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Review article

Budesonide/formoterol for maintenance and reliever therapy in the management of moderate to severe asthma

The Global Initiative for Asthma (GINA) guidelines aim at improving asthma control and preventing future risk. For patients with moderate to severe asthma an inhaled corticosteroid (ICS) or an ICS/long-acting β_2-agonist (LABA) combination with a short-acting β_2-agonist (SABA) as reliever is recommended. Despite the availability of effective maintenance therapies, a large proportion of patients still fail to achieve guideline-defined asthma control, and overuse of SABA reliever medication at the expense of ICS is commonly observed. New simplified treatment approaches may offer a solution and assist physicians to achieve overall asthma control. One such treatment approach, which is recommended in the GINA guidelines, is budesonide/formoterol for both maintenance and reliever therapy. This treatment strategy significantly reduces the rate of severe asthma exacerbations compared with ICS/LABA plus SABA and achieves equivalent daily symptom control compared with higher doses of ICS/LABA plus separate SABA for relief. These benefits are achieved at a lower overall steroid load, and budesonide/formoterol maintenance and reliever therapy is well tolerated in patients with moderate to severe asthma. This review discusses current asthma management in patients with moderate to severe disease and examines the evidence for alternative asthma management approaches.

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Asthma is a chronic inflammatory disorder of the airways with a highly variable clinical spectrum, but the presence of airway inflammation remains a consistent feature (1). Airway inflammation in asthma is persistent even though symptoms are episodic; however, a direct relationship between the severity of asthma and the intensity of inflammation has not been clearly established (1, 2). The disease is characterized by episodic symptoms and fluctuating levels of inflammation which may culminate in an exacerbation (1). Severe asthma exacerbations are linked with severe airflow limitation and potentially life-threatening symptoms. Asthma exacerbations are associated with an excessive rate of decline in lung function (3, 4), suggesting that these events may drive airway structural changes (airway remodelling). It is well documented that asthma exacerbations are a significant cause of morbidity and mortality and place an enormous burden on healthcare resources globally (1). The Global Initiative for Asthma (GINA) guidelines emphasize the importance of effective asthma management to achieve and maintain control of daily symptoms, improve patient quality of life and reduce future disease risk by preventing exacerbations and progressive loss of lung function while minimizing the potential of the adverse effects of treatment (1, 5, 6).

The development of effective asthma treatments including inhaled corticosteroids (ICS), long-acting β_2-agonists (LABA), short-acting β_2-agonists (SABA), leukotriene modifiers and anti-IgE therapy, together with improved delivery devices and increased recognition of asthma guidelines, has assisted physicians and patients in working together to improve asthma control. Despite this, many patients still fail to achieve guideline-defined goals for asthma control (7–10). In a recent patient survey, involving over 3000 patients treated with ICS with or without a LABA, 51% of patients were classified as 'uncontrolled' by the Asthma Control Questionnaire (10). The purpose of this review article is to assess why patients, in particular those with moderate to severe asthma, are not achieving control and to discuss whether new asthma management approaches now available to physicians can help address this issue.

The role of ICS and LABA in improving asthma control

Well-controlled asthma is characterized according to the GINA guidelines as no troublesome symptoms day or night, little or no reliever medication use, near-normal lung

function and no severe exacerbations (1). Furthermore, patients considered well controlled should have a good quality of life (both productive and physically active). In patients with mild asthma, good control is mostly achieved through treatment with a low-dose ICS plus a SABA, such as salbutamol or terbutaline, for control of breakthrough symptoms (1, 11). In more severe disease, stepwise increases in ICS or the addition of a LABA to ICS maintenance therapy is recommended in the GINA guidelines in order to increase the proportion of time during which asthma is well controlled (1). ICS and LABA can both be administered as monotherapy or as a combination in one inhaler. The two most commonly used ICS/LABA combination inhalers in patients with moderate to severe asthma are budesonide/formoterol (Symbicort®; AstraZeneca, Lund, Sweden) and salmeterol/fluticasone (Seretide™; GlaxoSmithKline, Uxbridge, UK).

Progressively increasing the dose of ICS may be effective for some patients, although whether it is the most effective treatment strategy for all patients with moderate to severe asthma is unclear (12). Studies suggest that daily asthma control improves to a greater extent with the addition of a LABA than with a higher ICS dose alone in patients with mild to severe asthma (13–16). Systematic reviews have found a 12–14% reduction in the risk of an exacerbation with traditional ICS/LABA maintenance therapy plus SABA for relief compared with a higher ICS dose plus SABA in patients with moderate to severe asthma (17, 18). However, the value of increasing ICS dose for improving daily asthma control may be limited (19).

The Formoterol and Corticosteroids Establishing Therapy (FACET) trial is the only study to have investigated the benefit of increasing the ICS dose with or without LABA with an appropriate control group with maintained ICS (14). In this 1-year double-blind study, patients with persistent asthma were randomized to receive a low [100 μg twice daily (b.i.d.)] or fourfold higher (400 μg b.i.d.) dose of budesonide with or without add-on formoterol (14). The rate of severe exacerbations was significantly reduced by 49% by increasing budesonide alone, by 26% with the addition of formoterol to the lower dose of budesonide and by 63% when formoterol was combined with the higher dose of budesonide ($P < 0.001$) compared with low-dose budesonide alone (14). With regard to symptom control, the effect of adding formoterol was more marked than that of increasing the ICS dose alone (14). A recent *post hoc* analysis of the FACET trial confirmed that in the absence of formoterol a fourfold increase in budesonide dose had no impact on the length of time with well-controlled asthma (20).

The Gaining Optimal Asthma controL (GOAL) trial was a 1-year double-blind study which involved the gradual stepping up of maintenance therapy with a combination of salmeterol/fluticasone or fluticasone alone (maximum dose: 500 μg fluticasone b.i.d.), with the aim of achieving total asthma control as defined in the GINA guidelines (no troublesome symptoms day or night, twice or less reliever medication use per week, normal lung function and no exacerbations) (12). Despite use of maximum doses of salmeterol/fluticasone and fluticasone, total asthma control was achieved only in 31% and 19% of patients, respectively, after dose escalation ($P < 0.001$; salmeterol/fluticasone *vs* fluticasone), and in 41% and 28% of patients, respectively, at 1 year (12). Well-controlled asthma was reported in 63% and 50% of patients after dose escalation and in 71% and 59% at 1 year, respectively, confirming the benefit of adding LABA to ICS. A *post hoc* analysis of the GOAL study reported that smoking, previous treatment history and poor control at entry with high SABA use were all barriers to achieving total control despite aggressive increases in ICS therapy (21).

A limitation of the GOAL study was that the contribution of the dose escalation of steroid to the increase in asthma control over time could not be assessed, as there was no control group that was maintained on a low-dose ICS (22). The question of whether the sustained use of maximal-dose ICS is required is significant here, as this issue may cause safety concerns (22). The use of high-dose ICS is known to be associated with a range of local and potential systemic side effects, including oral candidiasis, hoarseness, dysphonia, decreased bone density and adrenal effects (23, 24). However, there is limited evidence of systemic side effects with low to moderate doses of ICS [below 800 μg/day beclomethasone dipropionate (BDP) equivalent] (23).

Findings from GOAL highlight the fact that, even in the carefully managed setting of a clinical trial, few patients achieve total asthma control with high-dose ICS, emphasizing that a more effective approach for the management of asthma in routine clinical practice is needed. Foresi et al. (25) observed that in patients with a background of low maintenance dose ICS, a temporary increase in ICS dose at the time of asthma deterioration was as effective in maintaining asthma control and preventing exacerbations as a higher maintenance dose of ICS. Furthermore, in patients with uncontrolled asthma, more frequent dosing may provide additional benefits and ICS treatment may be more effective if the total daily dose is split into several doses administered over the course of the day (26) (Fig. 1). However, a maintenance regimen with several daily doses may be impractical and difficult to implement. Thus, tailoring the treatment regimen to the individual patient may significantly improve control of asthma.

The challenge of managing maintenance and reliever treatment

Physicians still face the challenge of educating asthma patients regarding the appropriate use of therapy. The recent Global Asthma Physicians and Patients (GAPP)

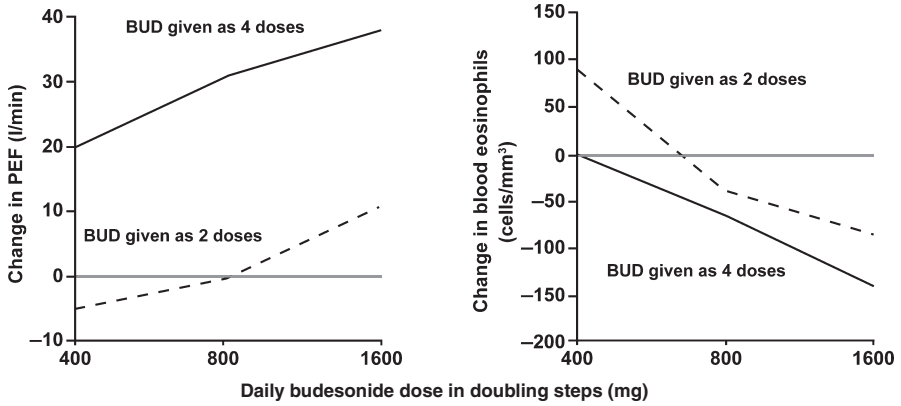

Figure 1. The effect of increasing the ICS dose frequency in patients with uncontrolled asthma (26). BUD, budesonide; PEF, peak expiratory flow. Reprinted from Toogood et al. (26); adapted with permission from Elsevier.

Survey highlighted a number of barriers experienced by physicians and patients during the effective management of asthma (27, 28). These include the need for more aggressive implementation of self-management education for patients and the need for the physician to discuss and alleviate patient concerns regarding medication safety (27, 28). Partridge (29) and Roberts et al. (30) highlighted the need for accurate diagnosis of patients with severe asthma and the development of a structured protocol-based approach to offset potential differences in treatment strategy between specialists with a particular interest in severe asthma and other respiratory physicians. In addition, the failure of patients to correctly use their prescribed medication is a significant challenge in asthma management (7, 9).

Short-acting β_2-agonists such as salbutamol and terbutaline have been the mainstay of reliever therapy for many years, and patients prescribed ICS either alone or in combination with a LABA can over-rely on SABA reliever therapy despite the effectiveness of their prescribed maintenance therapy (7, 10, 31). The overuse of traditional reliever therapy (SABA) may limit further advances in asthma control as it only provides temporary relief and does not improve the underlying bronchial inflammation. In a retrospective observational database study, 62% of patients prescribed combination therapy with salmeterol/fluticasone over a 6-month period collected sufficient SABA from their pharmacist to use two inhalations every day (31). In the patient survey by Partridge et al. (10), 74% of patients used a SABA daily and, when symptoms were at their worst, patients had a fourfold or greater increase in the mean number of SABA inhalations per day, regardless of maintenance therapy.

Underuse of ICS maintenance therapy is also one of the challenges physicians face in the management of moderate to severe asthma. Implementing effective use of ICS is important, as demonstrated in a 10-year asthma programme in Finland, which showed a significant decrease in the burden associated with asthma alongside a concomitant increase in ICS usage (32). A patient survey conducted by Rabe et al. (7) in patients with mild to severe persistent asthma reported that over 70% of patients had not used their ICS therapy in the past month. Partridge et al. (10) observed that an increase in SABA use occurred earlier and to a greater extent compared with ICS during periods of worsening asthma. This study also reported that ICS use was increased when asthma symptoms were at their worst and it was too late to prevent an impending worsening (10).

Overuse of SABAs, while providing effective temporary symptom relief, is thought to mask the underlying inflammation of asthma and, as a consequence, patients are more likely to underestimate the severity of their condition (33). If this leads to a delay in appropriate anti-inflammatory treatment, the consequence may be more severe exacerbations (33). A *post hoc* analysis of data from the FACET study suggests that exacerbations are typically preceded by several days of worsening symptoms. The increase in symptoms was paralleled by an increase in reliever use and gradual fall in peak expiratory flow (PEF) over several days, and more rapid changes over 2–3 days (33). The increased reliever use was the first clinical control measure to show signs of deterioration in the lead-up to an exacerbation. These observations highlight an important period, or 'window of opportunity', for early intervention and the potential successful prevention of an impending exacerbation. The patient survey by Partridge et al. highlighted patients' desire to control their asthma, with nearly 70% of patients responding that they prefer to adjust medication according to changes in their asthma and 85% feeling that they know their asthma well enough to be able to intervene early in order to offset a worsening of asthma symptoms (10).

New asthma management approaches: can they improve control in moderate to severe asthma patients?

A new treatment strategy has been developed for moderate to severe asthma patients which allows physicians to maximize the potential of the 'window of opportunity' in

preventing the progression and development of an exacerbation. Budesonide/formoterol (Symbicort®) used as both maintenance and reliever therapy (Symbicort SMART®, Astrazeneca, Lund, Sweden) and delivered in a Turbuhaler® (Astrazeneca, Lund, Sweden) means that patients use a regular maintenance dose to achieve day-to-day asthma control, and additional inhalations are used for symptom relief. Thus, ICS delivered in combination with formoterol reliever therapy targets the underlying inflammation of asthma and provides rapid control of symptoms. This one inhaler therapy automatically adapts to patients' changing needs, providing appropriate adjustments in both ICS and LABA therapy in a way that is not possible with separate maintenance and reliever inhalers. The GINA guidelines recommend the use of budesonide/formoterol as both maintenance and reliever therapy in patients with persistent asthma, highlighting that this option leads to improved asthma control at relatively low doses of treatment (evidence level category A: substantial number of studies involving substantial number of participants indicating that evidence is from endpoints of well-designed randomized controlled trials that provide a consistent pattern of findings in the population for which the recommendation is made) (1). Budesonide/formoterol maintenance and reliever therapy is approved for use with the Turbuhaler device. Although budesonide/formoterol 80/4.5 and 160/4.5 μg in a pressurized metered dose inhaler (pMDI) is approved in some countries, including the USA, as fixed-dose maintenance therapy for asthma, the suitability of this delivery device has not been investigated for use as maintenance and reliever therapy. Furthermore, compared with the Turbuhaler, the currently available pMDI device delivers a higher quantity of formoterol per dose, making it inappropriate for use as maintenance and reliever therapy.

Formoterol as a fast-acting reliever

Formoterol is a β_2-agonist with high intrinsic efficacy and a rapid onset of action, similar to that of terbutaline and salbutamol (34), which improves asthma control when used as an add-on to ICS for maintenance therapy (14, 35). When used as reliever, formoterol improves asthma control and reduces exacerbations compared with terbutaline in patients using ICS maintenance therapy (36). This finding was confirmed by Pauwels et al. (37) in a 6-month safety study of formoterol as needed compared with salbutamol. Cheung et al. (38) reported improved lung function and symptom control with formoterol Turbuhaler as needed compared with salbutamol Turbuhaler and this study highlighted that patients consider formoterol to provide rapid relief similar to salbutamol but prefer formoterol to salbutamol. One limitation of using formoterol alone as reliever is the concern that increasing doses of LABA would provide bronchoprotection against smooth muscle contraction but still allow increases in inflammation to go unchecked. To counter this problem it was suggested that a combination of budesonide/formoterol, developed initially as a maintenance therapy, could also be used for relief of symptoms.

The slower-acting partial β_2-agonist salmeterol (39, 40) cannot be used as reliever therapy for a number of reasons. The onset of action is not sufficient to provide immediate relief. Moreover, the partial agonist properties limit the benefit of increasing the dose above 100 μg/day (39, 41). In a study involving a methacholine challenge, increasing the dose of salmeterol did not lead to enhanced bronchoprotection, in contrast to the added protection observed with increased doses of formoterol (39).

Evidence of the efficacy and safety of maintenance and reliever therapy with budesonide/formoterol

Five large-scale, double-blind clinical trials and one open-label, dose-titration study, of 6–12 months duration and including over 15 000 asthma patients aged ≥ 12 years, have demonstrated the superior efficacy and safety of budesonide/formoterol maintenance and reliever therapy compared with two- to fourfold higher doses of ICS (budesonide) plus SABA (35, 42, 43) and similar or higher doses of maintenance budesonide/formoterol (35, 44, 45) or salmeterol/fluticasone (44, 46, 47) plus SABA as needed. An overview of these clinical trials is provided in Table 1 and they are individually discussed in detail elsewhere (35, 42–47).

Improving daily asthma control and reducing impairment

As defined in the GINA guidelines, the goal of asthma treatment is to achieve and maintain control, defined as no troublesome symptoms day or night, near-normal lung function, very limited reliever medication use and no severe exacerbations (1).

Reliever use. On most (approximately 60%) days, patients treated with budesonide/formoterol maintenance and reliever therapy do not require their reliever therapy and only use their maintenance therapy. GINA guidelines define asthma control as no troublesome symptoms day or night, near-normal lung function, very limited reliever use and no severe exacerbations (1). In all studies, patients using budesonide/formoterol maintenance and reliever therapy are controlled, on the majority of days, with a lower (35, 42–44, 47) or similar (46) mean daily dose of ICS compared with those on other therapies. In the study by Kuna et al. (44), patients receiving budesonide/formoterol maintenance and reliever therapy were reliever-free on 56.0% of days, compared with 59.1% and 57.8% of days in patients receiving conventional treatment (salmeterol/fluticasone plus terbutaline or budesonide/formoterol plus terbutaline, respectively) (44). Furthermore, Fig. 2

Table 1. Overview of budesonide/formoterol maintenance and reliever therapy clinical trial development programme and mean daily ICS load

	Study duration	Study intervention (maintenance plus reliever)	Number of patients	Mean daily ICS dose μg/day (BDP equivalent)*	Oral steroid usage (days)
Comparison with higher dose ICS maintenance therapy					
Rabe et al. (42)	6 months	BUD/FORM maintenance and reliever (2 × 80/4.5 μg q.d.)	354	240 (375)	114
		2 × BUD (2 × 160 μg q.d.) plus SABA	342	320 (500)	498
Scicchitano et al. (43)	12 months	BUD/FORM maintenance and reliever (2 × 160/4.5 μg q.d.)	947	466 (728)	1776
		2 × BUD (2 × 160 μg b.i.d.) plus SABA	943	640 (1000)	3177
Comparison with higher dose ICS or same dose BUD/FORM maintenance therapy					
O'Byrne et al. (35)	12 months	BUD/FORM maintenance and reliever (80/4.5 μg b.i.d.)	925	240 (375)	1255†
		4 × BUD (320 μg b.i.d.) plus SABA	909	640 (1000)	2577†
		BUD/FORM (80/4.5 μg b.i.d.) plus SABA	926	160 (250)	2918†
Comparison with same dose BUD/FORM maintenance therapy					
Rabe et al. (45)	12 months	BUD/FORM (2 × 160/4.5 μg b.i.d.) plus one of the following as reliever:			
		BUD/FORM (160/4.5 μg as needed)	1107	483 (755)	1204
		FORM (4.5 μg as needed)	1137	320 (500)	2063
		SABA (terbutaline 0.4 mg as needed)	1138	320 (500)	2755
Comparison with higher dose ICS/LABA maintenance therapy					
Kuna et al. (44)	6 months	BUD/FORM maintenance and reliever (160/4.5 μg b.i.d.)	1107	483 (755)	619
		Fixed-dose BUD/FORM (320/9 μg b.i.d.) plus SABA	1105	640 (1000)	1044
		Fixed-dose SAL/FLU (2 × 25/125 μg b.i.d.) plus SABA	1123	500 (1000)	1132
Bousquet et al. (47)	6 months	BUD/FORM maintenance and reliever (2 × 160/4.5 μg b.i.d.)	1154	792 (1238)	764
		High-dose SAL/FLU (50/500 μg b.i.d.) plus SABA	1155	1000 (2000)	990
Vogelmeier et al. (46)	12 months	Dose-titration study			
		BUD/FORM maintenance and reliever (permitted dose-titration range: 640/18–320/9 μg daily)	1067	653 (1019)	1980
		SAL/FLU plus SABA (permitted dose-titration range: 100/200–100/1000 μg daily)	1076	583 (1166)	2978

BUD, budesonide; FORM, formoterol; SAL, salmeterol; FLU, fluticasone, SABA, short-acting β_2-agonist; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; BDP, beclomethasone dipropionate.

*Budesonide = BDP equivalent (μg) × 1.5625; fluticasone = BDP equivalent (μg) × 2.0.

†Based on medication log data.

highlights that the median percentage of patients with no reliever days treated with budesonide/formoterol maintenance and reliever therapy was equivalent compared with maximal-dose ICS/LABA plus SABA and slightly lower than with higher fixed-dose ICS/LABA plus SABA (median 58% compared with 61% of patients, respectively, had no reliever use days) (P. Kuna, J. Bousquet, unpublished data). These findings suggest that asthma patients treated with budesonide/formoterol maintenance and reliever therapy do not tend to overuse reliever therapy compared with traditional fixed-dose ICS/LABA. The use of ≤ 4 inhalations of as-needed medication per week is considered to represent the upper limit for well-controlled asthma (12, 48) and can be used as a measure of asthma control (49). Using this definition of asthma control, Buhl and Vogelmeier (49) reported equivalent control with budesonide/formoterol maintenance and reliever therapy compared with fixed-dose ICS/LABA plus SABA. In a dose-titration study, a greater proportion of patients (76% *vs* 66%) achieved well-controlled asthma with budesonide/formoterol maintenance and reliever therapy compared with salmeterol/fluticasone plus SABA, and with higher probability of achieving this level of control (odds ratio 1.68; 95% CI 1.38–2.05; $P < 0.001$) (46).

Periods with high reliever use, indicating poorly controlled asthma, are a risk factor for life-threatening asthma (50). In a study by Bousquet et al. (47), a loss of asthma control, defined as days with >4, >6 and >8 inhalations/day of reliever, occurred in 29%, 13% and 4% of patients, respectively, treated with high-dose salmeterol/fluticasone (100/1000 μg/day) plus SABA, compared with 27%, 9% and 3% of budesonide/formoterol maintenance and reliever therapy-treated patients, respectively. During periods of poor asthma control, budesonide/formoterol maintenance and reliever therapy resulted in a lower incidence of severe exacerbations compared with high-dose salmeterol/fluticasone plus SABA (Fig. 3). Following the first day with high reliever use (>4 inhalations), the rate of severe exacerbations and the rate of hospitalization/emergency room (ER) treatments was significantly reduced with budesonide/formoterol maintenance and reliever therapy compared with high-dose salmeterol/fluticasone plus SABA ($P = 0.0012$ and 0.0037, respectively). These findings further suggest the enhanced protection against exacerbations offered by budesonide/formoterol maintenance and reliever therapy when compared with high-dose salmeterol/fluticasone during periods of worsening.

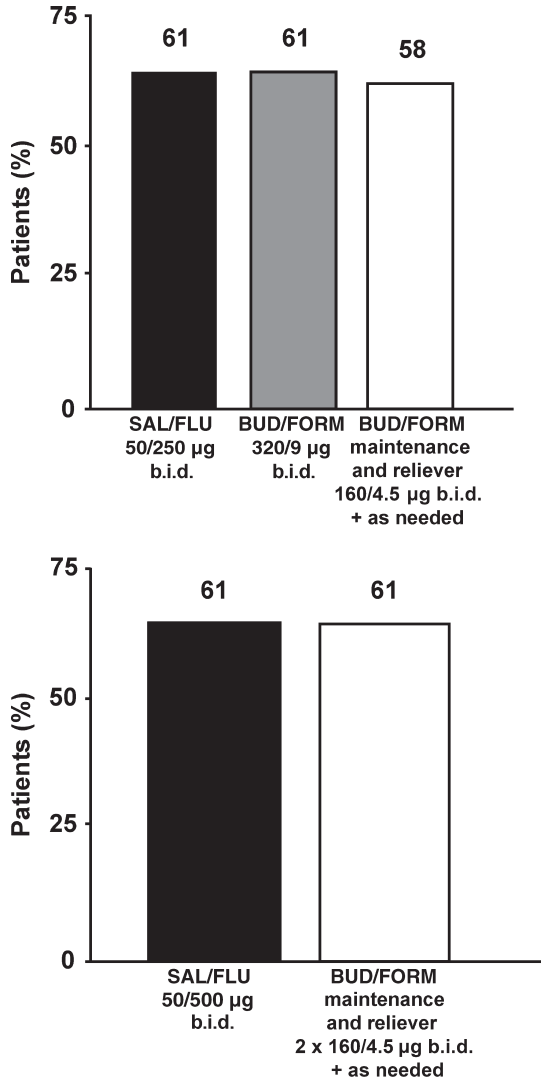

Figure 2. The percentage of asthma patients with no reliever days (median) following treatment with budesonide/formoterol maintenance and reliever therapy (44) and higher fixed-dose ICS/LABA plus SABA as needed (47). SAL/FLU, salmeterol/fluticasone; BUD/FORM, budesonide/formoterol.

Symptom-free days. Compared with two- to fourfold higher doses of ICS, treatment with budesonide/formoterol maintenance and reliever therapy leads to significant increases in symptom-free days (35, 42, 43). Budesonide/formoterol maintenance and reliever therapy was also significantly superior compared with the same dose of budesonide/formoterol plus SABA (35, 45). Compared with higher doses of ICS/LABA plus SABA, similar improvements from baseline in symptom-free days were observed, with no statistically significant difference between treatment groups (44, 47).

Night-time awakenings. Compared with two- to fourfold higher doses of ICS and similar doses of budesonide/formoterol plus SABA, treatment with budesonide/formoterol maintenance and reliever therapy reduces the percentage of nights with awakenings (35, 43, 45). In patients who were all receiving budesonide/formoterol as maintenance, those receiving budesonide/formoterol as needed had reduced night-time awakenings by 3% compared with terbutaline as needed ($P = 0.0025$) and by 2% (equivalent to seven nights per year) ($P = 0.018$) compared with formoterol as needed (45). Similarly, budesonide/formoterol maintenance and reliever therapy significantly reduced night-time awakenings by 20.1% from baseline and this was similar to that achieved with double the maintenance dose of ICS/LABA (18.9%) (47).

Peak expiratory flow. Compared with two- to fourfold higher doses of ICS, treatment with budesonide/formoterol maintenance and reliever therapy leads to significant improvements in morning and evening PEF ($P < 0.001$) (35, 42, 43). Consistent and significant improvements in morning PEF are also observed compared with the same dose of budesonide/formoterol plus SABA in studies conducted by O'Byrne et al. (35) and Rabe et al. (45). The beneficial effects of budesonide/formoterol maintenance and reliever therapy are likely to be due to both the sustained bronchodilatory effect of formoterol as maintenance therapy and the complementary action of as-needed budesonide, as demonstrated by Rabe et al. (45). Compared with higher doses of ICS/LABA plus SABA, similar improvements from baseline in morning and evening PEF were observed (44, 47), with no significant differences between the treatment groups.

Improvements in quality of life. The Asthma Quality of Life Questionnaire (AQLQ) was used to evaluate the impact of budesonide/formoterol maintenance and reliever therapy *vs* comparators on everyday functioning and well-being (51). A change of 0.5 units in AQLQ score from run-in represents a clinically relevant improvement in quality of life (52, 53).

Kuna et al. (44) reported similar clinically relevant improvements in overall AQLQ scores (increases of 0.76–0.78) and in scores from each of the AQLQ domains with budesonide/formoterol maintenance and reliever therapy compared with higher fixed doses of ICS/LABA plus SABA. In a dose-titration study conducted by Vogelmeier et al. (46) designed to mirror the real-life clinical setting, similar and clinically relevant increases in overall AQLQ score from run-in (0.57–0.60) were reported. Changes in AQLQ were not significantly different between the treatment groups.

Preventing future disease risk in asthma

Exacerbations. The time to first severe exacerbation (defined as a deterioration in asthma resulting in hospitalization/ER treatment or the need for oral steroids for ≥ 3 days), the primary end point in almost all clinical trials investigating the efficacy of budesonide/formoterol

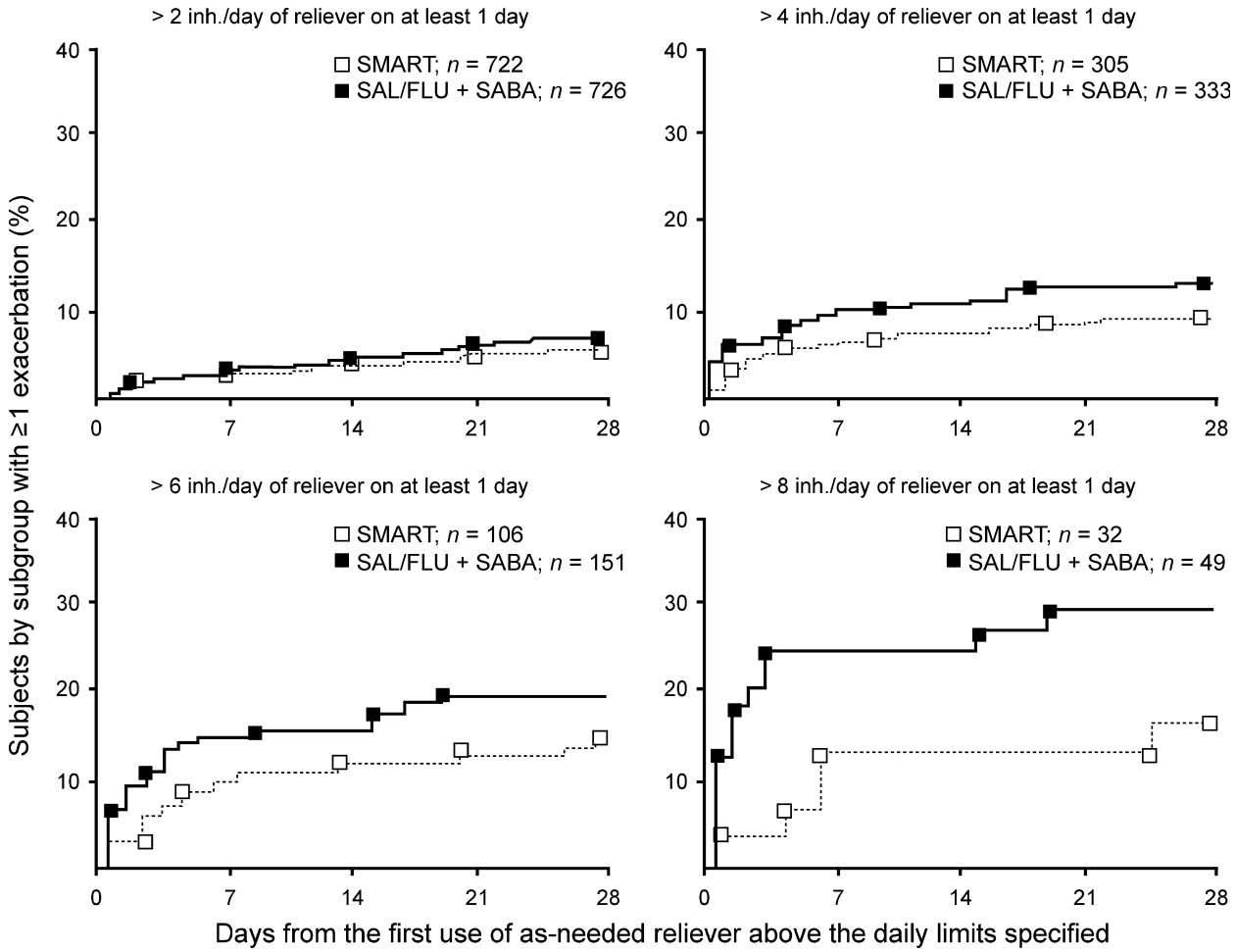

Figure 3. The association between high reliever use and the risk of a severe exacerbation (47). SAL/FLU, salmeterol/fluticasone; SMART, Symbicort maintenance and reliever therapy; inh., inhalation. Reprinted from Bousquet et al. (47); adapted with permission from Elsevier.

maintenance and reliever therapy, is significantly prolonged compared with higher-dose budesonide, the same dose of budesonide/formoterol and higher-dose ICS/LABA plus SABA (35, 42–46). Budesonide/formoterol maintenance and reliever therapy also significantly reduces the rate of severe exacerbations compared with a higher dose of budesonide (35, 42, 43), the same dose of budesonide/formoterol plus SABA (35, 45) and a higher dose of ICS/LABA plus SABA (44, 47), and compared with salmeterol/fluticasone in a dose-titration study, by 21–76% (46).

Looking at the most severe end of the spectrum of asthma exacerbations leading to hospitalization/ER treatment, the rate was also significantly reduced with budesonide/formoterol maintenance and reliever therapy compared with comparator therapies (42, 44, 45, 47) (Fig. 4). Rabe et al. (45) reported that the rate of severe exacerbations requiring hospitalization/ER treatments was reduced with as-needed budesonide/formoterol by 27% compared with formoterol and by 39% compared with terbutaline, suggesting that both the formoterol and the budesonide component of reliever therapy contributes substantially to preventing the most severe asthma exacerbations. Kuna et al. (44) reported a significant 39% reduction in the rate of hospitalization/ER treatments compared with fixed-dose (50/250 μg b.i.d.) salmeterol/fluticasone plus SABA ($P = 0.0015$), while Bousquet et al. (47) observed a 31% reduction compared with the highest approved dose of salmeterol/fluticasone plus SABA (100/1000 μg/day; $P = 0.046$).

Drug load. Physicians may have concerns about increased steroid load with budesonide/formoterol maintenance and reliever therapy. However, the reductions in severe exacerbations and similar improvements in daily asthma control observed with budesonide/formoterol maintenance and reliever therapy compared with other treatment options are achieved at a lower steroid load (Table 1) (42–44, 47). To facilitate comparisons, the range of mean daily BDP-equivalent ICS doses was calculated based on GINA estimations of equipotence of ICS in metered doses: fluticasone 500 μg = budesonide

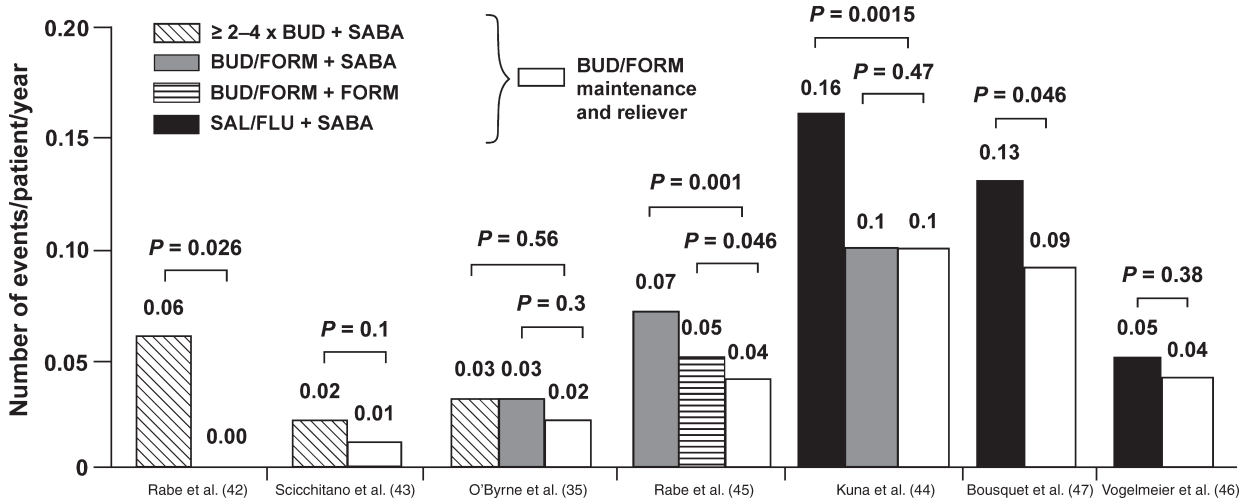

Figure 4. The incidence of severe asthma exacerbations leading to hospitalization/ER treatment with budesonide/formoterol maintenance and reliever therapy compared with higher ICS and similar or higher doses of ICS/LABA plus SABA (35, 42–47). BUD, budesonide; SAL/FLU, salmeterol/fluticasone; BUD/FORM, budesonide/formoterol; SABA, short-acting β_2-agonist.

800 μg = BDP 1000 μg (1). In the study by Kuna et al. (44), patients treated with budesonide/formoterol maintenance and reliever therapy had a significantly lower ICS dose compared with fixed-dose salmeterol/fluticasone and fixed-dose budesonide/formoterol (mean BDP-equivalent doses of 755, 1000 and 1000 μg, respectively; $P < 0.001$). In another study, BDP-equivalent doses were significantly reduced by 38% with budesonide/formoterol maintenance and reliever therapy compared with high-dose salmeterol/fluticasone (1238 and 2000 μg, respectively; $P < 0.0001$) (47). In the dose-titration study by Vogelmeier et al. (46), patients treated with budesonide/formoterol maintenance and reliever therapy and salmeterol/fluticasone had average BDP-equivalent doses of 1019 and 1166 μg/day, respectively. Compared with fourfold higher doses of ICS, budesonide/formoterol maintenance and reliever therapy resulted in fewer courses of oral steroids (35). With budesonide/formoterol maintenance and reliever therapy, despite using a lower maintenance dose with this regimen (160/4.5 μg b.i.d.) the overall number of days with oral steroids was lower than that with either a higher fixed dose of budesonide/formoterol of 320/9 μg b.i.d. plus SABA or salmeterol/fluticasone 50/250 μg b.i.d. plus SABA (619, 1044 and 1132 days, respectively) (44). Compared with high-dose salmeterol/fluticasone (50/500 μg b.i.d.) there was also a reduction in the need for oral steroids in patients receiving budesonide/formoterol maintenance and reliever therapy (990 and 764 days, respectively) (47).

Safety of budesonide/formoterol maintenance and reliever therapy

Overall, clinical studies have shown that budesonide/formoterol maintenance and reliever therapy is well tolerated (35, 42–45, 47). The incidence, frequency and severity of adverse events for budesonide/formoterol used as maintenance and reliever therapy has been reported as the same as for budesonide/formoterol fixed maintenance treatment, with the exceptions of fewer discontinuations and severe adverse events because of asthma with maintenance and reliever therapy (35, 42–45, 47). The most frequently reported adverse events were respiratory tract infections (35, 42–44). In addition, fewer patients receiving budesonide/formoterol maintenance and reliever therapy discontinued treatment because of adverse events (35, 43, 45, 47).

In recent years, concerns have been raised regarding the safety of LABA (salmeterol and formoterol) use in asthma patients (54, 55). In the Salmeterol Multicenter Asthma Research Trial, an increase in asthma-related mortality was observed with salmeterol compared with placebo when added to other asthma therapy. However, the design of this study has been criticized for not ensuring proper anti-inflammatory treatment, and also follow-up of concomitant medication was not conducted. A recent meta-analysis conducted by Salpeter et al. (55), where the majority of patients were from the previous study, reported an association between formoterol use and an increase in severe and life-threatening asthma exacerbations. A previous case–control study observed no adverse impact of medium- to long-term use of LABAs on mortality (56). A meta-analysis including 18 double-blind studies (17 of which were not included in the Salpeter meta-analysis) and 12 229 participants, where formoterol was used in combination with an ICS, reported a 29% reduction in hospital admissions and a 31% reduction in asthma-related serious adverse events with formoterol plus ICS compared with ICS alone (57). Another analysis of a large number of studies of formoterol reported that the use of this medication in

asthma patients mostly using ICS is associated with a reduction in serious adverse asthma events, and not associated with any significant increase in asthma-related deaths, of which there was a very low number (58). However, overuse of SABA or LABA without concomitant ICS can result in under-treatment of the inflammatory process associated with asthma and should, therefore, be avoided as the effective LABA-induced bronchodilation could mask underlying inflammation and so lead to the development of more severe and potentially life-threatening exacerbations (23, 49).

Why does this treatment approach offer benefits in asthma control and prevent future risk?

The exact mechanism for the beneficial effects of budesonide/formoterol maintenance and reliever therapy has yet to be fully elucidated. The defining feature of this treatment is the simultaneous administration of an additional dose of ICS (budesonide) in combination with every inhalation of reliever medication (formoterol), which allows the patient to gain symptomatic relief alongside an additional dose of ICS to attenuate the inflammatory response. The main difference between budesonide/formoterol maintenance and reliever therapy and fixed-dose ICS/LABA plus SABA is the way in which the ICS and LABA medications are used. The treatment strategy means that, as well as a regular maintenance ICS/LABA dose, an additional dose is given when symptoms appear, and further ICS/LABA doses are given if symptoms persist. This leads to an early intervention with increased treatment, and also to increased frequency of dosing during times of worsenings. All these features may contribute to the effectiveness of budesonide/formoterol maintenance and reliever therapy. Budesonide and formoterol are reported to have a synergistic relationship whereby their combined effects are complementary and additive (23, 59, 60), most likely contributing to the efficacy of this treatment approach (Fig. 5A,B).

Corticosteroids are known to rapidly reduce inflammation. Following binding to glucocorticoid receptors (GR) in the cell cytoplasm, translocation to the cell nucleus leads to activation of glucocorticoid response elements, recognition sites on the promoter regions of some genes which are activated by interaction with a GR (23, 59, 60) (Fig. 5A). This leads to upregulated expression of the β_2-receptor *in vitro* (61). Corticosteroids can also prevent the tolerance that can occur in response to prolonged administration of β_2-agonists (62) and reverse the uncoupling of β_2-receptors that occurs subsequent to β_2-agonist administration (63). In smooth muscle, the dose-related bronchoprotection provided by formoterol compared with salmeterol may be an important added benefit of this LABA (39), particularly during an exacerbation where there is an increase in airway tone caused by cytokine-mediated bronchoconstriction. In addition,

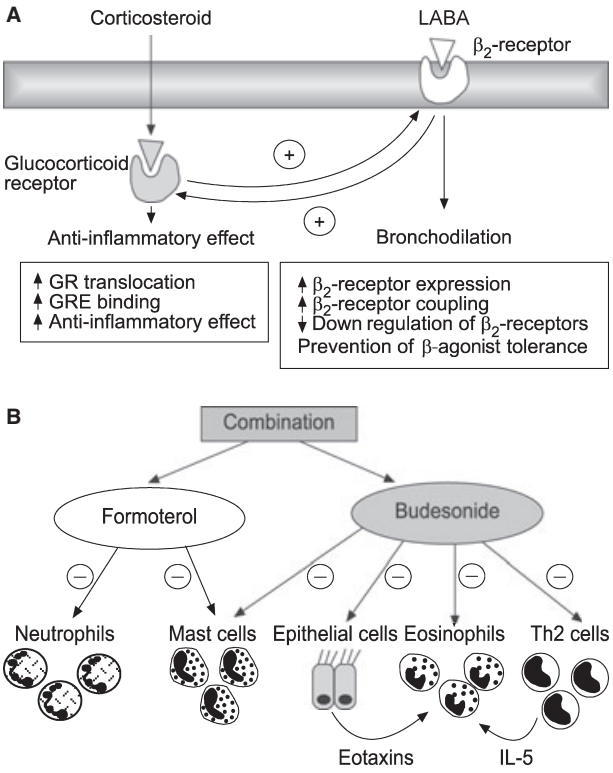

Figure 5. Interactions between corticosteroids and LABA relevant to the use of budesonide/formoterol as maintenance and reliever (A) and the anti-inflammatory effect of budesonide/formoterol maintenance and reliever therapy (B) (23). GR, glucocorticoid receptor; GRE, glucocorticoid response element; LABA, long-acting β_2-agonist; IL, interleukin; Th2, helper T cells. Reprinted from Barnes (23); adapted with permission from European Respiratory Society Journals.

the benefits of a stronger agonist on inflammatory cells such as mast cells and neutrophils which have few functioning receptors may also be important (23, 64) (Fig. 5B). Corticosteroids also reduce inflammation via effects on cell signalling. The suppression of inflammatory genes, which have been activated by pro-inflammatory transcription factors, is the principal anti-inflammatory action of corticosteroids, and *in vitro* time-course studies have reported that these actions occur within minutes. Budesonide has an array of other non-genomic effects, including rapid vasoconstriction (within 30 min), resulting in a reduction in airway oedema (23, 65, 66). Evidence shows that a single dose of budesonide significantly decreases sputum eosinophils in as little as 6 h (67) and reduces the level of nitric oxide in exhaled air (68), raised levels of which are predictive of loss of asthma control (69). Single doses of budesonide/formoterol protect against late-phase bronchial hyper-responsiveness provoked by allergens; this bronchoprotective/airway-stabilizing effect was not seen with budesonide and formoterol monotherapies (70). Sears et al. conducted a study in a subgroup of patients to examine the changes in induced sputum eosinophil count in patients receiving

budesonide/formoterol maintenance and reliever therapy (160/4.5 μg b.i.d.) compared with conventional best practice and concluded that budesonide/formoterol maintenance and reliever therapy achieved similar control of eosinophilic inflammation compared with conventional best practice, despite a lower mean ICS dose (71) (Fig. 6).

The rapid and sustained effects of formoterol on bronchodilation/bronchoprotection are well documented and have been mentioned earlier in this review (39, 40). Other positive effects reported with LABAs include a reduction in the airway oedema that can occur during an asthma exacerbation by relaxing the endothelial cells (72), inhibition of the release of bronchoconstrictors, such as histamines, from mast cells (73) and beneficial effects on neutrophilic inflammation (23) (Fig. 5B). LABAs can also enhance the translocation of the GR from the cytoplasm into the cell nucleus, where the attached corticosteroid exerts its anti-inflammatory effects (74), and also promote the anti-inflammatory effects of corticosteroids in airway smooth muscle cells (75). The interaction between the two components may provide part of the explanation for the positive effects observed when budesonide/formoterol is used as both maintenance and reliever therapy.

Practical considerations for physicians using budesonide/formoterol maintenance and reliever therapy in clinical practice

Which patients are suitable for treatment with budesonide/formoterol maintenance and reliever therapy?

Budesonide/formoterol maintenance and reliever therapy is recommended by the GINA guidelines for the treatment of patients with moderate to severe disease that is uncontrolled with ICS (1). Thus, this treatment approach should be considered in any patient who requires combination treatment with an ICS/LABA. Budesonide/formoterol maintenance and reliever therapy for use in a Turbuhaler is approved in more than 85 countries. The patient age group in which budesonide/formoterol maintenance and reliever therapy is approved varies between countries. Two doses of budesonide/formoterol are approved for use as maintenance and reliever therapy: 160/4.5 and 80/4.5 μg per inhalation. Budesonide/formoterol 320/9 μg per inhalation is not approved or recommended for use with this treatment approach. A maintenance dose of one inhalation b.i.d. (35) or two inhalations once daily (42, 43) has been reported to be highly effective compared with higher doses of ICS alone in patients with moderate to severe asthma. Two inhalations b.i.d. may also be prescribed for some patients with more severe asthma (47). Additional inhalations for symptom relief are taken in the same way as patients have previously used their SABA. More than eight inhalations as total daily dose is not normally needed, but a dose of up to 12 inhalations per day could be used temporarily. As previously mentioned, patients should be educated to take their maintenance medication daily, even when they feel well. Patients should take one additional inhalation as needed in response to symptoms. If symptoms persist for more than a few minutes, an additional inhalation should be taken. These instructions should be discussed with patients and, where possible, it is recommended that a personalized written action plan is also provided, as advocated with other asthma management approaches (76). As discussed earlier, budesonide/formoterol 80/4.5 and 160/4.5 μg pMDIs are approved for use in some countries, including the USA, as fixed-dose therapy for asthma. However, the pMDI delivery device has not been studied and the double actuation results in 9 μg of formoterol per dose, which makes it unsuitable for use as maintenance and reliever therapy, which is currently approved for use with the Turbuhaler.

During pregnancy and lactation budesonide/formoterol should only be used after special consideration, particularly during the first 3 months and shortly before delivery (77). Fält et al. (78) reported that in asthmatic women maintenance treatment with budesonide (200 or 400 μg b.i.d.) results in negligible systemic exposure of breast-fed infants. Reliever inhalations of budesonide/formoterol should be taken in response to asthma symptoms but are not intended for regular prophylactic use, for example before exercise. Patients less suitable for budesonide/formoterol maintenance and reliever therapy may include those who are prone to habitual unnecessary high reliever use (79). Furthermore, physicians need to be aware of a small group of patients who may not perceive symptoms or use too little reliever therapy and thus may require lung function testing to guide therapy. For these

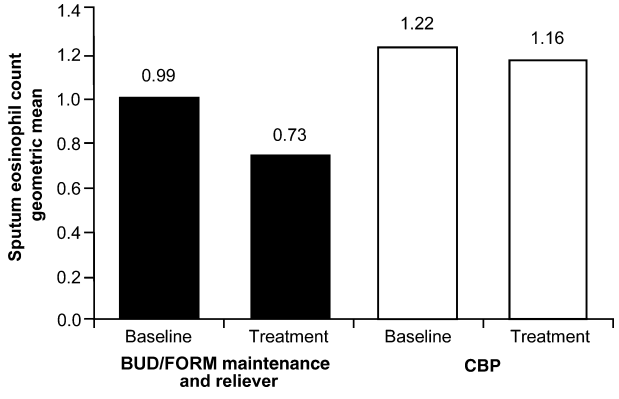

Figure 6. Change in sputum eosinophil count in patients receiving budesonide/formoterol as maintenance and reliever therapy or conventional best practice (71). Patients in the budesonide/formoterol maintenance and reliever therapy group received 748 μg/day ICS in BDP equivalents and patients in the conventional best practice (CBP) treatment group received 1015 μg/day ICS in BDP equivalents ($P < 0.0001$). Reprinted from Sears et al. (71); adapted with permission from European Respiratory Society Journals. BUD/FORM, budesonide/formoterol.

patients, the most important factor may be optimizing the dosage of maintenance medication.

Cost-effectiveness of budesonide/formoterol maintenance and reliever therapy

Health economic analyses of clinical trials using budesonide/formoterol maintenance and reliever therapy have indicated its efficacy and cost-effectiveness (80–82). In a study designed to reflect routine clinical practice, this treatment option provided a reduction in the number of severe exacerbations at no significant increase in costs compared with dose titration of salmeterol/fluticasone plus SABA when unit costs for Germany, France, the UK and Italy were applied (81). Cost-effectiveness of budesonide/formoterol maintenance and reliever therapy has also been demonstrated in comparison with higher fixed-dose ICS/LABA plus SABA (80). In this study, the application of UK unit costs or Australian costs to pooled resource use data demonstrated that the incidence of severe exacerbations was reduced at a lower cost compared with fixed-dose ICS/LABA plus SABA (80). Bousquet et al. (82) also observed that the maximum approved dose of budesonide/formoterol maintenance and reliever therapy leads to reduced healthcare and total costs compared with the maximum approved dose of salmeterol/fluticasone when Canadian and Spanish unit costs are applied.

Conclusion

With traditional asthma treatment options, patients with moderate to severe asthma are often suboptimally controlled and overuse SABAs without adjusting maintenance therapy. As a result, levels of SABA use far exceed guideline targets despite prescription of effective maintenance therapies. Studies have consistently reported increased use of SABA during the period of asthma worsening that precedes an exacerbation. However, overuse of SABA may mask the underlying inflammation of asthma. Budesonide/formoterol maintenance and reliever therapy is a very effective, simple and flexible treatment option for patients with moderate to severe asthma. By providing an additional dose of ICS with every inhalation of reliever therapy, it targets the loss of anti-inflammatory control during a 'window of opportunity' when deterioration in asthma symptoms is experienced, thus providing added protection against exacerbations. In addition, budesonide/formoterol maintenance and reliever therapy is an effective and well-tolerated treatment which provides improvements in asthma control, minimizing impairment to daily life caused by symptoms and reducing future risk by preventing exacerbations and by avoiding unnecessary increases in maintenance therapy. The evidence suggests that budesonide/formoterol used as maintenance and reliever for patients with moderate to severe asthma represents an important addition to the therapeutic tools currently available to physicians and patients for the effective management of asthma.

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Conflicts of interest

MH received reimbursement for attending scientific conferences and/or fees for speaking and/or consulting from Altana, AstraZeneca, Bayer Schering, Chiesi, GlaxoSmithKline, Merck, Sharp & Dohme, Novartis and Pfizer. RB has received reimbursement for attending scientific conferences, and/or fees for speaking and/or consulting from Aerocrine, Altana, AstraZeneca, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Pfizer and Zambon. The Pulmonary Department at Mainz University Hospital received financial compensation for services performed during participation in single- and multicentre clinical Phase I–IV trials organized by various pharmaceutical companies. TA is employed by AstraZeneca and hold shares in the company.

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