoterol maintenance and reliever therapy is associated with slightly higher airway eosinophil counts, but this was not manifested by any increase in asthma exacerbations or worsening asthma control.

Conclusions

Asthma treatment should focus on achieving optimal asthma control. Combination ICS-LABA therapy is the recommended treatment approach in adult patients when a low-dose ICS alone is not providing asthma control.^{1,7} Studies in children have also indicated that adding an LABA to ICS treatment is more likely to provide a better response than increasing doses of an ICS or adding a leukotriene receptor antagonist to an ICS, although children responded to each of these treatment approaches.²⁸ One ICS-LABA combination containing budesonide and formoterol is also used in many countries as both maintenance and reliever therapy because this combination has been demonstrated to further reduce future risks of severe asthma exacerbations when compared with ICS-LABA combination therapy and an SABA as rescue therapy. This approach has also resulted in lower total ICS use in patients with difficult-to-treat asthma and is associated with a similar percentage of patients with well-controlled asthma when compared with high doses of an ICS. There is, however, still room for improvement in achieving asthma control, no matter which treatment approach is used in difficult-to-treat asthma.

References

- [1] Bateman ED, Hurd SS, Barnes PJ, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J*. 2008;31:143–178.

- [2] O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. *Am J Respir Crit Care Med*. 2001;164(8 pt 1):1392–1397.
- [3] Pauwels RA, Pedersen S, Busse WW, et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet*. 2003;361:1071–1076.
- [4] Laitinen LA, Laitinen A, Haahtela T. A comparative study of the effects of an inhaled corticosteroid, budesonide, and a beta 2-agonist, terbutaline, on airway inflammation in newly diagnosed asthma: a randomized, double-blind, parallel-group controlled trial. *J Allergy Clin Immunol*. 1992;90:32–42.
- [5] Cheung D, Timmers MC, Zwinderman AH, Bel EH, Dijkman JH, Sterk PJ. Long-term effects of a long-acting beta 2-adrenoceptor agonist, salmeterol, on airway hyperresponsiveness in patients with mild asthma. *N Engl J Med*. 1992;327:1198–1203.
- [6] Pauwels RA, Lofdahl CG, Postma DS, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma: Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. *N Engl J Med*. 1997;337:1405–1411.
- [7] Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *J Allergy Clin Immunol*. 2007;120(5 suppl):S94–S138.
- [8] British Thoracic Society and Scottish Intercollegiate Guidelines Network. British Guideline on the Management of Asthma: a national clinical guideline. Available at www.brit-thoracic.org.uk/guidelines/asthma-guidelines. Accessed September 10, 2012.
- [9] O'Byrne PM, Naya IP, Kallen A, Postma DS, Barnes PJ. Increasing doses of inhaled corticosteroids compared to adding long-acting inhaled β_2 -agonists in achieving asthma control. *Chest*. 2008;134:1192–1199.
- [10] Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *BMJ*. 1993;306:1034–1037.
- [11] Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest*. 2006;129:15–26.
- [12] Jaeschke R, O'Byrne PM, Mejza F, et al. The safety of long-acting beta-agonists among patients with asthma using inhaled corticosteroids: systematic review and metaanalysis. *Am J Respir Crit Care Med*. 2008;178:1009–1016.
- [13] Bateman E, Nelson H, Bousquet J, et al. Meta-analysis: effects of adding salmeterol to inhaled corticosteroids on serious asthma-related events. *Ann Intern Med*. 2008;149:33–42.
- [14] Palmqvist M, Ibsen T, Mellen A, Lotvall J. Comparison of the relative efficacy of formoterol and salmeterol in asthmatic patients. *Am J Respir Crit Care Med*. 1999;160:244–249.
- [15] Pauwels RA, Sears MR, Campbell M, et al. Formoterol as relief medication in asthma: a worldwide safety and effectiveness trial. *Eur Respir J*. 2003;22:787–794.
- [16] Anderson GP. Formoterol: pharmacology, molecular basis of agonism, and mechanism of long duration of a highly potent and selective beta 2-adrenoceptor agonist bronchodilator. *Life Sci*. 1993;52:2145–2160.
- [17] Scicchitano R, Aalbers R, Ukena D, et al. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. *Curr Med Res Opin*. 2004;20:1403–1418.
- [18] Vogelmeier C, D'Urzo A, Pauwels R, et al. Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option? *Eur Respir J*. 2005;26:819–828.
- [19] O'Byrne PM, Bisgaard H, Godard PP, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med*. 2005;171:129–136.
- [20] Tattersfield AE, Lofdahl CG, Postma DS, et al. Comparison of formoterol and terbutaline for as-needed treatment of asthma: a randomised trial. *Lancet*. 2001;357:257–261.
- [21] Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet*. 2006;368:744–753.
- [22] Kuna P, Peters MJ, Manjra AI, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. *Int J Clin Pract*. 2007;61:725–736.
- [23] Bousquet J, Boulet LP, Peters MJ, et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. *Respir Med*. 2007;101:2437–2446.
- [24] Chapman KR, Barnes NC, Greening AP, Jones PW, Pedersen S. Single maintenance and reliever therapy (SMART) of asthma: a critical appraisal. *Thorax*. 2010;65:747–752.
- [25] Bateman ED, Reddel HK, Eriksson G, et al. Overall asthma control: the relationship between current control and future risk. *J Allergy Clin Immunol*. 2010;125:600–608.
- [26] Bateman ED, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med*. 2004;170:836–844.
- [27] Pavord ID, Jeffery PK, Qiu Y, et al. Airway inflammation in patients with asthma with high-fixed or low-fixed plus as-needed budesonide/formoterol. *J Allergy Clin Immunol*. 2009;123:1083–1089.
- [28] Lemanske RF Jr, Mauger DT, Sorkness CA, et al. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *N Engl J Med*. 2010;362:975–985.