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Review

Asthma maintenance and reliever therapy

Should this be the standard of care?

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Key Messages

- Low- to moderate-dose inhaled corticosteroids and long-acting β-agonist combinations (ICS-LABA) are more effective asthma treatment options than high-dose ICS alone.
- The ICS-LABA combination budesonide-formoterol can be used as both a maintenance and reliever therapy for asthma.
- Budesonide-formoterol maintenance and reliever therapy is more effective than ICS plus short-acting β_2-agonist (SABA) or ICS-LABA plus SABA in reducing risks of severe asthma exacerbation and provides similar levels of day-to-day asthma control.
- Budesonide-formoterol maintenance and reliever therapy requires lower doses of maintenance ICS and simplifies asthma therapy.
- Budesonide-formoterol as a reliever is superior to SABA as a reliever in mild asthma for all outcomes and is equivalent to maintenance ICS plus SABA in reducing severe asthma exacerbations, but it is less effective than maintenance ICS plus SABA for measures of asthma control.

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ABSTRACT

Objective: The goal of asthma management is to achieve optimal asthma control, defined by the absence of daytime symptoms, nighttime waking, reliever use, functional limitation, and lung function stability, and to also reduce the future risks of asthma exacerbations, deterioration in lung function, and the medication's adverse effects. The most widely used maintenance therapy is inhaled corticosteroids (ICSs). This review considered the evidence in which the combination of the ICS budesonide and the rapid-onset long-acting β-agonist (LABA) formoterol can be used as a standard of care for maintenance and reliever therapy in moderate to severe asthma.
Data Sources: The archival literature of peer-reviewed studies on the efficacy and safety of budesonide-formoterol as maintenance and reliever therapy in moderate to severe asthma.
Results: The ICS-LABA combination containing budesonide-formoterol reduces future risk of severe asthma exacerbations and provides similar levels of day-to-day asthma control when compared with using high-dose ICS alone, or combination ICS-LABA therapy and short-acting β_2-agonist as a reliever.
Conclusion: Budesonide-formoterol as a single combination maintenance and reliever inhaler is effective in reducing asthma exacerbation risk, requires a lower maintenance dose of ICS, and results in a simplified approach to asthma management.

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Introduction

Asthma is a common chronic inflammatory disease of the airways with a worldwide prevalence of nearly 340 million people.[1] Asthma is characterized by variable airflow obstruction with airway inflammation resulting in symptoms of cough, wheezing, chest tightness, and breathlessness.

The aim of asthma treatment is to improve day-to-day control of symptoms, defined by the absence of daytime symptoms, nighttime waking, reliever use, functional limitation, and lung function stability, and to also reduce the future risks of asthma exacerbations, deterioration in lung function, and the medication's adverse effects.[2] However, achieving optimal asthma control can be difficult in many patients, despite the availability of effective and safe asthma treatments.[3] The cause of uncontrolled asthma is multifactorial, but poor adherence to treatment is one of the major factors leading to treatment failure.[4]

Asthma medications have traditionally been classified as relievers (most commonly rapid-onset short-acting inhaled β_2 agonists [SABAs]), which are used infrequently (only whenever needed) to treat symptoms, and controller (maintenance) medications, which are taken regularly to control the underlying airway inflammation.[2] The most widely used maintenance therapy is inhaled corticosteroids (ICSs). This review considered the evidence in which the combination of an ICS and a rapid-onset long-acting β-agonist (LABA) can be used as a standard of care as maintenance and reliever therapy in moderate to severe asthma. This treatment strategy reduces the risk of future severe asthma exacerbations and improves symptom control.

Maintenance Inhaled Corticosteroid Therapy

The use of ICSs has been the cornerstone of asthma therapy for more than 40 years.[5] Studies have reported that ICSs improve all symptoms and physiological abnormalities that characterize asthma and markedly decrease the risks of patients experiencing severe asthma exacerbations, thereby reducing or eliminating the need for maintenance oral corticosteroid therapy.[5,6] However, in the 1970s and early 1980s, treatment was limited to patients with moderate to severe asthma owing to concerns regarding adverse effects associated with regular use of steroids. Because asthma mortality increased in the 1980s, and it was associated with an overuse of SABAs, the benefits of ICSs reemerged, with studies advocating the use of ICSs not only in moderate to severe asthma but also as a maintenance therapy in mild asthma.[6] In addition, ICSs are the most effective controller medications and have been shown to improve symptom control,[7] airflow obstruction,[8] and airway hyperresponsiveness;[7] moreover, ICSs reduce the risk of exacerbations[9] and asthma mortality.[10] These improvements are due to their anti-inflammatory effects, in particular, their ability to reduce eosinophilic inflammation within the airway.[11] Furthermore, ICSs improve many of the pathologic abnormalities that characterize asthma, including the structural changes that occur within the airway epithelium,[12] the increased deposition of subepithelial collagen,[13] and a reduction in the airway neovascularization observed in asthma.[14]

These wide-ranging benefits of maintenance ICSs in asthma, even when used in low daily doses, indicate that they remain the treatment of choice for most patients with asthma, even those with infrequent symptoms (>2 days per month).[15] This is because patients who are considered to have mild asthma remain at risk for severe asthma exacerbations,[15] which can rarely be fatal.[16]

There are patients with asthma who do not achieve optimal asthma control despite being adherent to the recommended low doses of ICSs. The tendency in these cases was to assume that if low doses of ICSs were not providing optimal control, the doses of ICSs should be increased; this is despite the fact that there was little evidence of additional benefit at high ICS doses and clear evidence of increased risk of adverse effects.[17]

Combination of Inhaled Corticosteroid and Long-Acting β-Agonist Therapy

A landmark study by Greening et al[18] in 1994 led to the realization that a combination of ICSs and LABAs is superior to high-dose ICSs alone in asthma management among patients not controlled on low doses of ICSs alone. This randomized, double-blind trial reported that the combination of low-dose ICSs-LABAs compared with ICSs alone in patients with asthma (who remained symptomatic despite the twice-daily dose of 200-μg beclomethasone therapy) resulted in significantly reduced symptoms and improved peak expiratory flows at all time points, but with no differences in asthma exacerbations. This study resulted in a major shift in the general thinking about asthma management. Subsequent studies found that ICSs and β_2-agonists have a synergic effect in combination, given that ICSs prevent the loss of function of β_2-agonists that occurs with long-term use, whereas β_2-agonists enhance the anti-inflammatory effects of ICSs.[19]

Despite these benefits of ICS-LABA combinations for asthma management, there were fears that the addition of LABAs to low-dose ICSs would mask underlying inflammation and potentially lead to asthma exacerbations. This concern was addressed by a meta-analysis of 9 parallel-group trials involving 3685 patients aged 12 years and older and symptomatic despite ICS use, which showed that the addition of a LABA to ICS resulted in improved lung function, reduced symptoms, and also did not increase exacerbations of any severity.[20] Despite this reassuring evidence, other investigators published a meta-analysis, which concluded that the use of LABAs in asthma increased the risk of asthma mortality, even when used in combination with ICSs.[21] In 2010, the Food and Drug Administration issued a public health warning stating that LABAs should not be used as a first-line therapy in asthma and required all products that contained a LABA to have a boxed warning. In addition, the Food and Drug Administration mandated large clinical trials to evaluate the safety of ICS-LABA combinations compared with ICS alone. Busse et al[22] reported a meta-analysis of these 4 prospective clinical trials of more than 36,000 patients with asthma, which resolved this question. This analysis showed that there was no difference in serious asthma-related events between either treatment group (0.60% in the ICS group and 0.66% in the ICS-LABA group); however, the ICS-LABA treatment resulted in fewer asthma exacerbations (11.7% in the ICS group vs 9.8% in the ICS-LABA group). Thus, the combination of ICS-LABA did not result in a higher risk of asthma-related adverse events and resulted in a lower rate of asthma exacerbations. The use of low- or moderate-dose ICS-LABA combinations in the same inhaler not only simplified the treatment for patients but also resulted in improved asthma control[23] and reduced severe asthma exacerbations than that of high-dose ICS alone.[24] Therefore, all current asthma treatment guidelines now recommend changing the treatment to ICS-LABA combinations, delivered in a single inhaler, if a moderate dose of an ICS fails to control asthma.[2,25,26]

Budesonide and Formoterol Combinations Used Both As Maintenance and Reliever Therapy

There are currently 3 LABAs approved for use in asthma: salmeterol, vilanterol, and formoterol. Formoterol differs from the other 2 in that it is almost a full agonist on the β_2-receptor. Therefore, onset of bronchodilation in formoterol is similar to that of all the SABAs and demonstrated a dose-response (increasing bronchodilation with increasing doses)[27] but with a longer duration of effect (>12 hours). As a result of these pharmacologic properties, formoterol has been approved as a rescue

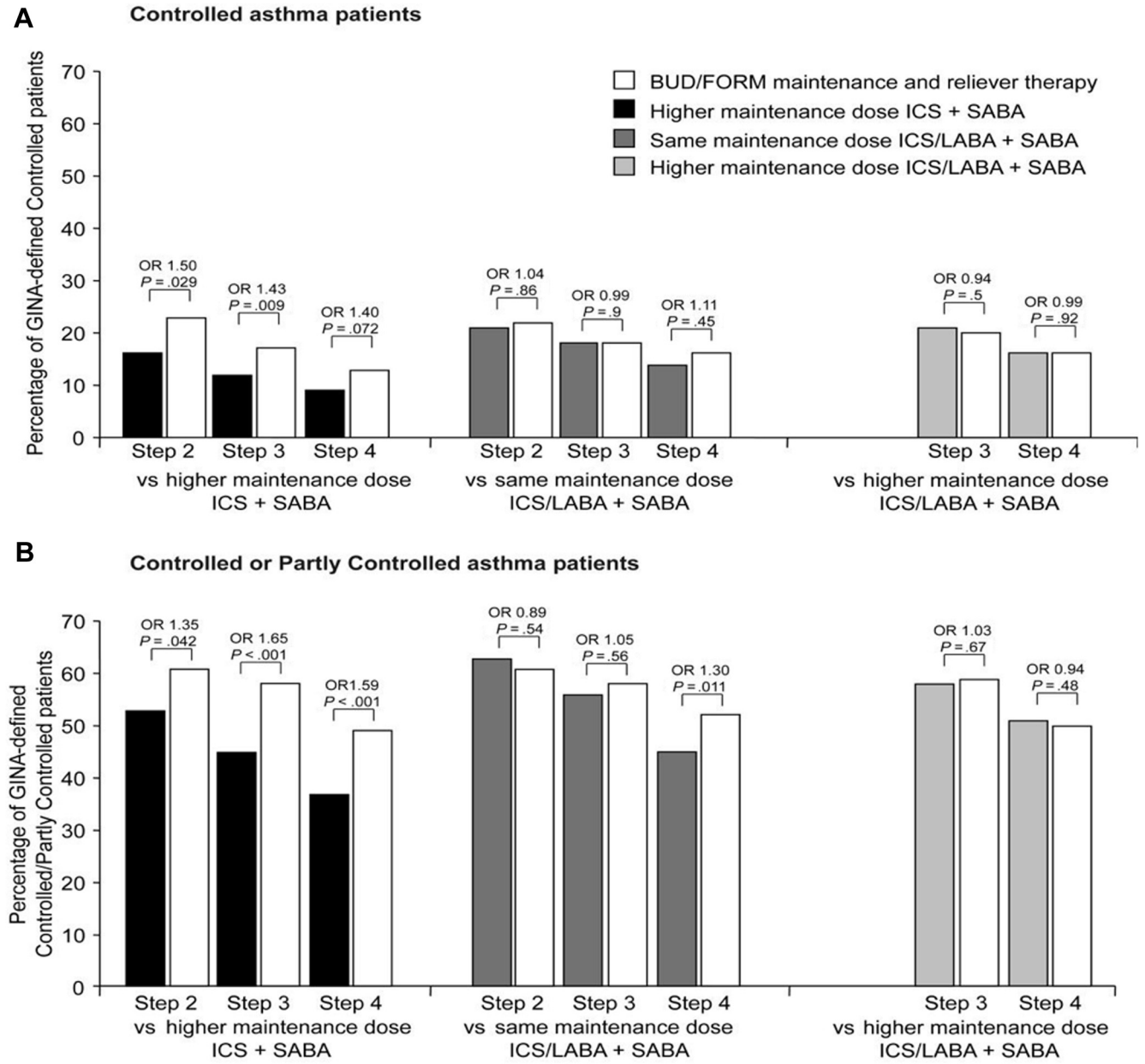

Figure 1. The proportion of patients with (A) controlled and (B) controlled or partly controlled asthma in the final week of treatment by study treatment and GINA treatment step. BUD-FORM, budesonide-formoterol; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; OR, odds ratio; SABA, short-acting β_2-agonist. (Reprinted with permission from Bateman ED, et al. *Respir Res*. 2011;12(1):38.)

bronchodilator in many countries.[28] A hypothesis was developed, which postulated that using a combination inhaler containing both an ICS and a LABA for both regular maintenance therapy and reliever therapy would be advantageous than using an ICS as maintenance therapy and SABA as needed. This implied that the additional anti-inflammatory effect of the ICS, when the combination was used for symptom relief, would provide additional clinical benefit, particularly in reducing the risks of severe asthma exacerbations that are known to be associated with worsening airway inflammation.

The evaluation of this hypothesis was possible with the combination inhaler containing budesonide-formoterol because of the rapid onset of bronchodilator action of formoterol.[27] The initial studies that evaluated the added value of using the combination of budesonide-formoterol both as maintenance and reliever treatment in asthma were a comparison with moderate-dose budesonide and the SABA, terbutaline.[24,29] These studies found a significant reduction of severe asthma exacerbations when the combination was used as maintenance and reliever therapy. A limitation of these studies, however, was that the comparator (ICS plus inhaled β_2-agonists as reliever) is not widely accepted as the ideal maintenance treatment for patients with moderate to severe asthma, which were the majority of the patients enrolled in the study.

The Symbicort Treatment As single therapY (STAY) study[30] overcame this limitation because it compared budesonide-formoterol, both as maintenance and reliever, with fixed low-dosing of either budesonide-formoterol or a 4-fold higher dose of budesonide alone, both with SABAs as a reliever. Based on the results of the Formoterol and Corticosteroids Establishing Therapy (FACET) study,[29] the expectation was that higher dose budesonide treatment with SABAs as a reliever would be significantly better in

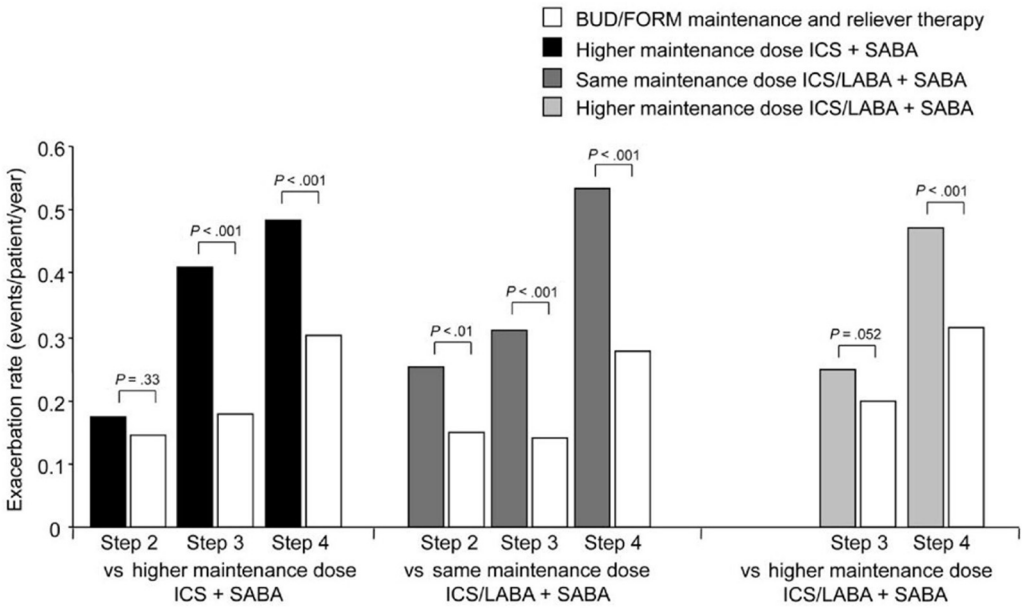

Figure 2. Exacerbation rate by study treatment and GINA treatment step at study entry. BUD-FORM maintenance and reliever therapy vs higher maintenance dose ICS plus SABA, exacerbation rate ratio (95% CI): step 2, 0.829 (0.570, 1.207); step 3, 0.431 (0.353, 0.526); step 4, 0.624 (0.512, 0.761). BUD-FORM maintenance and reliever therapy vs same maintenance dose ICS-LABA plus SABA, exacerbation rate ratio (95% CI): step 2, 0.583 (0.389, 0.874); step 3, 0.455 (0.371, 0.558); step 4, 0.519 (0.434, 0.620). BUD-FORM maintenance and reliever therapy vs higher maintenance dose ICS-LABA + SABA, exacerbation rate ratio (95% CI): step 3, 0.795 (0.631, 1.002); step 4, 0.665 (0.549, 0.807). BUD-FORM, budesonide-formoterol; CI, confidence interval; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; OR, odds ratio; SABA, short-acting β2-agonist. (Reprinted with permission from Bateman ED, et al. *Respir Res.* 2011;12(1):38.)

reducing the risks of severe exacerbations than the lower, fixed-dose budesonide-formoterol combination, with terbutaline as a reliever. This study aimed to evaluate whether using budesonide-formoterol as a reliever, instead of terbutaline, would provide a benefit in reducing severe exacerbations, similar to the higher dose budesonide. Adults could use a maximum of 10 (and children, 7) as-needed inhalations per day. The study found that budesonide-formoterol, given both as maintenance and reliever, significantly prolonged the time to the first severe exacerbation than both budesonide-formoterol as maintenance plus SABA as a reliever and higher dose budesonide plus SABA as a reliever. The risk of experiencing a severe asthma exacerbation was 45% lower when budesonide-formoterol was used for maintenance and reliever than that of budesonide-formoterol plus SABA as a reliever, and 47% lower than that of a 4-fold higher dose of budesonide plus SABA as a reliever. This magnitude of reduction in severe exacerbations was consistent in children ($\geq$5 years old), adolescents, and adults. The use of budesonide-formoterol as maintenance and reliever was also found to significantly prolong the time to repeat exacerbations with no notable difference in adverse events between the treatment groups. Children (4-11 years old) in both the budesonide-formoterol groups grew significantly more, with an adjusted mean difference of 1 cm in growth (height) than those in the higher dose budesonide and SABA as reliever group. Moreover, this study has been the only study, to date, that has included children younger than 12 years.

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 medication use was significantly lower for patients using budesonide-formoterol as maintenance and reliever than for either comparator using SABA as reliever.[30] Patients who used budesonide-formoterol as maintenance and reliever also required fewer courses of oral steroids than either comparator group.[30]

Another important issue that needed to be addressed was whether it was the use of formoterol alone, or the combination of budesonide-formoterol, which provided this clinical benefit in reducing asthma exacerbations. Tattersfield et al[31] had previously reported that formoterol was significantly more effective than the SABA terbutaline, when used as a reliever medication, in reducing severe asthma exacerbations; patients took fewer inhalations and had larger increase in forced expiratory volume in 1 second. For this reason, a study was conducted, in which a fixed maintenance dose of budesonide-formoterol (160 μg/4.5 μg twice daily) was administered to more than 3000 symptomatic patients,[32] with 3 treatment groups receiving a different reliever medication, in a double-blind randomized fashion (formoterol alone, terbutaline alone, or the combination of budesonide-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-formoterol was significantly better than both the other reliever medications. This study identified that the majority of the benefit achieved with this treatment approach was due to the additional ICSs delivered to the airways when patients were more symptomatic as an asthma exacerbation developed.

The approach of using budesonide-formoterol as a maintenance and reliever therapy has been studied using lower maintenance doses of combinations of ICS-LABA, in which patients were being treated with at the time of recruitment into the studies. The approach has also been compared with much higher maintenance doses of ICS-LABA combinations with SABAs as a reliever.[33,34] These studies identified that a lower maintenance dose of the combination with the combination as reliever was superior in reducing asthma exacerbations.

Another concern that has been raised was that using lower maintenance doses of the combination would not provide an effective current (day-to-day) control of asthma.[35] This was evaluated in a retrospective analysis of all the studies that have

compared this treatment approach with a variety of maintenance doses of ICS-LABA combinations.[36] 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 higher dose ICS alone (56% vs 45%), same-dose ICS-LABA (56% vs 53%), and higher dose ICS-LABA (54% vs 54%). However, in every instance, the risk of severe asthma exacerbations was lower with budesonide-formoterol maintenance and reliever therapy. It was concluded that there is still room for improvement in achieving asthma control, no matter which treatment approach is used for difficult-to-treat asthma.

The approach of using budesonide-formoterol maintenance and reliever therapy in Global Initiative for Asthma (GINA) steps 2, 3, and 4 was evaluated in a post hoc analysis of 5 clinical trials involving more than 1200 patients.[37] Budesonide-formoterol maintenance and reliever therapy was similar or superior at each GINA treatment step in achieving control or partial control of symptoms compared with same or higher dose fixed maintenance ICS-LABA dose (Fig 1). Budesonide-formoterol maintenance and reliever therapy also resulted in a significant reduction in exacerbation rates in GINA steps 2, 3, and 4, when compared with the same maintenance dose of ICS-LABA plus SABA as a reliever, and a significant reduction in exacerbation rates in steps 3 and 4, when compared with higher maintenance dose ICS-LABA plus SABA as a reliever (Fig 2). Thus, budesonide-formoterol as maintenance and reliever therapy may be a preferable option for patients with GINA steps 2 to 4, when compared with high fixed-dose alternatives.

The potential risks of using lower maintenance doses of ICS-LABA on allowing airway inflammation to be uncontrolled has also been evaluated.[38] This study compared budesonide-formoterol 160 μg/4.5 μg twice daily plus as reliever with budesonide-formoterol 640 μg/9 μg twice daily on airway eosinophilia. During the treatment for 1 year with budesonide-formoterol maintenance and reliever therapy, the geometric mean percent sputum eosinophils remained unchanged (1.6%-1.9%), whereas biopsy specimen subepithelial eosinophils increased from 6.2 to 12.3 cells/mm^2. In contrast, the sputum and biopsy eosinophil counts decreased with high fixed-dose treatment, 2.2% to 1.2%, and 7.7 to 4.8 cells/mm^2, respectively, which resulted in a significant treatment difference. There were no between-treatment differences in exacerbation frequency, forced expiratory volume, reticular basement membrane thickness, or exhaled nitric oxide. 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 not with an increase in the number of asthma exacerbations or worsening asthma control.

Budesonide and Formoterol Combination As Reliever in Mild Asthma

The most recent studies have evaluated the potential benefit of using budesonide-formoterol combination as a reliever in patients with mild asthma who require treatment with low doses of ICSs alone. The benefits of ICS monotherapy and the major issues with adherence to daily treatment have already been described previously, especially because patients with mild asthma can be free of symptoms most of the time. This means that many patients with mild asthma only use SABAs as relievers, which have no anti-inflammatory properties. This raised the possibility that the intermittent use of budesonide-formoterol as a reliever might reduce asthma exacerbation risk, given that an ICS was being administered when the patient had symptoms.

To date, 4 studies evaluating this hypothesis have been reported. The first 2 (SYmbicort Given as needed in Mild Asthma [SYGMA] 1 and SYGMA 2)[39,40] were double-blind, randomized trials in more than 7000 patients with mild asthma, which found that budesonide-formoterol was superior to SABA for all outcomes, including reducing severe asthma exacerbations by more than 65%, and were not inferior to low-dose ICSs for reducing asthma exacerbation risk. Low-dose ICSs, however, were slightly (but statistically) better at improving asthma control and lung function, although these differences were not clinically relevant.

The other 2 studies[41,42] followed the same treatment options as the SYGMA trials, but they used a pragmatic, open-label design. The results were consistent with those of the SYGMA trials; however, in both studies, the budesonide-formoterol as a reliever was superior to low-dose budesonide in reducing severe asthma exacerbation risk. This is probably because, in these pragmatic studies, adherence to the maintenance budesonide was lower than in the SYGMA studies, in which adherence was electronically monitored in all patients.

Conclusion

Asthma treatment should be focused on achieving optimal asthma control, which includes reducing asthma exacerbation risk. Combination therapy with ICS-LABA is the recommended treatment approach in adult patients when low-dose ICSs alone is not providing asthma control.[2,7] The ICS-LABA combination containing budesonide-formoterol is used in many countries both as maintenance and a reliever therapy because it has been found to further reduce future risks of severe asthma exacerbations than using combination ICS-LABA therapy plus SABA as a reliever. This approach has also resulted in lower total ICS doses used 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 ICS. However, there is still room for improvement in achieving asthma control, no matter which treatment approach is used in difficult-to-treat asthma.

Budesonide-formoterol maintenance and reliever therapy may be a preferable option for patients requiring combination ICS-LABA treatment than high-dose ICS alone and other fixed-dose alternatives. Finally, the use of budesonide-formoterol as a reliever in mild asthma has been found to be more beneficial than SABAs alone, but maintenance low-dose ICSs remain the most effective treatment option for patients with mild asthma if they are adherent to the daily maintenance dosing.

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