Budesonide/formoterol for maintenance and reliever therapy: new quality in asthma management

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Asthma is a chronic inflammatory disease of the airways with variable symptoms and airway obstruction. The strategy of asthma management aims to prevent and relieve acute attacks and achieve long-term control of symptoms. Symbicort® is a fixed combination of the corticosteroid budesonide and the long-acting β_2-agonist formoterol – the first component treats inflammation, the second provides rapid and long-term smooth muscle relaxation. These two components make budesonide/formoterol suitable for both maintenance and reliever asthma therapy (Symbicort SMART®). There is increasing evidence from clinical trials that such a regimen is an effective and safe treatment option. The patient taking budesonide/formoterol for symptom relief simultaneously increases the dose of inhaled corticosteroids. Therefore, the pharmacological intervention provides an earlier step up in controller therapy, just prior to asthma deterioration, and thus prevents exacerbations. Such a regimen better reflects the nature of asthma and allows patients to match the anti-inflammatory dose to the patient's actual clinical state. Moreover, SMART is a more convenient regimen for patients and may increase therapy compliance. SMART is a new quality in asthma management and may become the future gold standard in asthma treatment.

Asthma is a chronic lung disease that affects people all over the world regardless of age, gender or race. It is responsible for considerable restrictions in the physical, emotional and social aspects of life for sufferers and their families.

The WHO estimates that currently 300 million people suffer from asthma, and 255,000 die as a result of this disease every year [101]. At present, it is impossible to cure asthma, but effective treatment can minimize its influence on patient life by reducing daytime and nocturnal symptoms and stabilizing control. Achieving asthma control means a reduction of a need for relief medication, maintenance of normal activity levels, including exercise, preservation of normal lung function and prevention of exacerbations. In recent years, we have achieved a better understanding of the pathological mechanisms involved in asthma. This knowledge has made it possible to develop more effective drugs and better strategies for asthma management.

Asthma is a chronic dynamic inflammatory disorder of the airways, resulting in various symptoms of airway limitation. The current strategy of asthma management is based on prevention and relief of acute attacks and achieving long-term stable control. Effective therapy relies on the treatment of both asthma components: inflammation and bronchial constriction. Two types of medicine are used in asthma treatment: controllers and relievers. Controllers are characterized by anti-inflammatory effect and are usually required on a regular basis. Relievers are medications used 'as needed' to reverse bronchoconstriction and relieve symptoms.

Glucocorticosteroids are currently the most effective anti-inflammatory medication for the treatment of asthma. When administered by an inhalatory route, they are safe and usually well tolerated. Rapid-acting β_2-agonists are first-line relievers in asthma management. These drugs form the basis of management in all persistent asthma, regardless of the stage of severity and asthma control. The goal of long-term asthma management is to achieve complete control of symptoms and prevention of exacerbations. When asthma is not optimally controlled on low-dose inhaled corticosteroids (ICS), the next recommended step is the addition of long-acting β_2-agonists (LABA) for regular use. Such a course of action improves the effectiveness of ICS, and even allows for dose reduction without worsening asthma control [1,2].

Synergistic effect of budesonide & formoterol combination

There is increasing evidence that concurrent use of ICS and LABA provides a synergistic, or at least additive, effect on airway inflammation, by increasing the effectiveness of ICS therapy at

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lower doses, increasing smooth muscle relaxation due to increased efficiency of the β_2-agonist signaling pathway [3]. This positive interaction leads to an increase in the effectiveness and safety of anti-asthmatic treatment.

Changes on a molecular level

Effects of ICS on β_2-receptors & nongenomic vascular ICS effect on LABA disposal by smooth muscle cells

Budesonide acts by way of a cytoplasmatic glucocorticoid receptor (GR), to which it binds after passing through the cell membrane. Next, the activated complex moves to the nucleus and interacts with DNA and various transcriptional factors. This inhibits the synthesis of pro-inflammatory factors, and induces anti-inflammatory factors and the transcription of β_2-receptor genes. Mak *et al.* observed that the activation of GR increased β_2-receptor mRNA levels and the number of β_2-receptors in human peripheral lung *in vitro* [4]. Baraniuk *et al.* showed that ICS increased β_2-receptor mRNA levels *in vitro* and *in vivo*, and also increased β_2-receptor function as assessed by submucosal gland exocytosis *in vitro* [5]. The effect of corticosteroids on β_2-receptor expression occurs within only a few hours. In animal studies, corticosteroids prevent the downregulation of lung β_2-receptors [6]. Such an effect may have clinical implications for preventing the development of tolerance to β_2-agonists in long-term administration. Horvath *et al.* studied the uptake of LABA bronchodilators by bronchial and vascular smooth muscle cells [7]. They found that corticosteroids, through organic cation transporter inhibition (inhibitory potency: corticosterone > budesonide > fluticasone), rapidly interfere with the disposal of cationic formoterol by smooth muscle cells in the airway. This immediate nongenomic interaction between budesonide and formoterol may have clinical implications.

Effect of β_2-receptor on corticosteroid response

Formoterol acts by means of the β_2-membrane receptor. Stimulation of this receptor increases intracellular cAMP levels, which activates protein kinases responsible for smooth muscle relaxation. Eickelberg *et al.* have shown that β_2-agonists could, *in vitro*, activate the GR and augment ICS effects [8]. Roth *et al.* confirmed this observation in an *in vivo* study [9]. They demonstrated that inhaled formoterol induced translocation of the GR from the cytoplasm to the nucleus, and binding of the GR to glucocorticoid response elements, and activated *p21* gene expression in circulating peripheral blood leukocytes. In a separate study, involving bronchial smooth muscle cells, the same group of investigators obtained similar results. In addition to this, they demonstrated that budesonide and formoterol reduced proliferation of these cells via GR-mediated activation of the *p21* gene [8].

Anti-inflammatory effect of the budesonide & formoterol combination

Korn *et al.* showed that, when administered together, budesonide and formoterol decreased GM-CSF levels in cultured human bronchial epithelial cells *in vitro*, and that the effect was stronger than when these drugs were used separately [10]. Spoelstra *et al.* observed similar effects in human lung fibroblast cultures [11]. Both drugs individually inhibited upregulation of ICAM-1, VCAM-1 and GM-CSF production induced by IL-1β. A greater inhibitory effect was seen when co-administered.

Anti-remodeling effect of the budesonide & formoterol combination

Proteoglycans contribute to extracellular matrix remodeling in asthmatic airways. Todorova *et al.* demonstrated that total proteoglycan production in cultured human lung fibroblasts is modestly inhibited by budesonide, and that this effect is synergistically enhanced [12]. The combination of budesonide and formoterol is more efficient than either drug alone in the inhibition of versican, biglycan and perlecan (proteoglycans known as markers of an early inflammatory ECM), as well as decorin (which is usually upregulated in the more fibrotic ECM). The drug effects were exerted primarily at the post-transcriptional level.

These results obtained *in vitro* must be confirmed in clinical studies. These data suggest that the simultaneous use of ICS and LABA ensures a more effective and safer therapy. This effect has been demonstrated in clinical studies.

Clinical studies on the concurrent use of budesonide & formoterol

The Formoterol and Corticosteroids Establishing Therapy (FACET) study by Pauwels *et al.* was the first study to demonstrate the complimentary effect of combining budesonide and formoterol for clinical use on important outcome measures such as asthma exacerbations [1]. In this study, formoterol 12 µg twice daily was

added to either budesonide 100 or 400 µg twice daily for patients with moderate asthma over a 12-month period. The combination of formoterol and budesonide reduced the rate of severe and mild exacerbations by a greater extent than budesonide alone. Improvement in lung function and symptoms achieved by the budesonide and formoterol group was greater than that observed after a fourfold increase in the budesonide dose alone. The addition of formoterol to the higher dose of budesonide was the most effective option for reducing severe exacerbations (the rate decreased by 63%). Such a combination also significantly improved health-related quality of life (HRQoL). This benefit was sustained over 12 months [13] and resulted in a decrease in the cost of asthma exacerbation treatment [14].

The benefits of combined formoterol and budesonide therapy at lower doses have been confirmed in the OPTIMA study by O'Byrne *et al.* [2]. In patients with mild persistent asthma who were already receiving ICS, the addition of formoterol to a low dose of budesonide reduced the risk of severe exacerbations and improved lung function and symptoms to a greater extent than doubling the dose of budesonide alone. The treatment of corticosteroid-naive patients with budesonide and formoterol resulted in better lung function than with budesonide alone, but did not provide an additional effect on the rate of severe exacerbations over that obtained with ICS alone. More recently, it has been shown that in steroid-naive patients the added benefits of the combination therapy over ICS alone on symptoms relates to the duration of time since asthma diagnosis, with combination therapy having superior benefits over ICS alone if asthma has been present for several years [15].

Some doubts emerged concerning the regular use of LABA, and whether this masked inflammation by inhibiting symptoms that, when present, are the signal to intensify treatment. Kips *et al.* investigated the influence of budesonide and formoterol combination on inflammatory markers [16]. After 1 year of treatment, the number of eosinophils and other inflammatory cells in induced sputum did not differ significantly between patients receiving lower doses of budesonide with formoterol and those treated with a higher dose of budesonide alone. In addition, Tattersfield *et al.* reviewed the profile of 425 exacerbations in the FACET study and showed that patients treated with LABA had fewer severe exacerbations. These exacerbations that did occur on combination therapy were no more severe than on budesonide alone – thus, adding formoterol to ICS did not mask inflammation in a manner that would increase the severity of exacerbation when they did occur [17]. These findings indicate that concurrent administration of budesonide and formoterol does not mask increased airway inflammation, even during periods of exacerbation.

Budesonide/formoterol in maintenance therapy

The greater efficacy of combination treatment has led to the development of fixed-dose combination inhalers, which combine both medications and deliver them simultaneously. Such a form of drug administration greatly simplifies the treatment plan and is more convenient for patients.

Symbicort® is an inhaler containing budesonide, a corticosteroid with a potent and prolonged anti-inflammatory effect, and formoterol, a potent and selective β_2-agonist with a unique profile: a rapid onset of effect and a long duration of action.

In a 12-week double-blind, randomized, double-dummy study, Zetterström *et al.* compared the efficacy and safety of budesonide/formoterol in the fixed combination (160/4.5 µg, two inhalations twice daily), with corresponding doses delivered via separate inhalers and with budesonide alone [18]. Both budesonide/formoterol combination treatments, fixed and separate inhalers, resulted in a statistically significant improvement in lung function, symptoms and asthma control days, which was greater than budesonide alone. There was no significant difference in effectiveness between budesonide/formoterol and budesonide plus formoterol therapy at the end of the study. However, during the first 30 days of treatment, budesonide/formoterol tended to show a more rapid improvement in lung function and asthma symptoms than its separate components administered concurrently.

In addition to this, several other clinical studies have shown the greater effectiveness of budesonide/formoterol compared with higher doses of corticosteroids. In the study performed by Lalloo *et al.,* budesonide/formoterol (80/4.5 µg twice daily) was compared with a twofold higher dose of budesonide alone in the treatment of patients with mild to moderate asthma [19]. After 12 weeks of treatment, patients receiving budesonide/formoterol showed a greater improvement in lung function and relief of asthma symptoms, as well as a reduction of mild asthma exacerbations, when compared with budesonide alone.

Bateman *et al.* obtained similar results when budesonide/formoterol (160/4.5 µg twice daily) was compared with a higher dose of fluticasone

(250 µg twice daily) in patients with moderate asthma after 12 weeks of treatment [20]. Budesonide/formoterol provided greater improvement in lung function and better asthma control than fluticasone.

Eliraz *et al.* compared the effectiveness of an even lower dose of budesonide/formoterol (80/4.5 µg twice daily) with fluticasone (250 µg twice daily) in steroid-free patients with mild persistent asthma [21]. Budesonide/formoterol provided significantly faster and greater improvement in morning and evening peak expiratory flow (PEF).

The budesonide/formoterol fixed combination is equally effective when administered twice or once daily. Two studies by Buhl *et al.* [22] and Kuna *et al.* [23] have both demonstrated that budesonide/formoterol (160/4.5 and 80/4.5 µg in two inhalations, respectively) administered once daily in the evening is just as effective as equal doses of budesonide/formoterol given twice daily in improving morning lung function, relief of symptoms, use of relievers and number of asthma control days. Likewise, it is also more effective than budesonide alone used once daily.

Budesonide/formoterol as needed in acute symptoms

Clinically, asthma manifests as episodes of chest tightness, dyspnea, wheezing and cough caused by bronchoconstriction. Therefore, patients require medications that can quickly reverse bronchial obstruction and relieve symptoms.

Formoterol is a unique LABA with a characteristic rapid onset of action. The bronchodilatory effect appears within 1–3 min after inhalation, which is comparable with short-acting β_2-agonists (SABA), such as terbutaline [24] and salbutamol [25]. The effectiveness of formoterol in relief of acute airway obstruction was investigated in a methacholine-induced bronchoconstriction model by Politiek *et al.* [26]. They found that a single 9-µg dose of formoterol reversed severe acute airway obstruction induced by methacholine as rapidly as salbutamol and significantly faster than salmeterol – a LABA.

The effectiveness and safety of formoterol at high doses in the treatment of acute severe airway obstruction was first investigated by Malolepszy *et al.* [27]. Adult asthma and chronic obstructive pulmonary disease patients who had been admitted to intensive care units with acute severe bronchoconstriction (FEV_1 was 20–50% of predicted value) were randomized to receive 20 inhalations of either formoterol (4.5 µg) or terbutaline (0.5 mg) within the first 3 h of therapy. After 90 min, each patient also received methylprednisolone 40 µg intravenously. High doses of formoterol were equally effective as terbutaline with respect to lung function improvement, and were well tolerated by patients. Formoterol therapy resulted in significantly lower pulse rates than with terbutaline, which confirmed the safety profile of formoterol administered in high doses. Similar studies have also been performed comparing formoterol with salbutamol in an emergency setting [28]. In this study, formoterol 54 µg versus salbutamol 3600 µg provided a greater acute lung function improvement obtained over the 4-h assessment period.

The reason for a greater response to formoterol is that it is a strong agonist with defined dose-dependent effects when used in combination with steroids, as demonstrated in the study by Schreurs *et al.* on patients with moderate asthma [29]. Formoterol produced a dose-dependent increase in PEF and a reduction in the use of relievers when taken in doses of 6, 12 and 24 µg.

The effectiveness of formoterol used 'as needed' in long-term treatment was investigated by Tattersfield *et al.* [30]. Patients with poorly controlled asthma by ICS were randomized to receive either formoterol or terbutaline as their relief medication. After a 3-month study, morning and evening PEF and the percentage of patients free from severe exacerbations were significantly higher in the formoterol group. Patients in the formoterol group also required significantly less relief medication than patients using terbutaline and had a better quality of life (QoL) [31]. In the OZON study by Cheung *et al.*, as-needed formoterol was compared with salbutamol [32]. This cross-over study revealed that as-needed formoterol better improved symptoms and lung function than salbutamol, and was perceived by patients to be more effective and at least as fast acting for symptom relief. Moreover, a greater number of patients (68% of the study group) preferred the formoterol treatment to salbutamol.

Traditionally, it has been the belief that ICS have a slow onset of action. For instance, reduced airway hyper-resposiveness takes several months; however, other signs of clinical response, such as improvement of nocturnal and daytime symptoms and PEF, occur after several days. More recent studies have shown that some aspects of ICS action may produce a relatively rapid effect.

The rapid anti-inflammatory action of ICS was demonstrated with a single high dose of inhaled budesonide (2400 µg) [33]. In patients with mild asthma, a significant reduction in sputum eosinophils and increased protection against hypertonic saline-induced bronchoconstriction was observed as early as 6 h after budesonide inhalation.

The benefits of increasing budesonide dose and dose frequency with increased symptoms suggestive of an asthma exacerbation were shown in the study by Foresi *et al.* [34]. In this study, patients received maintenance treatment with budesonide 100 µg twice daily. On presenting the first signs of asthma exacerbation (i.e., 30% fall in PEF on 2 consecutive days) they were given either extra inhalations of budesonide to a total daily dose of 1000 µg, the extra dose given as 200 µg four-times daily, or placebo four-times daily for 7 days. Increasing the dose of budesonide resulted in a reduction of incidence and duration of asthma exacerbations and the need for oral corticosteroid (OCS) treatment when compared with placebo. Moreover, treatment with low doses of budesonide, which were increased during deterioration of asthma, reduced the need for OCS to the same extent as maintenance treatment with a fourfold higher dose of budesonide maintained for 6 months.

The acute effect of budesonide was also studied by Ellul-Micallef *et al.* [35]. Investigators observed the response to a single inhaled dose of budesonide, expressed as a change in morning PEF. They noticed a dose-dependent increase in morning PEF after inhalation of budesonide in doses from 100 to 1600 µg. The inhalation of budesonide 400 and 1600 µg caused significant increase in PEF after only 1 h, which persisted at 12 h. The rapid-onset effects may relate to the nongenomic effects of ICS [36].

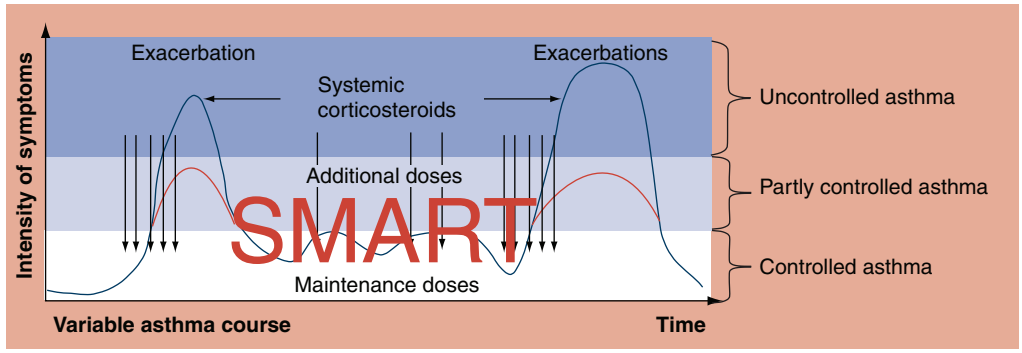
As shown, both budesonide and formoterol show early onset of action and dose-dependent effects. Dose increase of either formoterol or budesonide, in response to asthma deterioration, results in a reduction of the incidence and duration of asthma exacerbation. Since budesonide/formoterol is a combination of these two drugs, it may have a similar or even greater synergistic effect.

The effectiveness of budesonide/formoterol combination in the relief of acute metacholine-induced bronchoconstriction and asthma symptoms was proven in the study by van der Woude *et al.* [37]. In this study, the effect of budesonide/formoterol was compared with salmeterol/fluticasone and placebo. Median recovery times to 85% of baseline FEV_1 were shorter for budesonide/formoterol (one or two inhalations: 3.3 and 2.8 min, respectively) than salmeterol/fluticasone (8.9 min; $p < 0.001$) and placebo (>30 min). Patient-perceived relief from dyspnea following budesonide/formoterol was significantly greater (Borg score -0.86 units, both doses) compared with salmeterol/fluticasone (-0.55 units; $p < 0.05$) and placebo (-0.23 units; $p < 0.001$) 1 min after inhalation. Budesonide/formoterol provides immediate bronchodilation relief of symptoms, faster than salmeterol/fluticasone, in patients with acute methacholine-induced bronchoconstriction. Balanag *et al.* confirmed an equivalent bronchodilatory effect of budesonide/formoterol fixed combination compared with high doses of salbutamol in treating acute asthma [38]. High-dose budesonide/formoterol (total dose: 1280/36 µg) was effective and well tolerated for the treatment of acute asthma, with a rapid onset of efficacy and a safety profile over 3 h that is similar to that of high-dose salbutamol.

Clinical studies on budesonide/formoterol in the SMART regimen

The aim of asthma treatment is to achieve disease control and prevent progression. Clinically, asthma is characterized by stable periods with episodic exacerbation. Both severity and asthma control may change for each patient over time. Even patients with mild and well-controlled asthma suffer from exacerbations, as shown in the studies by Fuhlbrigge [39] and Reddel [40]. Asthma is a variable disease (**Figure 1**), and fixed-dose treatment plans are not capable of maintaining overall control of asthma. Long-term control requires a flexible management scheme that adapts to the needs of the patient. Typically, when asthma deteriorates, the ICS dose is increased or an extra controller therapy is added. Later, when control is regained, gradual reduction of daily ICS dose or number of controllers can be attempted. A full-blown exacerbation is usually preceded by progressively increased symptoms and use of β_2-agonists [17,41]. There is a window of opportunity lasting on average 1 week for early intervention [17]. Early increase in dose and frequency of dosing with anti-inflammatory therapy at onset of the first symptoms may prevent an exacerbation (**Table 1**). Budesonide/formoterol is characterized by a dose–response effect; thus, increasing its usage results in a better effect. Budesonide/formoterol,

Figure. 1. Asthma variability and need for treatment.



SMART: Symbicort maintenance and reliever therapy.

when taken as a reliever drug early on, increases the bronchoprotective effect via formoterol and the daily dose of corticosteroid to enhance the anti-inflammatory effect. There is some evidence that increasing the dosing frequency of budesonide may have a similar significant effect as increasing the total daily dose during periods of poor asthma control, but no benefit for increasing dose frequency is apparent outside of these periods [42]. The addition of inhaled budesonide (200 µg four-times daily) for 7 days to the low maintenance dose (100 µg twice daily) at the onset of exacerbation (30% fall in lung function) had a significant beneficial clinical effect in reducing the need for systemic corticosteroid therapy. Furthermore, this benefit from a 1-week increase in dosing was as effective as a regular fourfold higher maintenance dose of budesonide over 6 months [34].

Based on this observation, the budesonide/formoterol Adjustable Maintenance Dosing (AMD) program was created. Fitzgerald *et al.* evaluated the data from eight clinical studies (over 10,000 patients) on the efficacy and tolerability of adjustable-dose budesonide/formoterol, published in 2004 [43]. All patients receiving adjustable maintenance dosing of budesonide/formoterol (80/4.5 or 160/9 µg/inhalation) increased their dose independently during the period of deteriorating asthma from two or four per day as a fixed lower limit implemented by the clinician with a two- or fourfold increase in dose up to a maximum of eight inhalations per day for 1 or 2 weeks, based on clinical symptoms and in accordance with a specified action plan provided by their clinician. Comparative groups received fixed doses of budesonide/formoterol (two inhalations twice daily) or salmeterol/fluticasone (50/250 µg twice daily). In all these studies, AMD reduced the mean number of budesonide/formoterol inhalations per patient per day by 13–40% compared with fixed dose while maintaining or even improving asthma control. In the meta-analysis by Edwards *et al.*, including 11 studies with AMD, exacerbations leading to an oral steroids course and hospital treatment were significantly reduced, and maintenance and reliever therapy was significantly reduced compared with fixed-dose budesonide/formoterol therapy [44]. Both treatment regimens were well tolerated.

Table 1. Goals of asthma therapy and SMART efficacy.

GINA aim of asthma treatment	SMART effects vs comparator therapy
No daytime symptoms	Improvement (STAY [46], STEP [53], STEAM [45] and SMILE [48])
No nocturnal symptoms	Improvement (STAY [46], STEP [53] and SMILE [48])
No limitation of activities	Not assessed
No need for reliever	Decrease of demand (STAY [46], STEP [53], STEAM [45], SMILE [48] and COSMOS [50])
Normal lung function	Improvement (STAY [46], STEP [53], STEAM [45], SMILE [48] and COSMOS [50])
Minimize exacerbations	Prevention (STAY [46], STEP [53], STEAM [45], SMILE [48], COSMOS [50] and COMPASS [49])

GINA: Global Initiative for Asthma; SMART: Symbicort maintenance and reliever therapy.

The next step in the improvement of efficacy and simplification of the regimen was single-inhaler therapy. It has been well documented that budesonide/formoterol may be used as a maintenance and reliever therapy. This presented the opportunity for a new asthma treatment strategy: budesonide/formoterol for maintenance and reliever therapy, so called Symbicort Maintenance And Reliever Therapy (SMART®). The assumption in this strategy was that intervention and treatment of symptoms of an exacerbation or deterioration of asthma control take place early on when the symptoms first appear, and that this therapy may prevent them from fully developing. In this plan, patients regularly take a maintenance dose of budesonide/formoterol that is previously determined by a doctor; next, additional doses are taken immediately when the patient senses that symptoms are beginning to develop. Therefore, patients can intuitively increase corticosteroid doses when needed.

One of the first clinical trials to evaluate the new budesonide/formoterol strategy was the study by Rabe *et al.* [45]. This was a 6-month randomized trial in patients with mild-to-moderate asthma that compared SMART (80/4.5 µg, two inhalations once daily) with a higher dose of budesonide (160 µg, two inhalations once daily), plus as-needed SABA (terbutaline). Patients receiving budesonide/formoterol showed greater improvements in morning PEF and FEV_1 than patients receiving budesonide alone. Improvements in total asthma symptoms score, symptom-free days, asthma control days and decreased demand for relievers and night-time awakenings were significantly greater in the SMART group. The risk of having a severe exacerbation was 54% lower with SMART versus budesonide. The number of patients on SMART requiring hospitalization/emergency department treatment was significantly (ten-times) less than in the higher-dose budesonide group. Moreover, the increased efficacy with SMART was achieved with less ICS than in the budesonide group (mean dose: 240 vs 320 µg/day, respectively) and with 77% fewer oral steroid treatment days as compared with budesonide (114 vs 498 days, respectively).

In the O'Byrne study, patients with asthma aged 4–80 years received either budesonide/formoterol (80/4.5 µg twice daily) plus SABA or a higher dose of budesonide alone (320 µg twice daily) or budesonide/formoterol in maintenance (80/4.5 µg twice daily) and reliever therapy (80/4.5 µg; SMART) [46]. SMART prolonged the time to the first, second and third exacerbation requiring medical intervention, reduced the severe exacerbation rate by 45–47%, and improved symptoms, awakenings and lung function compared with both fixed-dosing regimens.

A similar study was performed by Bisgaard *et al.*, but was limited to patients aged 4–11 years [47]. These children received SMART (budesonide/formoterol 80/4.5 µg once-daily maintenance, plus additional inhalations for symptom relief), budesonide/formoterol (80/4.5 µg once daily) for maintenance (fixed combination) or higher-dose budesonide 320 µg once daily (fixed-dose budesonide). SMART prolonged time to the first exacerbation versus both fixed regimens, and reduced rates of exacerbation requiring medical intervention by 70–79% compared with fixed-dose budesonide and fixed-dose combination, respectively. Mild exacerbation days and awakenings were also significantly lower with SMART. In addition to this, investigators measured children's yearly growth. In the SMART group, children grew 1.0 cm more as compared with the fixed-dose budesonide group.

In another study published by Rabe *et al.*, the efficacy of budesonide/formoterol plus formoterol or terbutaline used as reliever medicine with budesonide/formoterol maintenance therapy (160/4.5 µg twice daily) was investigated [48]. Time to first severe exacerbation was longer with the as-needed budesonide/formoterol versus formoterol, and with the as-needed formoterol versus terbutaline. The rate of severe exacerbations was 19, 29 and 37 per 100 patients per year with as-needed budesonide/formoterol, formoterol and terbutaline, respectively.

Kuna *et al.* performed a 6-month study comparing the efficacy of SMART (160/4.5 µg, one inhalation twice daily, plus as needed) with fixed-dose budesonide/formoterol (320/90 µg, one inhalation twice daily) and salmeterol/fluticasone (25/125 µg, two inhalations twice daily) [49]. All treatments provided similar marked improvements in lung function, asthma control days and asthma-related QoL. SMART displayed greater protection from severe asthma exacerbations than fixed-dose therapies (39% reduction in rate vs salmeterol/fluticasone, 28% vs fixed budesonide/formoterol). In addition, hospitalization/emergency room visits were reduced with the budesonide/formoterol regimen (39% reduction in rate with SMART vs salmeterol/fluticasone, 32% with fixed budesonide/formoterol versus salmeterol/fluticasone). There was no difference between the two budesonide/formoterol arms in relation to hospitalizations/emergency room

visits. This phenomenon occurred despite a 50% reduction in regular maintenance doses of ICS/LABA with the SMART approach.

Vogelmeier *et al.* compared SMART 160/4.5 µg (one or two inhalations twice daily, plus as needed) with salmeterol/fluticasone (50/100 to 50/500 µg twice daily, plus salbutamol as needed) in a maintenance-dose titration study [50]. Maintenance plus as-needed budesonide/formoterol prolonged the time to first severe exacerbation versus salmeterol/fluticasone (25% risk reduction). The total number of severe exacerbations was significantly reduced in the SMART group (255 vs 329). Both regimens provided sustained improvements in symptoms, as-needed use, QoL and FEV_1, with statistical differences in favor of the SMART group for relief and FEV_1 (post-β_2-agonist values). Mean ICS dose during treatment was similar in both groups (budesonide 653 µg/day vs fluticasone 583 µg/day).

Lundborg *et al.* evaluated the efficacy of SMART at low doses below those currently approved (budesonide/formoterol 160/4.5 µg, one inhalation once daily [unapproved use] or 160/4.5 µg twice-daily maintenance plus additional doses as needed: one × SMART or two × SMART) compared with higher fixed-dose budesonide/formoterol plus formoterol as needed (160/4.5 µg two inhalations twice daily plus formoterol 4.5 µg as needed) in a 6-month, randomized, open study in a population aged 6–82 years [51]. Budesonide/formoterol usage in the SMART groups was 30–40% lower compared with the fixed treatment group, while no differences were seen in Asthma Control Questionnaire scores and the rate of exacerbations. The one dose once-daily maintenance treatment (one × SMART) showed a significant decrease in asthma-controlled days compared with the two other groups, but is currently not recommended for use in adult patients.

Another two studies published by Rabe *et al.* [52] and Scicchitano *et al.* [53] evaluating once-daily usage of budesonide/formoterol as maintenance therapy in the SMART regimen have used only the approved maintenance therapy, that is, two inhalations once daily. Both of these double-blind studies compared this treatment approach with fixed higher doses of budesonide. Patients received either budesonide (160 µg, two inhalations once daily [52] or 160 µg, two inhalations twice daily [53]) plus terbutaline 0.4 mg as needed or a daily maintenance dose of budesonide/formoterol (80/4.5 or 160/4.5 µg, two inhalations once daily) with additional inhalations of budesonide/formoterol 160/4.5 µg as needed. The time to first severe exacerbation was prolonged, and the risk of having a severe exacerbation was lower for SMART compared with a higher dose of budesonide in both studies, and marked improvements in daily symptoms and lung function were observed with both once-daily SMART regimens. The number needed to treat in order to prevent one severe exacerbation requiring medical intervention per year with SMART, compared with the double-maintenance-dose budesonide, was four or five in both studies. The higher efficacy of SMART was achieved with a lower mean daily ICS dose compared with the budesonide groups (240 vs 320 µg/day [52] and 466 vs 640 µg/day [53], respectively).

Safety of SMART

Budesonide/formoterol, both in maintenance and relief therapy, is well tolerated. Doubts that ICS may be overdosed in SMART therapy have not been confirmed. Adverse effects noted in all recent published studies with the SMART regimen were generally mild to moderate. No difference was observed between patients on SMART, fixed-dose budesonide/formoterol with corresponding or higher maintenance dose, and budesonide alone. Respiratory-tract infections were the most frequent adverse events. A study on the influence of SMART on adrenal function did not reveal any abnormality [53]. No severe adverse events related to SMART therapy were recorded, which is particularly important in light of some recent concerns regarding the safety of LABA in long-term asthma management. This was the result of a published observational study regarding the addition of salmeterol to usual asthma therapy in over 26,000 patients [54]. Small but significant increases in asthma mortality and life-threatening events were observed in the total population receiving salmeterol. This has raised the discussion of whether LABA treatment was somehow connected to these deaths. Unfortunately, the study was not planned in such a way as to determine the cause of such events. It has been suggested, based on previous data, that the cause may be underusage of corticosteroids, as nine of the 13 asthma deaths occurring on salmeterol were in patients with no record of ICS use at study entry and during treatment. Race was also taken into account, as a subpopulation analysis revealed a similar risk in African–Americans compared with Caucasians, but the rate of events was highest in African–Americans.

The problem of β_2-agonist overusage without corticosteroid treatment does not apply to budesonide/formoterol therapy, as these two components are both present. Thus, the Global Initiative for Asthma (GINA) strongly recommends the use of such medicines. Two strengths of the budesonide/formoterol Turbuhaler® are appropriate for SMART: 160/4.5 and 80/4.5 µg per inhalation [102]. The daily dose of Symbicort SMART does not usually exceed eight inhalations per day. The maximum recommended daily dose of Symbicort in SMART therapy is 12 inhalations per day. Such a dose should be used for a limited period. Patients using more than eight inhalations daily should be advised to seek medical advice. They should be reassessed and their maintenance therapy reconsidered.

SMART & GINA guidelines

The Global Initiative for Asthma determines the standards of asthma care throughout the world. Its goal is the reduction of asthma morbidity and mortality. GINA brings together experts in asthma management who prepare recommendations for clinicians on the basis of scientific evidence. Every year, new data from published studies are evaluated and an up-to-date report is prepared. The last report was published in November 2006 [103]. The goals of successful asthma management defined by GINA are:

- Achieve and maintain control of symptoms
- Maintain a normal activity level, including exercise
- Maintain pulmonary function as close to normal as possible
- Prevent asthma exacerbations
- Avoid adverse effects from asthma medications
- Prevent asthma mortality

SMART therapy is a new effective and safe option in asthma management. How SMART therapy fulfills GINA guidelines is currently a subject of intense study (**Table 1**).

What is the position of budesonide/formoterol therapy with regards to GINA recommendations? The proven effectiveness of the ICS and LABA fixed combination, both budesonide plus formoterol and salmeterol plus fluticasone, resulted in them being recommended by GINA. Fixed combination was recommended for all stages of asthma therapy where the addition of LABA was indicated. The GINA Report emphasizes that combination inhalers are as effective as each component drug separately. However, they are more convenient for patients, and therefore may improve compliance. Another very important feature emphasized by GINA is that LABA are always used with corticosteroids, which leads to improved safety.

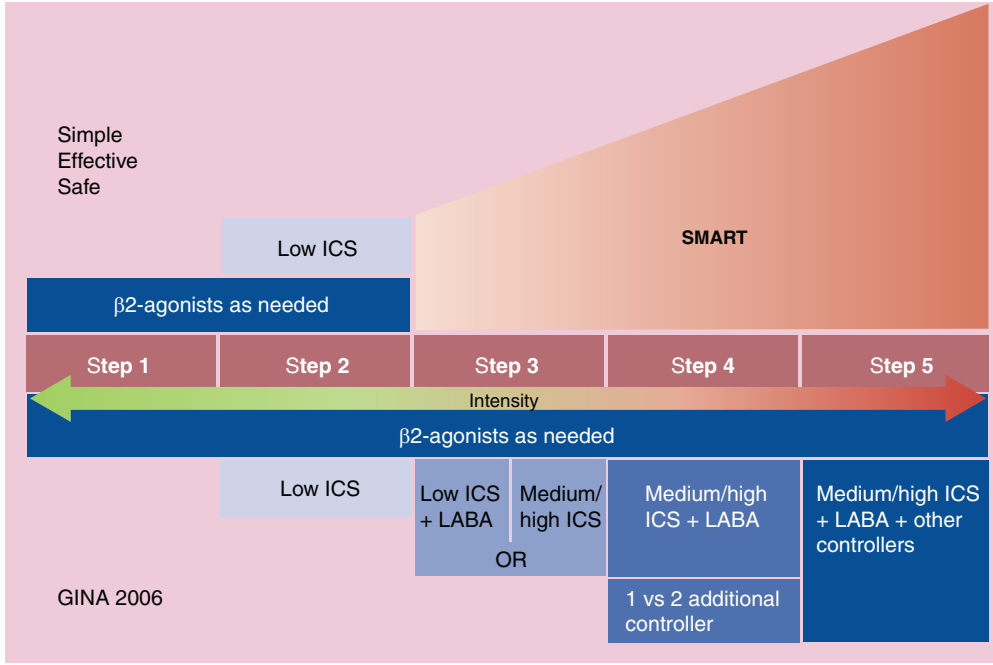
The GINA Report published in 2006 presents one novelty in combined treatment: the combination of formoterol and budesonide is accepted for both maintenance and reliever therapy. This is owing to the rapid bronchodilatory effect of formoterol. GINA recommends this fixed combination for use as needed, in particular for patients already receiving such a combination as maintenance, because it enhances protection against severe exacerbation and provides improvement in asthma control with relatively low treatment doses.

SMART has been proven to decrease daytime and nocturnal symptoms, decrease the use of relievers, improve lung function and QoL and prevent future risk to patients by minimizing asthma exacerbations. Asthma control and protection from asthma exacerbation are the two main goals of management as indicated by GINA.

The guidelines for asthma management recommend the use of a minimum effective dose of ICS to minimize possible longer-term side effects. SMART therapy allows for a reduced dose of ICS without compromising control, owing to flexible dosing corresponding to the variable drug requirements in asthma. In the Kuna *et al.* study, the SMART approach not only did not show an increase in mean ICS daily dose, but even decreased this by a quarter compared with fixed combination and was still more effective in prevention of severe exacerbations including hospitalizations/emergency room treatment [49]. Similar results obtained by O'Byrne [46], Bisgaard [47], Rabe [45] and Scicchitano [53] when comparing the SMART regimen with a high dose of budesonide have been reported.

The GINA guidelines have already been accepted in over 100 countries around the world and nowadays are a marker of Good Medical Practice in asthma management. This is the reason why GINA recommendation is so important. There are still some unresolved problems, that is, can SMART therapy be administrated from the start, immediately after diagnosis of asthma, and is it suitable for all asthma control levels and steps of treatment? It is possible that once SMART therapy becomes popular, the steps of asthma treatment will have to be changed once again (**Figure 2**). However, as

Figure 2. Steps of asthma treatment according to the GINA and SMART.



GINA: Global Initiative for Asthma; CS: Corticosteroids; ICS: Inhaled corticosteroids; LABA: Long-acting β_2-agonists; SMART: Symbicort maintenance and reliever therapy.

SMART, by definition, includes a maintenance ICS and LABA, it is presently at step 3–5 of the current guidelines.

Patient expectations & behavior

Patients with chronic conditions tend to have a strong influence on the treatment process, regardless of the efficacy of the therapy. Therefore, asthma management must be a compromise between patient and physician preferences. The goal for physicians is complete asthma control, whilst from the patient's perspective, limiting the influence of asthma on real life is most important. SMART has been shown to improve both asthma control and HRQoL [49,50].

A patient's acceptance of any proposed treatment determines the successful outcome of all long-term therapies. Understanding the factors that influence patient behavior may help decide on the most suitable regimen (**Table 2**). The Respiratory Patients Opinions Survey (RESPONSE) [55] performed in Europe showed that the majority of patients prefer to use fewer asthma drugs and to have just one inhaler; therefore, SMART fulfills

Table 2. SMART in real life: how it fulfills patient needs.

Patient preferences	How SMART meets patient expectations
Normal lifestyle	Improve quality of life
No influence on work and/or school	More days with asthma control, fewer exacerbations, fewer visits to emergency room and/or hospitalization – lower absenteeism at work and school, lesser degree of disability
No problem with social contacts	Better asthma control and quality of life, potential that less fear of attacks will increase social activity
Comfort	Convenient single-inhaler therapy
Low cost	Lower overall doses maintain asthma control and prevent exacerbations, better cost–effectiveness profile
No side effects	Well tolerated with lower mean ICS doses

ICS: Inhaled corticosteroids; SMART: Symbicort maintenance and reliever therapy.

patient expectations in this regard. Further studies of patient behavior revealed that over half of them tend to rely on reliever medication [56] and underuse ICS [57]. This is due to the fact that patient perceive ICS as having a lower immediate efficacy in contrast to β_2-agonists, that provide rapid improvement of symptoms. Budesonide/formoterol merges these two drug groups and provides a dual effect: rapid bronchodilation and anti-inflammatory treatment. It has been well documented that underusage of ICS and excessive use of β_2-agonists is associated with increased morbidity and mortality [58–60]. Interestingly, patients who frequently used high doses of β_2-agonists while taking ICS as well had a 70% lower risk of hospitalization compared with those using β_2-agonists alone [60]. Fixed-combination ICS with β_2-agonists as a reliever therapy eliminates the risk of the use of β_2-agonists relievers alone, and thus increases safety.

Regardless of the fact that people forget to take drugs regularly, they are also concerned about the side effects of long-term therapy and dependence [61], and therefore decrease the doses themselves or even stop taking drugs when they feel better. The use of fixed-combination budesonide/formoterol as reliever medication may partly compensate for poor compliance in maintenance anti-inflammatory therapy.

The participation of patients in the therapeutic process is especially important in chronic diseases such as asthma. Owing to the fact that SMART is a simple and intuitive method of therapy, it is convenient for the patient to use in self-management plans.

SMART & improvement of adherence to anti-asthmatic treatment

Asthma control is not achieved by prescribing an effective and well-tolerated medicine by a doctor. It is common knowledge that patient compliance with asthma therapy is low and may be one of the reasons for decreased asthma control. Less than 50% of patients adhere to prescribed schema [62,63]. Adherence to the regimen depends on many factors, including psychological, sociological and cultural issues (**Table 3**). Identification of the factors that influence patient behavior may be the key to improving the effectiveness of asthma therapy; the complexity of the regimen is one of the most important.

In asthma treatment, several medicines are quite often prescribed to improve efficacy of therapy as recommended in the GINA guidelines. Such regimens may be complicated and inconvenient for patients who prefer a simpler course of therapy using fewer drugs [64]. Budesonide/formoterol is a combination of two medicines in one device, and is thus more convenient for patients. Moreover, budesonide/formoterol due to the rapid action of formoterol, is licensed to be used for both maintenance and relief therapy in many countries, which in turn further simplifies the treatment regimen. Thus, SMART offers a simple schema for drug administration in one device, which fulfills the patient expectations and may potentially improve adherence. Another factor that affects patient adherence to prescribed medication is dosing frequency. Complicated dosing schemes decrease compliance, while less-frequent dosing improves it [65]. It has been demonstrated in two separate studies that budesonide/formoterol SMART may be administered even once daily, and such a regimen is effective in preventing asthma exacerbations [52,53].

Other problems affecting adherence are a poor perception of asthma severity by some patients [50], or dissimulation of symptoms when visiting a physician [66]. SMART offers intuitive drug administration by providing increased ICS doses with the first appearance of symptoms, and, as such, at the start of any exacerbation. Such a regimen also compensates for any lack of patient education or miscommunication. However, the idea of SMART is not to eliminate the role of a physician in patient education and to create a good doctor–patient relationship.

Cost–effectiveness of SMART for healthcare system

Asthma is not only a health problem, but also has an impact on the socioeconomic situation. The costs of asthma treatment are US$520 to US$1300 per patient per year, and mainly depend on asthma severity and levels of control [67]. The overall direct costs of asthma management in the European Union were estimated as €6429 million. They consist of the following: hospitalization costs €2068 million, physician services €2671 million, immunotherapy and pharmacotherapy €1690 million. Indirect costs of asthma are much greater and amount to €13,905 million. It has been demonstrated that the 20% of patients suffering from severe asthma in Finland are responsible for 60% of the national budget expenses for asthma [68]. Furthermore, almost 50% of these costs are generated by poorly controlled asthmatic patients (emergency room visits, hospitalization and death) [69]. Thus, appropriate asthma management is also an economic challenge. As a result

Table 3. Factors of poor patient compliance and the role of SMART therapy.

Factors for poor compliance	Repair by SMART regimen
Complexity of regimen:	
– Too many medicines	Two medicines in one device Single inhaler for maintenance and reliever therapy
– Dosing frequency	Effective once-daily dosing in maintenance therapy of moderate-to-severe asthma
Miscommunication and inadequate education	Simple and intuitive regimen
Concerns about side effects	Lower-dose ICS to achieve asthma control and prevent exacerbations
Overusage of β_2-agonists and underusage of ICS	Simultaneous administration of ICS with all β_2-agonist therapy
Underestimation of asthma severity – negation of symptoms of exacerbation	Increased dose of ICS with on-demand use of β_2-agonist
Poor motivation for ICS intake	Addition of formoterol to ICS – rapid onset of action may increase adherence
Irregular usage of medicines	Additional dose of ICS taken as needed with β_2-agonist

ICS: Inhaled corticosteroids; SMART: Symbicort maintenance and reliever therapy.

of its high efficacy in asthma control with reduced drug doses when compared with fixed-dosing regimens, SMART may provide a highly cost-effective therapy.

Rosenhall *et al.* compared the cost of treating asthma using either budesonide/formoterol or corresponding doses of budesonide and formoterol administered via separate inhalers [70]. The direct costs in the budesonide/formoterol group were significantly lower than the corresponding group (4677 SEK vs 5555 SEK per patient during 6 months of therapy, respectively).

Economic analysis carried out by Berggren *et al.* showed that formoterol as a relief medication was cost-effective in comparison with terbutaline, saving approximately 323 SEK per patient during a 12-week treatment [71].

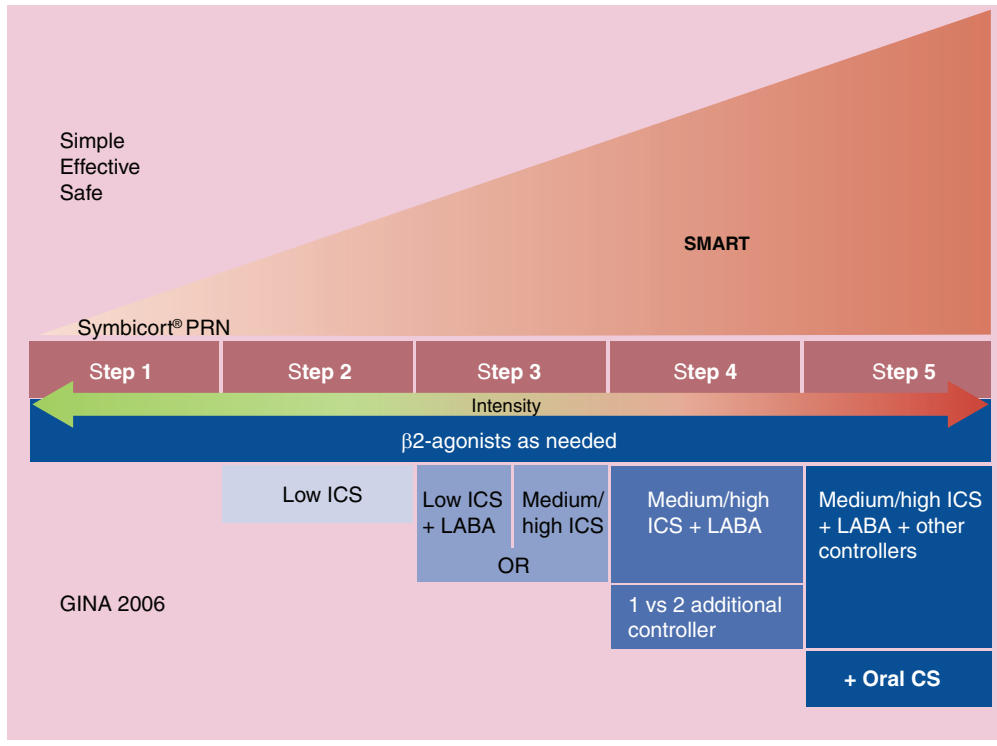
Fitzgerald *et al.* evaluated the cost–effectiveness of adjustable therapy compared with fixed-dose budesonide/formoterol [72]. Total costs per patient were lower (C$141) for the adjustable regimen. This was due to a twofold reduction of asthma exacerbations during adjustable dosing compared with the fixed-dose combination (4.0 vs 8.9%; $p = 0.002$; number needed to treat: 21 [95% CI: 13–59]) and lower overall doses of budesonide/formoterol by 36% (2.5 vs 3.9 inhalations/day; $p < 0.001$).

Similar results were obtained in the CAST study [73]. Patients on adjustable maintenance dosing used 24% less study drugs compared with fixed maintenance dosing (2.95 vs 3.86 inhalations daily; $p < 0.0001$), which resulted in a significant ($p < 0.0001$) reduction in total costs (direct plus indirect) compared with fixed maintenance dosing.

In the ASSURE study, adjustable maintenance dosing with budesonide/formoterol provided equivalent QoL to fixed dosing at significantly lower cost – the mean daily cost per patient was GB£1.13, compared with GB£1.31 for fixed dosing [74]. The difference in mean daily costs resulted in an annual per-patient cost difference of GB£65.70. Brüggenjürgen *et al.* compared the costs and effectiveness of adjustable maintenance dosing with budesonide/formoterol in a single inhaler versus fixed dosing for the same drugs [75]. Both treatments were equally effective in maintaining HR-QoL and asthma control. However, overall, patients in the adjustable maintenance dosing group took fewer daily inhalations of budesonide/formoterol than those in the fixed-dosing group (mean: 2.63 vs 3.82 inhalations; $p < 0.001$). Adjustable maintenance dosing was associated with significantly lower asthma-related direct costs compared with fixed dosing (mean: €221 versus €292; $p < 0.001$).

To date there have been three clinical studies assessing the pharmacoeconomic aspects of the SMART regimen. Lundborg *et al.* assessed the cost–effectiveness of SMART (budesonide/formoterol 160/4.5 µg, one inhalation twice-daily maintenance, plus as needed: one × SMART or two × SMART) compared with higher fixed budesonide/formoterol dose plus formoterol as needed (160/4.5 µg, two inhalations twice daily,

Figure 3. The future of budesonide/formoterol and budesonide/formoterol maintenance and reliever therapy regimen.



GINA: Global Initiative for Asthma; CS: Corticosteroids; ICS: Inhaled corticosteroids; LABA: Long-acting β_2-agonists; SMART: Symbicort maintenance and reliever therapy.

plus formoterol 4.5 µg as needed) in a 6-month assessment [76]. Treatment costs were significantly lower in the SMART groups as compared with the fixed-combination groups due to the 30% lower doses of budesonide/formoterol. No differences were observed in Asthma Control Questionnaire scores and the rate of exacerbations.

Johansson *et al.* compare the cost–effectiveness of the SMART regimen with salmeterol/fluticasone 50/100 or 50/500 µg twice daily [77]. The doses of salmeterol were titrated up and down at the discretion of the clinician. SMART provided a reduction in the number of severe exacerbations per patient per year, with no statistically significant increase in cost – or even lower costs – compared with the fixed combination.

More recently, Price *et al.* compared the cost–effectiveness of SMART 160/4.5 µg twice daily, plus as needed, with budesonide/formoterol 320/9 µg twice daily and salmeterol/fluticasone 50/250 µg twice daily in a 6-month study [78]. This study showed that SMART reduces the incidence of severe exacerbations at a lower or similar overall cost, and can be considered a cost-effective treatment regimen when compared with higher fixed-dose budesonide/formoterol and salmeterol/fluticasone.

These data demonstrate that SMART is cost effective in the long-term management of patients with asthma, which is in accordance with public interest.

Future perspective

Since 2000, budesonide/formoterol has been effectively and widely used as a traditional maintenance treatment for asthmatic patients around the world. GINA recommends such fixed combinations as more safe and convenient for patients, as they prevent the use of LABA monotherapy.

In 2006, Symbicort SMART was launched as an effective and safe option for asthma treatment. At present, Symbicort SMART has been approved in 37 countries (European Union countries, Switzerland, Australia, Argentina, Brazil, Mexico, the Philippines and Thailand). Since GINA accepted budesonide/formoterol as a reliever therapy in addition to, but not as a replacement for, maintenance therapy in 2006, the SMART regimen has strong appeal for use in clinical practice.

In July 2007, the *New England Journal of Medicine* published the polling results of the readers' preferences in mild asthma management [79]. Participants (6085 recorded votes) were from all over the world (113 countries), and the majority were physicians (80%). Three options in a step-down strategy were proposed by the experts:

- A fixed combination of ICS and SABA given as needed
- Fixed combinations of ICS and LABA once daily, with SABA as reliever therapy
- Leukotriene-receptor antagonist with SABA

The most popular (receiving 37.5% of the votes cast) was ICS and LABA in a single inhaler taken once daily; ICS with SABA on demand received almost the same number of votes (37.4%). The remaining option was an oral leukotriene-receptor antagonist plus SABA as needed (25.2%). This poll indicates that 75% of clinicians favor the use of combination therapy either as needed or as once-daily maintenance therapy with a separate SABA as reliever therapy in mild asthma. The once-daily SMART regimen could therefore have appeared in this setting, but at present it has been assessed in mild to moderate patients uncontrolled by ICS.

On the basis of the previous presented clinical studies and the knowledge of patients' preferences, the authors assume that budesonide/formoterol may be suitable for all asthma stages and at all steps of asthma treatment. The therapy in milder states, when symptoms are rare and the patients do not need stable maintenance therapy, may be provided with use of budesonide/formoterol as a reliever. In patients who suffer from symptoms requiring use of the reliever more than twice a week, with limitation of activities, the regimen should be switched to budesonide/formoterol for maintenance and reliever therapy. As the patients' perception of ICS effectiveness is low and, therefore, ICS usage compliance is insufficient, budesonide/formoterol may improve the anti-inflammatory therapy, both in mild and more severe asthma stages. The use of one inhaler with a simple and intuitive regimen is the preference of most patients and doctors. It is obvious that such a regimen is not suitable for all patients (i.e., for patients who suffer from difficult-to-treat asthma it may be insufficient), but the authors believe that SMART is suitable for a significant majority of them. Budesonide/formoterol SMART has been shown to be effective, well tolerated and cost effective in clinical trials involving over 14,000 patients with mild to severe persistent asthma – these features must now be confirmed in real life.

Conclusions

Inhaled corticosteroids are the mainstay of chronic asthma therapy, but are not always sufficient for complete asthma control. Adding LABA to ICS in patients with poorly controlled asthma is a proven, effective action and the first-line add-on recommendation in GINA guidelines. The development of fixed-combination ICS and LABA simplifies the asthma regimen and is more convenient for patients. Further simplification is administration of budesonide/formoterol both as the maintenance and reliever medication. Such regimens better reflect the nature of asthma, and make it possible to correspond the drug dose to the patient's actual condition. Patients intuitively increase ICS doses as symptoms develop and inflammation intensifies. Therefore, pharmacological intervention may be modified at an earlier step before asthma deterioration, and thus may prevent exacerbation. The use of a single inhaler for maintenance and reliever therapy in asthma may improve patient compliance, or at least compensate for regular underdosing of ICS. This is also a way to improve the effectiveness of therapy. A fixed ICS plus LABA combination regimen eliminates the selective use of LABA, which may be life threatening. Moreover, it is has been demonstrated that SMART provides better asthma control with a lower total dose of ICS than conventional treatment plans. SMART therapy offers a new quality of treatment and is likely to be the future in advanced asthma management.

Financial & competing interests disclosure

Kuprys-Lipinska has been an investigator in several AstraZeneca-sponsored clinical trials. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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

Executive summary

- Asthma is a chronic inflammatory disease with variable airway limitation.
- Effective asthma therapy relies on the treatment of both asthma components: inflammation and bronchial constriction.
- Glucocorticosteroids are currently the most effective anti-inflammatory medications for asthma treatment.
- Rapid-acting β_2-agonists are the first-line relievers in asthma management.
- Concurrent use of glucocorticosteroids and long-acting β_2-agonists provides a synergistic effect on both airway inflammation and smooth muscle relaxation.
- The addition of long-acting β_2-agonists to glucocorticosteroids results in lung-function improvement and reduction of mild and severe exacerbations, improving the health-related quality of life to a greater extent than glucocorticosteroids alone.
- Symbicort® is a fixed combination of an anti-inflammatory agent, budesonide, and a bronchodilator, formoterol.
- Budesonide is a glucocorticosteroid with a potent and prolonged anti-inflammatory effect.
- Formoterol is a potent and selective β_2-agonist with a unique profile: a rapid onset and long duration of action.
- Budesonide/formoterol is as effective and safe as budesonide and formoterol in corresponding doses given via separate inhalers.
- Budesonide/formoterol is more effective when compared with a twofold higher dose of budesonide alone.
- The efficacy and safety profile of budesonide/formoterol in the treatment of acute asthma is similar to that of high-dose salbutamol.
- Asthma is a disease with a variable course over time; thus, long-term control requires a flexible management scheme that easily adapts to the current needs.
- Due to its rapid bronchodilatory effect and potent and prolonged anti-inflammatory activity, budesonide/formoterol may be used in maintenance and reliever asthma therapy.
- The Symbicort for maintenance and reliever therapy (SMART) program was created in response to patients' need for a simplified treatment.
- Patients take the base dose of budesonide/formoterol recommended by the doctor, and additional doses when the symptoms appear, thus intuitively increasing the dose of glucocorticosteroids when symptoms deteriorate and inflammation intensifies.
- SMART is more effective than fixed treatment, and asthma control is achieved with a lower dose of glucocorticosteroids.
- The SMART regimen better reflects the nature of asthma, and matches the treatment to the condition of the patient.

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