The whole story: treatment outcomes with Symbicort®

O. Zetterström¹, R. Buhl², H. Mellem³ and F. Andersson⁴

¹Karolinska Hospital, Stockholm, Sweden, ²Mainz University Hospital, Mainz, Germany, ³Ullevål Hospital, Oslo, Norway and ⁴Clinical Science, AstraZeneca R&D, Lund, Sweden

Abstract  Asthma is a chronic inflammatory disorder of the airways that has a considerable socioeconomic impact. Asthma management guidelines have been introduced to help provide better long-term control of asthma. Although recommended guidelines may increase the direct medication costs, the overall direct costs of asthma may be reduced due to fewer exacerbations. In addition, indirect costs due to lost productivity and mortality are reduced and patients have an improved quality of life. Inhaled corticosteroids are first-line therapy in the treatment of persistent asthma. Against this background, we have assessed the cost-effectiveness of Symbicort® (budesonide and formoterol in a single inhaler), a treatment that provides better control of asthma compared with budesonide alone. While the prescribing costs of Symbicort® were found to be higher than for budesonide alone, these were partially offset by reduced costs due to fewer asthma exacerbations and a reduced need for other medications. Combined long-term therapy with budesonide and formoterol also improves patient quality of life compared with budesonide alone. Two other factors associated with asthma treatment success and cost-effectiveness are patient/physician education and good patient adherence to prescribed therapy. The introduction of a single inhaler that is easy to use in simple treatment regimens may improve patient adherence to prescribed medication, thus resulting in improved asthma control and fewer exacerbations. Treatment with Symbicort® is more cost-effective than treatment with budesonide alone.

INTRODUCTION

Asthma is a common and chronic inflammatory disorder of the airways that has increased in prevalence (1) and cost (2). Asthma not only has a social impact on patients and their families, but also places a considerable economic burden on healthcare resources in developed countries (3,4). In particular, poorly controlled asthma can greatly reduce patient quality of life and incur avoidable costs.

Asthma treatment guidelines have been introduced to improve the quality of asthma patient care with the aim of providing better asthma control (5–8). Current treatment options in all but intermittent cases of asthma include inhaled corticosteroids to control the underlying inflammation together with inhaled bronchodilators to relieve the symptoms of asthma (5–8). In those patients whose asthma remains inadequately controlled with inhaled corticosteroids, guidelines recommend increasing the dose of the corticosteroid in a stepwise fashion or adding a long-acting β₂-agonist or additional drugs to the treatment regimen (7,8). The guidelines also recommend that a short-acting β₂-agonist should be prescribed as needed.

The costs of asthma are increasing and there is increasing pressure on physicians to make the most cost-effective choices in the management of this disease. Cost-effectiveness is the relationship between total costs of a specified treatment and the health outcome achieved by that treatment. The total costs associated with asthma therapy are far-reaching and can be difficult to calculate. Total costs can be separated into direct, indirect and intangible costs (9). The direct costs of asthma are the most straightforward to understand and to calculate; they are the health service costs associated with the diagnosis, assessment and treatment of the disease and include the costs of medications, hospitalization, emergency care, medical consultations, lung function tests, peak flow meters, chest X-rays, etc. They also include costs incurred by the patient for travelling and waiting to attend consultations, and for special diets or appliances. The indirect costs are those costs that are as-
associated with lost productivity by the patient due to days off work, under-performance at work, premature retirement or death, or adverse effects of asthma medications. Parents often have to take off work to care for an asthmatic child and these costs should also be included as indirect costs. Such indirect costs can be difficult to estimate accurately. Intangible costs are the most difficult to calculate as they relate to the personal and emotional consequences of having asthma and include diminished quality of life, psychological effects, social costs and asthma-related "pain and suffering", all of which can restrict the patient from leading a normal active life. Intangible costs are rarely included in studies of the economic impact of asthma. Thus the total cost of asthma treatment can be reduced by reducing either the direct or indirect costs or both.

It has been suggested that if asthma is managed appropriately such that patients have optimal control of their asthma, then the socioeconomic burden of asthma for society should be reduced (9). To optimize asthma control, all aspects of asthma care need to be considered—from treatment options and costs of treatment to appropriate asthma education for patients and their carers. To this end, if the direct cost of medication or education is increased the treatment may still be considered cost-effective if the benefits of the treatment in terms of health outcomes and reduction in total costs outweigh the original increase in cost. This paper will review these aspects of asthma care with particular reference to Symbicort®, the new combination of the inhaled glucocorticosteroid, budesonide, and the inhaled long-acting $\beta_2$-agonist, formoterol, delivered by a single inhaler.

THE ECONOMIC BURDEN OF ASTHMA

The high and increasing prevalence and morbidity of asthma place a huge burden on healthcare resources. In particular, asthma is a common cause of hospital admission among children, and the annual healthcare costs of childhood asthma in the UK have been estimated at between £100 million and £150 million (10). The economic impact of asthma has been studied in several countries in an attempt to identify areas where resources may be saved. A study conducted in Sweden reported that, in 1991, the direct (37%) and indirect (63%) costs of asthma amounted to a total of (Swedish krona) SEK 3.0 billion (1 SEK = 0.09 US$), approximately 1% of the costs of all diseases (II). In another report (12), more than half of the total cost of asthma in the USA (54%) and Australia (77%) was associated with direct costs for medical treatment whereas in Sweden the direct costs (43%) were lower than the indirect costs (57%). This difference appears to be largely due to a higher proportion of in-patient and emergency care costs in the USA and Australia compared with Sweden (12). A comparison of the cost of asthma per affected individual per year in six countries is shown in Figure 1. The costs ranged from US$3326 to 1315 per year.

Drug costs make up the single largest component of direct costs of asthma (usually 30–40%) and are the major cost among patients with mild to moderate asthma (4). The cost of treating patients with asthma increases according to the degree of disease severity, and it is greatest in the relatively small proportion of patients with severe asthma (12). In Spain, Serra-Batllés et al. (13) found that the total costs of asthma for patients with moderate disease were almost twice as high as those with mild asthma, whereas patients with severe asthma were almost five times as costly as those with mild asthma. Hospitalization costs are the major cost in patients with severe asthma. Thus, there is considerable interest in the potential to reduce the high medical costs of asthma by reducing the risk of hospitalization through better asthma control. This approach may also reduce the indirect and intangible costs of asthma by reducing the number of days absent from school or work and offering the patient a better quality of life.

Although each asthma case is different, guidelines have been introduced to help physicians in their diagnosis and choice of therapy, and it is important that these recommendations for asthma management are put into practice. Studies have shown that when asthma patients are treated with anti-inflammatory drugs according to the guidelines, their long-term health outcome is better and the treatment is also cost-effective (14). Although the widespread use of anti-inflammatory drugs results in increased medication costs, these are more than offset by reductions in emergency room visits and hospitalizations, thus reducing the overall healthcare costs. A recent study in the UK estimated that the annual prescribing costs for adult asthma treatment could rise by nearly 30%, from £388 million to a possible £533 million, if the guidelines were followed more stringently (15).

![Figure 1. Comparison of the cost of asthma per affected individual (adjusted to 1991 US Dollar) [data from Sullivan 1998 (12)].](image-url)
However, there is increasing evidence that asthma treatment guidelines are not being followed by physicians (16,17). In addition, many patients do not take their treatment as prescribed (18). As a result, large numbers of patients have poorly controlled asthma, which leads to an increased risk of attacks or exacerbations of asthma, some of which require hospitalization—the most costly component of asthma care. In a recent study by Anderson et al., the mean total cost of a mild exacerbation in the UK in 1999 was reported to be £57 (95% confidence interval [CI]: £27–£96) compared with £1377 (95% CI: £321–£452) for a severe exacerbation (19). In another study in the UK involving over 10000 adult asthmatics, it was reported that almost 50% of the patients were being under-treated; they should have been treated at a step higher to be in accordance with the British Thoracic Society (BTS) Guidelines (5). Although patients at any step of the guidelines are at risk of having an asthma attack, the risk increases as the severity of the asthma increases (20).

The aims of asthma therapy should be to acquire rapid control of the disease followed by maintained asthma control, and this should be achieved in a cost-effective manner. Much of the expenditure in poorly controlled asthma is avoidable. Thus, efforts must be made to encourage physicians to follow treatment guidelines and to increase patients' understanding and cooperation regarding their prescribed therapy.

Educating both physicians and patients about effective asthma management may reduce asthma costs (21,22). It is recognized that an essential element of enhanced asthma care is the formation of an effective partnership between the patient and the healthcare professional (22). Good communication is crucial in the management of asthma and a better doctor–patient relationship needs to be encouraged, especially in primary care (23). Physicians need to gain as much information from the patient as possible so that the most effective therapy can be applied.

The asthma guidelines emphasize the importance of patient self-management combined with regular physician review (5–8). This approach relies on the physicians' ability to give their patients the necessary knowledge, skills and attitudes to control their asthma symptoms and to be able to recognize and cope with any changes in their condition. This can be achieved using specific educational programmes and there is growing evidence that self-management and educational programmes in asthma are cost-effective (22,24). For example, in the USA, intervention with a self-management training programme, costing US$85/person, resulted in a significant reduction in emergency room costs from US$1036 to US$408 per person per year (Δ=US$628; P=0.02) (25). Thus, training programmes are seen as a cost-effective way of reducing the overall burden on the healthcare service.

**COST-EFFECTIVE THERAPY FOR ASTHMA: FOCUS ON SYMBICORT®**

When considering the cost-effectiveness of inhaled corticosteroids, there are four important issues to take into account:

1. need for long-term daily treatment;
2. adverse effects;
3. adherence to prescribed medication;
4. cost of inhaler devices.

First, asthma is a chronic disease that requires long-term daily anti-inflammatory treatment. Inhaled corticosteroids are the most effective controller medication for asthma, and a reduction or discontinuation of inhaled corticosteroids can cause asthma exacerbations even in patients with mild asthma (26,27). Thus, the costs of inhaled glucocorticosteroid treatment are likely to be lifelong costs. Nevertheless, inhaled corticosteroids do not cure asthma; rather, they simply help control asthma by exerting a range of anti-inflammatory effects (28). Recent studies have indicated that if treatment with inhaled corticosteroids is started early in the course of the disease, they may protect against the development of irreversible structural changes and progressive deterioration in lung function that occurs over time (29). As a result, there is a trend towards greater and earlier use of inhaled corticosteroids in patients with milder disease.

The second important issue is adverse effects. Those associated with inhaled corticosteroids are minor and usually do not require additional treatment (30). This is in contrast to oral steroids which, despite being low-cost drugs, can cause adverse effects that incur additional costs. Furthermore, because inhaled corticosteroids help control asthma, they can reduce the pain and suffering associated with asthma and improve patient quality of life (31). Consequently, there may be a reduced need for extra medication to control other complications, such as anxiety and depression.

The next issue is one of adherence to prescribed medication; for inhaled glucocorticoids to be effective and/or cost-effective, patients must take them. Unfortunately, adherence to prescribed medication is poor, especially inhaled corticosteroids (18). Although there may be many reasons for this (see later) (32), fear of possible side-effects is a major reason that patients give for not taking their inhaled corticosteroids (33). Various approaches can be taken to try to improve adherence: for example, educating the patients about asthma and its management, making inhalers more 'user-friendly' and providing the patients with more effective medication. For drugs with a rapid onset of effect which offer rapid relief from asthma symptoms, adherence to prescribed medication is likely to be higher than when there is no perceived effect on breathing (34). Thus the addition of formoterol, with its rapid onset of effect, to budesonide
in a single inhaler may improve adherence to prescribed medication.

The final key issue when considering the cost-effectiveness of asthma therapy is the differences in cost of the various devices used to administer inhaled corticosteroids. Dry powder inhalers are more expensive than pressurized metered dose inhalers (pMDIs) in some countries (e.g., the UK), but are less expensive in others (e.g., Canada). It has been shown that budesonide delivered via Turbuhaler® is more cost-effective than budesonide delivered via a pMDI (35). Moreover, the dry powder inhalers are breath-activated and easier to use than the pMDIs.

In asthma patients who remain inadequately controlled on inhaled corticosteroids, guidelines recommend an increase in the dose of inhaled corticosteroids or addition of a long-acting β2-agonist (5-8). Recent studies indicate that adding a long-acting β2-agonist is not only more effective than using inhaled corticosteroids alone, but is also more cost-effective. In economic evaluations of asthma, cost-effectiveness is often assessed using a composite outcome measure—the symptom-free day or the episode-free day (also called the asthma control day) (36). A symptom-free day is defined as no night-time awakening and a night and a day with no symptoms (i.e., a symptom score = 0), while an episode-free day is defined as a night and a day without symptoms, no intake of reliever medication and no asthma-related night-time awakenings.

Several randomized studies have demonstrated both the efficacy and cost-effectiveness of budesonide when given to patients previously taking short-acting β2-agonists alone (37-39). However, increasing the dose of budesonide from 400 to 800 µg day⁻¹ increased drug costs by 33% without resulting in increased efficacy in the short term, suggesting that this approach is not cost-effective (40). Since the use of combination therapy will increase direct costs of medication even further, it is important to determine whether combination therapy decreases healthcare service costs elsewhere by improving asthma control. In other words, the focus in treating asthma patients should be on gaining and then maintaining control of asthma and not just on the actual cost of the medication itself.

In the study by Pauwels and colleagues (41), the addition of the long-acting β2-agonist formoterol to low-dose or high-dose budesonide for 1 year improved asthma symptoms and lung function in patients with moderate asthma compared with budesonide treatment alone. Indeed, the use of this combination, administered via separate inhalers, decreased the incidence of mild and severe asthma exacerbations (41) and in a separate study the same combination did not mask increasing airways inflammation (42). Furthermore, sustained improvements in patient quality of life were also achieved with this combination of formoterol and budesonide (43). An economic assessment of the costs of adding formoterol to budesonide found that although there are higher prescribing costs, these are more than offset by reduced costs associated with mild or severe exacerbations or loss of productivity (19). Thus, adding formoterol to budesonide not only improves control of asthma but is also cost-effective and even cost-saving in the long term.

Further developments have been made such that budesonide and formoterol have now been combined together in a single, modified Turbuhaler® inhaler (Symbicort® Turbuhaler®). The efficacy and safety of Symbicort® have been studied in a 12-week, randomized, double-blind, active-controlled, multicentre trial performed in six European countries in 362 adult patients whose asthma was not adequately controlled with inhaled glucocorticosteroid treatment alone (44). The patients were treated twice-daily with Symbicort® (budesonide/formoterol 160/4.5 µg; two inhalations); budesonide (200 µg; two inhalations) and formoterol (4.5 µg; two inhalations) via separate inhalers; or budesonide (200 µg, two inhalations) alone (44). In an extension to this study, a health economic analysis has been performed comparing the Symbicort® group (n=123) with the budesonide alone group (n=124), and was conducted on the basis of the healthcare system and drug costs in Sweden with costs being calculated in SEK (45).

The results of this study showed that Symbicort® was more effective than budesonide alone; patients receiving Symbicort® had 45 asthma control days (i.e., no nocturnal waking, no asthma symptoms and no rescue medication) over 12 weeks of treatment compared with 29 asthma control days in patients receiving budesonide alone—a significant difference of 54% in favour of Symbicort® (45). Furthermore, there were significantly fewer mild exacerbations in the Symbicort® group than the budesonide alone group, with a trend in favour of Symbicort® in the number of severe exacerbations. Although the cost of Symbicort® was higher than the cost of budesonide, the costs due to exacerbations and use of other asthma medications were lower in the Symbicort® group compared with those for patients treated with budesonide alone. For example, the mean exacerbation cost per patient during the 12-week study period was SEK 476 in the Symbicort® group compared with SEK 641 in the budesonide group (45). These results, i.e., the greater number of asthma control days and the lower cost of exacerbations in the Symbicort® group, suggest that combined therapy of budesonide and formoterol in a single inhaler helps control asthma and is more cost-effective than budesonide alone.

**ASTHMA AND THE PATIENT**

Appropriate and cost-effective treatment of asthma is very important, but so too is the well-being of the
patient. Asthma can be quite distressing to the sufferer, with some patients feeling that they cannot partake in 'normal' activities such as exercise as a result of their asthma. Additionally, patients may experience anxiety caused by the fear of having an asthma attack (46). The misery associated with asthma can manifest itself in many ways, leading to a loss in productivity and embarrassment, as is the case with cough-variant asthma where the coughing associated with this type of asthma can be so severe as to cause incontinence, insomnia and a disturbed social life (47).

One of the aims of asthma treatment as outlined in the guidelines is that patients should have no restrictions on their ability to perform normal daily activities (physical, social and occupational). Healthcare professionals should be particularly concerned about the normal development of asthmatic children, both mentally and physically (6). They should use treatments that will control the child's asthma to such an extent that they can have a normal lifestyle that is no different from that of their peers. Over the past decade, asthma-specific questionnaires that assess the effects of various treatments on patient quality of life have been developed and validated (48). As part of the recent study by Pauwels and colleagues, the long-term effects of inhaled corticosteroids and long-acting $\beta_2$-agonists on asthma-specific quality of life were examined in 470 adults with asthma (43). After a 4-week run-in period during which they received budesonide (1600 $\mu$g day$^{-1}$), patients were randomized to budesonide (200 $\mu$g day$^{-1}$ or 800 $\mu$g day$^{-1}$) in combination with formoterol (24 $\mu$g day$^{-1}$) or placebo for 1 year. The Asthma Quality of Life Questionnaire (AQLQ) was completed seven times during the 12-month period. There was a significant improvement in the overall AQLQ score during the run-in period of approximately 0.50 ($P<0.001$), and a further significant improvement of 0.21 ($P=0.028$) in the budesonide (800 $\mu$g) plus formoterol (24 $\mu$g) group after randomization (43). The conclusion from this study was that the quality of life of an asthmatic patient may improve as a result of combined long-term therapy with budesonide and formoterol.

These improvements will only occur if patients continue to take their medication in the long term. Adherence to medication is a major factor determining the degree of asthma control. Unfortunately, adherence is poor worldwide, with fewer than 50% of asthma patients in some countries adhering to their recommended treatment regimen (18,49). The reasons behind this are complex, but may include: a lack of understanding or denial of their disease; confusion about treatments, especially when multiple inhalers are prescribed using different dosing frequencies; fear of side-effects from medications; poor doctor–patient communication; forgetfulness or complacency; psychological disorders such as depression; difficulties using the inhaler(s) prescribed (32,50–53). In a survey carried out on young asthmatics, 9% (4/45) admitted that lack of adherence was a result of problems they had with using their inhaler devices and the main reason for non-compliance was forgetfulness (53, 24/45) (32). Studies investigating patients' ability to use inhalers have demonstrated that many patients do not use pMDIs correctly; they cannot co-ordinate actuation of the device with inhalation (54). Asthma inhalers must be simple to use in order to maximize patient adherence to treatment. Dry powder inhalers are driven by inspiratory flow and can be used by almost all asthmatics aged older than 5 years. A direct comparison of the Turbuhaler® and Diskhaler® systems for delivery of asthma medication, in an open, randomized, crossover study in adult patients, showed that the Turbuhaler® is at least as effective and easy to use as the Diskhaler® (53). Furthermore, in other studies comparing the Turbuhaler® and Diskus® inhaler, more than 50% of patients (both adults and children) stated they were happy using the Turbuhaler® and would use it again (55,56). The simplification of asthma treatment regimens, such that patients are given perhaps only a single inhaler that they only have to use once or twice daily, is expected to have a significant impact on patient adherence and, therefore, on the control of the disease (57).

SUMMARY

Asthma imposes a significant burden on society as a whole and on individuals by reducing their well-being and quality of life. In addition, as the economic burden of asthma is increasing, efforts must be made to use the most cost-effective treatments available. Effective management of asthma involves optimizing asthma control. Inhaled corticosteroids, such as budesonide, effectively control airways inflammation in asthma. Addition of an inhaled, long-acting $\beta_2$-agonist, such as formoterol, to the existing anti-inflammatory treatment is an attractive option that may be beneficial to the patient by improving their asthma control and quality of life. Symbicort® — budesonide and formoterol in a single inhaler is a cost-effective treatment for asthma vs budesonide, that quickly gains and maintains control of asthma.

REFERENCES


