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Clinical outcome of adding long-acting β-agonists to inhaled corticosteroids

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Abstract Current asthma management guidelines state that where a patient is receiving a low to moderate dose of inhaled corticosteroids and is still experiencing symptoms the dose of corticosteroid should be increased and, if necessary, a long-acting bronchodilator should be added. Many studies have now shown that the addition of a β_2-agonist with long-acting properties is more effective at controlling asthma symptoms than increasing the dose of corticosteroid alone. The Formoterol and Corticosteroid Establishing Therapy (FACET) study was a 12-month study comparing exacerbation rates in patients treated with budesonide (100 μg or 400 μg) twice daily alone *vs.* treatment with budesonide (100 μg or 400 μg) twice daily plus formoterol 9 μg twice daily (delivered dose) (1). The addition of formoterol reduced the rates of mild and severe exacerbations compared with budesonide alone, with the lowest rates seen in patients receiving high-dose budesonide and formoterol. There was no difference in the profile of exacerbations in any groups, indicating formoterol does not mask any signs of inflammation. The addition of formoterol to budesonide was also shown to result in improved lung function (as measured by peak expiratory flow rate and forced expiratory volume in 1 second), night-time awakenings and the use of as-needed medication when compared with an increase in the dose of budesonide. In all cases, increasing the dose of budesonide and addition of formoterol resulted in the most improvement and a significant increase in quality of life, measured by Asthma Quality of Life Questionnaire (AQLQ), was noted. In conclusion, the addition of formoterol to established treatment with inhaled corticosteroids provides superior asthma control compared with an increase in the dose of corticosteroid alone.

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Keywords formoterol; corticosteroid; budesonide; exacerbation

INTRODUCTION

Over the past 100 years, the management of asthma has changed considerably. In the early part of the twentieth century asthma was recognized as a chronic disorder, but treatment was aimed at treating exacerbations, with little attention to the ongoing, day-to-day complications. With the introduction of first adrenaline and then oral corticosteroids, both of which were derived from adrenal extract, treatment was aimed more at preventing these exacerbations. Great strides forward were made with the introduction of inhaled therapy, both with short-acting β_2-agonists and, more recently, corticosteroids, in treating symptoms and providing maintenance therapy. Over time goals have changed, and we are now looking towards achievement of *normal* lung function for patients, rather than just preventing symptoms and exacerbations.

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Newer agents are becoming available and it is the use of these agents in combination with existing drugs that may help to achieve this goal. Such agents include salmeterol, a long-acting β_2-agonist, and formoterol, a β_2-agonist that has not only a long duration, but also a fast onset of action (2). These drugs have a potential application in maintenance therapy and, in the case of formoterol, also in as-needed therapy. Traditionally, if a patient was poorly controlled on a low to moderate dose of corticosteroid, increasing the dose was the accepted treatment strategy. However, recent evidence suggests that adding a β_2-agonist with a long duration of effect to current therapy produces a greater improvement in asthma control compared with increasing the dose of corticosteroid alone – patients have been shown to experience fewer symptoms, have improved lung function and require less as-needed medication. Also, the rate of both mild and severe exacerbations has been shown to decrease using this treatment strategy.

For a time there was some debate about whether it was appropriate to use β_2-agonists regularly as maintenance therapy (3). Several studies have suggested an in-

crease in mortality and morbidity associated with regular use of inhaled β_2-agonist bronchodilators, particularly fenoterol (4–6). Larger studies have since shown that maintenance therapy with β_2-agonists is not associated with increased risks compared with as-needed use. In the TRUST study (The Regular Use of Salbutamol Trial), there was no evidence that regular use of inhaled salbutamol increased the exacerbation rate of asthma when compared with as-needed use (7).

The aim of this paper is to review the position of β_2-agonists with long-acting properties and the place they have in combination therapy with inhaled corticosteroids.

THE ADDITION OF LONG-ACTING β_2-AGONISTS TO INHALED STEROIDS

The first study to suggest that the addition of long-acting β_2-agonists to inhaled corticosteroids would provide better asthma control was performed by Greening *et al.* (8). The guidelines for asthma management at this time stated that in patients poorly controlled on a low dose of inhaled corticosteroid, the first step should be an increase in the dose. In this study, patients receiving inhaled beclomethasone dipropionate (BDP) 200 μg twice daily, who were still experiencing symptoms, were randomized to receive either salmeterol 50 μg plus BDP 200 μg twice daily or a higher dose of BDP, 500 μg twice daily, for 6 months. An improvement in lung function, measured by mean morning peak expiratory flow (PEF), was noted in both groups, but the difference was significantly greater in the salmeterol group at all time points ($P < 0.05$) (Fig. 1). When considering the use of as-needed relief medication and asthma symptoms (day- and night-time), the results in the salmeterol group were also significantly improved compared with increasing the dose of BDP alone.

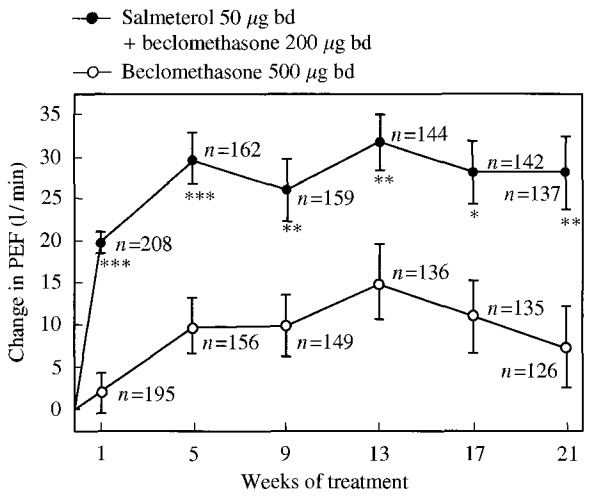

Figure 1. Effect on mean morning PEF rate of adding salmeterol to beclomethasone 200 μg twice daily compared with increasing beclomethasone dose to 500 μg twice daily (8). Changes from baseline (±SE) in mean morning and evening PEF rate during 6 months' study treatment. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. (Reproduced with permission from *The Lancet*.)

Similar results have been seen in a study by Woolcock *et al.* (9) who randomized moderate and severe asthmatic patients, poorly controlled on BDP 500 μg twice daily to receive either salmeterol 50 μg or 100 μg twice daily with their current dose of BDP or an increase in BDP to 1000 μg twice daily. Even though these patients were initially receiving a higher dose of inhaled corticosteroids than taken in the Greening study, the addition of either dose of salmeterol produced a significant improvement in lung function compared with increasing the dose of BDP. Both salmeterol groups also had a significantly increased percentage of symptom-free days and nights and reduced use of as-needed relief medication compared with BDP. Interestingly, there was no difference between the two salmeterol groups and exacerbation rates did not differ between all three groups. A meta-analysis of nine studies has confirmed that addition of salmeterol to a low dose of inhaled corticosteroids gives better asthma control, in terms of reduced symptoms, improved lung function and reduced as-needed β_2-agonist use, than doubling the dose of inhaled corticosteroids (10).

A landmark trial in this area is the FACET trial, which compared the effects of adding formoterol to budesonide with budesonide only over a longer period than previously studied, a total of 12 months (1). This study provided further evidence demonstrating that β_2-agonists with a long-acting profile do not have a detrimental effect on the long-term control of asthma. For the first time, frequency of exacerbations was chosen as the primary outcome in a trial of this type, defined as either: 1] severe, i.e. a requirement for oral glucocorticoids as judged by the investigator or following a decrease in the peak flow to more than 30% below the baseline value on 2 consecutive days; or 2] mild, i.e. 2 consecutive days when morning peak flow decreased more than 20% below baseline, the use of more than three additional inhalations of terbutaline in a 24 h period or night-time awakening due to asthma. As exacerbation rates give a clear indication of disease advancement, this study provides invaluable data about the underlying inflammatory disease. Other endpoints studied were lung function, measured by forced expiratory volume in 1 second (FEV_1) and PEF, asthma symptoms, night-time awakenings, and the requirement for as-needed β_2-agonist use.

Patients with asthma taking a mean daily dose of budesonide 800 μg were randomly assigned to one of four treatments delivered by means of a dry-powder inhaler (Turbuhaler®): 1] budesonide 100 μg twice daily plus placebo; 2] budesonide 100 μg twice daily plus formoterol 9 μg twice daily, delivered dose; 3] budesonide 400 μg

twice daily plus placebo; or 4] budesonide 400 μg twice daily plus formoterol 9 μg twice daily. During a 4-week, run-in period, patients were treated with a high dose of inhaled corticosteroid (budesonide 800 μg twice daily) to ensure they were stable and active treatment was then given for a 12-month period. Terbutaline was permitted as needed for relief of symptoms.

When compared with budesonide 200 μg daily and placebo, rates of severe and mild exacerbation were reduced in all other groups, with the lowest rates seen in patients who received the higher dose of budesonide plus formoterol (Figs 2 and 3). Patients in this group had a reduction in severe exacerbations of 63% ($P < 0.001$) and in mild exacerbations of 62% ($P < 0.001$). Although the decrease in the rate of severe exacerbations was not unexpected following previous research, the decrease in the rates of mild exacerbations observed had not been anticipated.

It had been suggested that use of formoterol might mask any underlying inflammatory process, preventing symptoms and therefore disguising the build up to an acute attack. This would result in exacerbations with a more rapid onset and greater severity. Interestingly, further analysis from FACET showed the time course, severity and duration of exacerbations to be similar in each study group (11).

During the run-in period FEV_1 increased in all groups and increased further with the addition of formoterol (Fig. 4). The greatest increases were again observed in the group receiving budesonide 800 μg and formoterol 18 μg daily, however, the addition of formoterol to low-

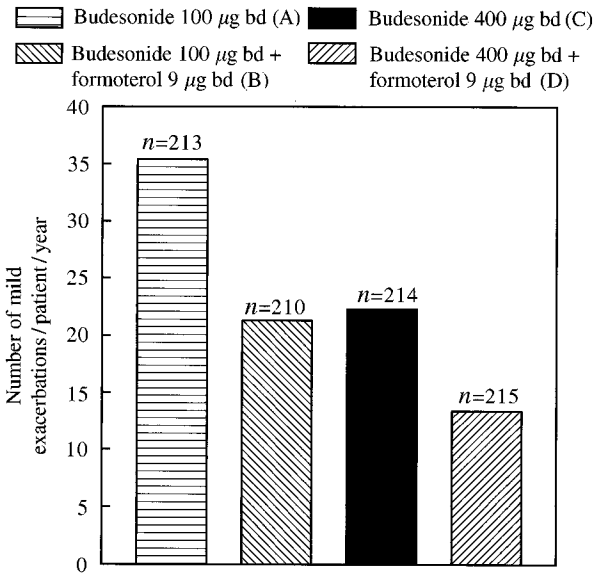

Figure 2. Rate of mild exacerbations during 12-months' treatment with formoterol and budesonide in the FACET study (1). Increasing the dose of budesonide (A *vs.* C): $P < 0.001$; adding formoterol, irrespective of budesonide dose (A+C *vs.* B+D): $P < 0.001$.

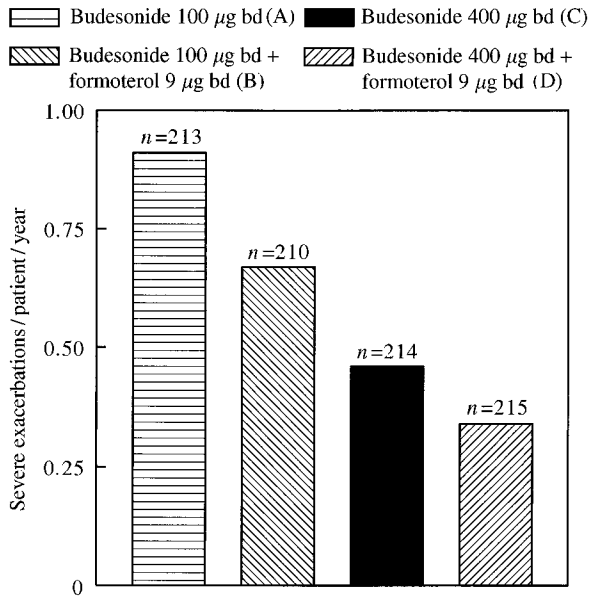

Figure 3. Rate of severe exacerbations during 12-months' treatment with formoterol and budesonide in the FACET study (1). Increasing the dose of budesonide (A *vs.* C): $P < 0.001$; adding formoterol, irrespective of budesonide dose (A+C *vs.* B+D): $P = 0.01$.

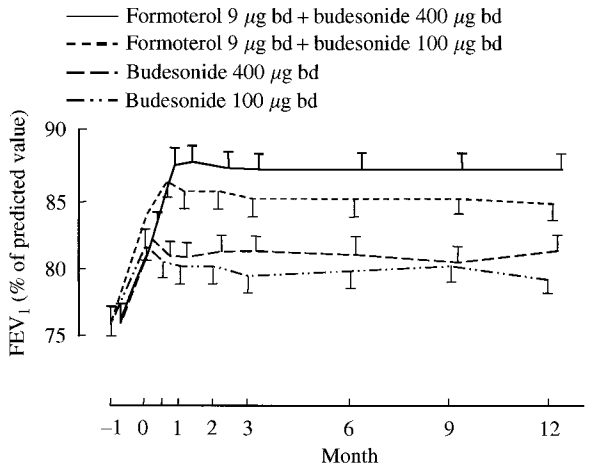

Figure 4. FEV_1 during the FACET study (1). FEV_1 is shown as a mean percentage of the predicted value during the run-in period and the treatment period. The bars indicate 2 SE. (Reproduced with permission from N Engl J Med.)

dose budesonide treatment had a greater effect than increasing the dose of budesonide alone. These results were maintained throughout the 12-month period of the study. Morning peak flow also increased on the addition of formoterol. This response was greatest over the first 2 days of treatment and then decreased slightly, suggesting a small degree of tolerance had developed. After this time point, the peak flow remained stable for the rest of the 12-month period, and was significantly higher than either of the budesonide-only groups. The tolerance

produced was felt to have little or no clinical significance. The requirement for as-needed medication, symptom scores and the number of days with symptoms were all significantly lowered following the addition of formoterol compared with budesonide alone.

The authors concluded that the addition of formoterol to budesonide resulted in superior asthma control compared with budesonide only over a long-term period. The greatest improvements were observed where the dose of budesonide was also increased. All treatments were well tolerated and no safety issues were identified.

As quality of life is an important outcome indicator for patients, the Asthma Quality of Life Questionnaire (AQLQ) was completed in 470 patients who completed the FACET study and analysed separately (12). An increase in AQLQ after the initial improvement during the run-in phase was observed in patients treated with budesonide 400 μg plus formoterol 9 μg twice daily. This improvement was sustained throughout the 12-month study. However, the correlation between changes in AQLQ and the results observed with respect to asthma control were weak.

Similar results as those seen in the FACET study have also been seen in a study in mild asthmatic patients. The addition of formoterol 4.5 μg twice daily to budesonide 100 μg twice daily resulted in fewer severe exacerbations and poorly controlled days compared with increasing the dose of budesonide to 200 μg twice daily (13).

CONCLUSIONS

The evidence presented indicates that patients with poorly controlled asthma will benefit from the addition of a β_2-agonist with long-acting properties to their established inhaled corticosteroid treatment. Increases in lung function and improvement in symptom control have been observed and, very importantly, a reduction in both mild and severe exacerbations has been shown with formoterol.

The mechanism for this effect is not understood. A possible explanation is that the dose-response curve for corticosteroids is relatively flat and, therefore, most of the anti-inflammatory effect can be obtained from lower doses of the drug (14). Thus, increasing the corticosteroid dose would have little effect compared with adding a β_2-agonist with long-acting properties.

Another possible reason for the decrease in exacerbation rate observed in the FACET study is the effect of formoterol in stabilizing mast cells, which may result in additional protective effects against specific stimuli (15). It also appears that β_2-agonists with a long-acting profile may potentiate the effects achieved with corticosteroid alone. Research has shown that β_2-agonists are potent activators of glucocorticoid receptors and this activity may substantially mediate the anti-inflammatory actions of corticosteroids, observed both *in vitro* (16) and *in vivo* (17).

In these cost-conscious times it is important that any treatment is not only efficacious, but also cost-effective. A group of independent physicians has estimated the average healthcare resources and productivity losses following exacerbations in FACET-like patients, and this information was evaluated against the clinical data from the FACET study (18). The conclusions were that, for a marginal net cost increase, considerable improvements for all outcome measurements were observed.

What, then, are the implications for patients? Patients with mild to moderate asthma, experiencing mild exacerbations, frequent night-time awakenings, limited daytime activity and high use of as-needed medication would generally benefit from the addition of a β_2-agonist with long-acting properties. For those patients with more severe symptoms, i.e. frequent and severe asthma exacerbations, often requiring hospitalization or oral corticosteroid therapy, an increase in the dose of their inhaled corticosteroid plus a β_2-agonist with a long duration of effect is likely to improve their condition. Although the effect of adding formoterol to all patient subgroups needs to be researched further, it appears that this treatment strategy provides a cost-effective treatment with rapid control of symptoms and is both well tolerated and effective in the long term.

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