Adding formoterol to budesonide in moderate asthma—health economic results from the FACET study

F. ANDERSSON*, E. STÅHL*, P. J. BARNES†, C.-G. LOFDahl†, P. M. O’BYRNE‡, R. A. PAUWELS‡, D. S. POSTMA†, A. E. TATTERSFIELD** and A. ULLMAN*, for the Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group

* AstraZeneca R&D Lund, Lund, Sweden, † Imperial College, London, U.K., ‡ University Hospital, Lund, Sweden, § McMaster University, Hamilton, Canada, * Ghent University Hospital, Ghent, Belgium, ‡ University Hospital, Groningen, The Netherlands and ** City Hospital, Nottingham, U.K.

The FACET (Formoterol and Corticosteroid Establishing Therapy) study was conducted to assess the role of the long-acting β2-agonist formoterol (Oxis® Turbuhaler®) in treating patients with moderate, persistent asthma (2). The double-blind, 1-year study assessed the effects of adding inhaled formoterol to both a low and a moderate dose of the inhaled corticosteroid budesonide (Pulmicort® Turbuhaler®). The rates of mild and severe exacerbations were reduced significantly by adding formoterol. The FACET study established that there is clear clinical benefit in adding formoterol to budesonide therapy in patients who have persistent symptoms of asthma despite treatment with low to moderate doses of an inhaled corticosteroid.

The primary objective of the present study was to assess the health economic value of adding formoterol to budesonide in the treatment of moderate, persistent asthma—health economic results from the FACET study.
asthma. Thus, we compared the different treatment strategies in the FACET study.

Materials and methods

THE FACET STUDY

The FACET study examined the clinical efficacy and the safety of adding formoterol to budesonide over a 12-month period (2). The study was carried out in nine countries. During the 4-week run-in period, patients received inhaled budesonide at a dose of 800 \( \mu \)g twice daily to stabilize their asthma. A total of 852 patients, aged 18–70 years, who had had asthma for at least 6 months, had been treated with an inhaled corticosteroid for at least 3 months, had a daily pre-run in corticosteroid dose of less than 1600 \( \mu \)g(brelocmethasone, budesonide pressurized metered-dose inhaler) or 800 \( \mu \)g (budesonide Turbuhaler\textsuperscript{®} or fluticasone), and successfully completed the run-in period, were randomized to one of four treatment groups:

- Low-dose budesonide (total daily dose 200 \( \mu \)g) plus placebo
- Low-dose budesonide plus formoterol (total daily dose 24 \( \mu \)g)
- Moderate-dose budesonide (total daily dose 800 \( \mu \)g) plus placebo
- Moderate-dose budesonide plus formoterol (total daily dose 24 \( \mu \)g)

Of the randomized patients, 81% completed the study. Patients were withdrawn if they had three severe exacerbations within 3 months or five during the 12-month period. This included 10 patients in the low-dose budesonide arm, seven in the low-dose combination arm, four in the moderate-dose budesonide arm, and none in the moderate-dose combination arm. The main reasons for not completing the study were, for example, incorrect randomization, non-compliance with study procedures, adverse events, and being lost to follow-up.

The primary outcome studied was the incidence of mild and severe exacerbations of asthma. A mild exacerbation was defined as: 2 consecutive days with any combination of:

- A peak expiratory flow (PEF) in the morning that was more than 20% below the baseline value
- The use of more than three additional inhalations of terbutaline per 24 h as compared with the baseline period
- Awakening at night due to asthma.

A severe exacerbation was defined as:

- Requiring treatment with oral glucocorticoids, as judged by the investigator, and/or
- A decrease in PEF as measured in the morning, on 2 consecutive days, of more than 30% below the baseline value.

The rates of mild and severe exacerbations were reduced by 40 and 26%, respectively, when formoterol was added to budesonide. The clinical results were tested for homogeneity across study centres.

THE ECONOMIC ANALYSIS

The analysis combined the outcome data from the FACET study with an expert survey. The purpose of the survey was to obtain complementary estimates of average resource utilization in connection with a mild and severe exacerbation, respectively.

The perspective of the economic analysis was that of society, and the countries included were Sweden, U.K. and Spain. (The FACET study included 126 patients from the U.K. and 107 from Spain. Sweden did not participate.) These countries were selected because they represent Northern, Central and Southern Europe, and hence may be reasonably representative of other countries in these regions in terms of treatment patterns and relative prices. The primary analysis encompassed direct medical costs (drugs, physician visits, emergency visits, etc.) only, since we judged physicians to be slightly less capable of estimating patients’ absence from work than their use of healthcare resources.

The sample comprised 17–18 physicians in each of the three countries. They consisted of physicians who were specialists in pulmonary medicine (seven or eight per country) or who were general practitioners (10 per country), and who were interviewed individually, face-to-face, by an independent, trained nurse from a company specializing in conducting surveys. The interviews took between 45 and 60 min. The physicians were recruited from a database of experts who had participated in previous surveys, by calling hospitals in selected locations, or at random from the official country lists of physicians. The physicians provided wide geographical representation but were mainly from the largest urban areas in each country.

A questionnaire was developed, and following a pilot test it was sent to the physicians, together with information on the purpose of the survey, a few days before the interview. Before being accepted in the survey the physicians had to fill in and return a screening questionnaire which included questions on specialty (GP or specialist), age (to exclude retired physicians), and the number of asthma patients treated per month (to include physicians with day-to-day contacts with asthmatics). The physicians were asked to estimate average resource use for a FACET-like patient in connection with a mild or severe asthma exacerbation (as defined in the FACET study).

The expert group mean estimates were combined with FACET data (medication, hospitalization) and average prices from official price lists\textsuperscript{*} in order to calculate the cost of a mild and a severe exacerbation in each country. Examples of direct costs included costs of physician visits, emergency visits and hospital stays, in connection with the exacerbations. Indirect costs included the cost of absence from work in connection with an exacerbation, adjusted for

\textsuperscript{*}A list of sources is available from the authors upon request.
employment rates. The cost estimates for the two types of exacerbations were then related to individual, per patient incidence data from the study.

Information on the use of budesonide, formoterol, other medication and hospitalizations was prospectively recorded during the course of the FACET study. This was the basis for the largest part of the costs.

The clinical outcomes from the FACET study and the costs incurred were calculated per patient-year (3).

All costs were expressed as Euros at 1999 values. Earlier values were updated to 1999 values using the local consumer price index. The exchange rates for one Euro were GBP 0.61, SEK 8.39 and ESP 166.39 in September 2000.

OUTCOME VARIABLES

The FACET study had a number of clinical outcome measures, including exacerbations avoided and symptom-free days gained, so we conducted a cost-consequence study, i.e. a study presenting costs in relation to the specific outcomes (4). When costs were larger in the combination group we calculated an incremental cost-effectiveness ratio, relating the extra costs to the extra gains in symptom-free days (SFDs).

Exacerbations, episode-free days (EFDs) and symptom-free days were used in the health economics analysis. An episode-free day was defined as a day that satisfied all of the following criteria: morning PEF > 80% of baseline, no inhalation of a β₂-agonist, no asthma symptoms, no awakenings at night due to asthma and no adverse events. A symptom-free day was defined as a day with no symptoms.

SENSITIVITY ANALYSIS

It has been recommended that health economic results be presented both with and without indirect costs (5). Thus, in the first sensitivity analysis we studied total costs, including indirect costs. The physician panels in each country estimated likely absence from work in connection with a mild or severe exacerbation.

In the second sensitivity analysis we determined the percentage by which the physicians’ estimates of costs for a mild and a severe exacerbation would have to be changed to reverse the results. This threshold analysis was done to take into account the variation among the costs of exacerbations and is a rather demanding way of validating the results in that the estimates of both mild and severe exacerbations are being altered in the same direction at the same time.

STATISTICAL ANALYSIS

We used the Student’s t-test to test for differences between groups. The Student’s t-test is based on the assumption that the underlying distributions of the two samples are normal (Gaussian), and have a common variance. The test is fairly robust regarding violations of the assumptions, at least with larger sample sizes (6). The 95% confidence intervals for the cost of exacerbations were estimated using bootstrap and Efrons percentile method.

Results

THE COST OF AN EXACERBATION

The resources used in connection with a mild and a severe exacerbation, the frequency of utilization of the resources, and the unit cost of each resource are listed in Table 1. There were some country-specific differences in how patients were treated, such as in the use of GPs or asthma specialists for example. To some extent the resource use in connection with an exacerbation was complementary, e.g. visits to a specialist instead of a GP (Sweden/Spain vs. U.K.), or emergency visits instead of GP visits (Sweden/Spain vs. U.K.). As a result of these differences, but mainly because of the differences in unit costs, the U.K. exacerbation estimates are only about 60–80% as high as the Swedish estimates.

OUTCOMES

The outcome measures in the health economic analysis are presented in Table 2. All outcomes improved significantly when formoterol was added, with the best results for the moderate-dose budesonide plus formoterol arm.

COSTS

A detailed comparison of the costs for the four treatment strategies is presented in Table 3. The cost of adding formoterol was generally offset by a reduction in the use of other resource items, primarily in association with frequent mild exacerbations (the main cost-driver was GP visits), thus generating cost savings in Sweden, and cost-savings for low dose budesonide in Spain. For the U.K. the reduction in direct costs did not completely counterbalance the cost of adding formoterol, but between 45–61% of the extra cost of formoterol could be offset. This resulted in an incremental cost of Euro 4.67 and 6.60 per SFD gained. In Spain, 78% of the extra cost of adding formoterol to a moderate dose of budesonide could be offset, thus resulting in a cost per SFD of Euro 2.51.

The cost offsets were larger in all three countries when adding formoterol to the low dose of budesonide. However, in all three countries the combination of the moderate dose of budesonide and formoterol was the most cost-effective alternative.

SENSITIVITY ANALYSIS

When productivity losses were included in the analysis (Fig. 1), adding formoterol generated cost savings in all three countries. This cost saving was statistically significant in Sweden when formoterol was added to the low dose of budesonide.
Table 1: The estimated resource use and cost per mild and severe exacerbation (1999 values).

<table>
<thead>
<tr>
<th>Resources</th>
<th>Unit cost</th>
<th>Estimated percentage of all patients who would require the resource</th>
<th>Unit cost</th>
<th>Estimated percentage of all patients who would require the resource</th>
<th>Unit cost</th>
<th>Estimated percentage of all patients who would require the resource</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(GBP)</td>
<td>Mild</td>
<td>Severe</td>
<td>(SEK)</td>
<td>Mild</td>
<td>Severe</td>
</tr>
<tr>
<td>Visit to a GP</td>
<td>17.28</td>
<td>35.9</td>
<td>69.1</td>
<td>790</td>
<td>29.4</td>
<td>56.9</td>
</tr>
<tr>
<td>Visit to a specialist</td>
<td>70.18</td>
<td>2.4</td>
<td>7.7</td>
<td>1491</td>
<td>9.4</td>
<td>28.1</td>
</tr>
<tr>
<td>Visit to a nurse</td>
<td>6.48</td>
<td>20.1</td>
<td>27.2</td>
<td>339</td>
<td>9.7</td>
<td>18.3</td>
</tr>
<tr>
<td>House-call by physician</td>
<td>50.75</td>
<td>2.2</td>
<td>22.1</td>
<td>790</td>
<td>1.8</td>
<td>6.7</td>
</tr>
<tr>
<td>House-call by nurse</td>
<td>15.20</td>
<td>0.6</td>
<td>2.9</td>
<td>339</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Phone-call to physician</td>
<td>9.29</td>
<td>5.4</td>
<td>12.4</td>
<td>110</td>
<td>30.3</td>
<td>49.4</td>
</tr>
<tr>
<td>Phone-call to nurse</td>
<td>1.44</td>
<td>5.8</td>
<td>7.3</td>
<td>34</td>
<td>24.5</td>
<td>26.2</td>
</tr>
<tr>
<td>Emergency unit visit</td>
<td>38.70</td>
<td>2.2</td>
<td>20.5</td>
<td>2794</td>
<td>9.5</td>
<td>31.1</td>
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<tr>
<td>Admission to hospital*</td>
<td>170.67</td>
<td>0</td>
<td>7.0</td>
<td>2479</td>
<td>0</td>
<td>7.0</td>
</tr>
<tr>
<td>Days in hospital*</td>
<td>181</td>
<td>0</td>
<td>7.4</td>
<td>3599</td>
<td>0</td>
<td>7.4</td>
</tr>
<tr>
<td>% employed</td>
<td>—</td>
<td>82.6</td>
<td>56.6</td>
<td>—</td>
<td>65.8</td>
<td>43.2</td>
</tr>
<tr>
<td>% absence from work</td>
<td>21.6</td>
<td>72.5</td>
<td>20.4</td>
<td>34</td>
<td>24.5</td>
<td>26.2</td>
</tr>
<tr>
<td>Days absent from work</td>
<td>75.81</td>
<td>3.0</td>
<td>7.6</td>
<td>1133</td>
<td>2.6</td>
<td>7.1</td>
</tr>
<tr>
<td>Total cost†</td>
<td>57</td>
<td>377</td>
<td>1228</td>
<td>6712</td>
<td>19213</td>
<td>84749</td>
</tr>
<tr>
<td></td>
<td>(93)</td>
<td>(615)</td>
<td>(146)</td>
<td>(800)</td>
<td>(109)</td>
<td>(509)</td>
</tr>
<tr>
<td>Of which direct costs</td>
<td>12</td>
<td>146</td>
<td>735</td>
<td>3973</td>
<td>7743</td>
<td>29380</td>
</tr>
<tr>
<td></td>
<td>(8; 16)</td>
<td>(139; 155)</td>
<td>(463; 1028)</td>
<td>(3602; 4371)</td>
<td>(5374; 9946)</td>
<td>(26625; 32272)</td>
</tr>
<tr>
<td>(Euro)</td>
<td>(20)</td>
<td>(238)</td>
<td>(88)</td>
<td>(474)</td>
<td>(46)</td>
<td>(177)</td>
</tr>
<tr>
<td>Of which indirect costs</td>
<td>45</td>
<td>230</td>
<td>493</td>
<td>2739</td>
<td>11470</td>
<td>55369</td>
</tr>
<tr>
<td></td>
<td>(17; 84)</td>
<td>(173; 285)</td>
<td>(201; 876)</td>
<td>(1815; 3864)</td>
<td>(1954; 27504)</td>
<td>(34760; 81923)</td>
</tr>
<tr>
<td>(Euro)</td>
<td>(73)</td>
<td>(375)</td>
<td>(59)</td>
<td>(326)</td>
<td>(69)</td>
<td>(332)</td>
</tr>
</tbody>
</table>

Example: For the U.K., on average 2.4% of all FACET-like patients visit a specialist when having a mild exacerbation and close to 8% visit a specialist when having a severe exacerbation. For Sweden, the percentages are about 9 and 28 and for Spain 22 and 27, respectively. Percentages are the group means.

Sources of unit costs available from the authors on request.

Exchange rates as of September 2000: 1 Euro = GBP 0.613, SEK 8.39, PES 166.386.

*Collected within the FACET trial.

†95% confidence interval within brackets.
The second sensitivity analysis showed that the direct costs of exacerbations would need to increase by 69% (low dose budesonide plus formoterol) and 135% (moderate dose budesonide plus formoterol) respectively, over the estimates provided by the experts for the formoterol costs to be completely recouped in the U.K. In Sweden the exacerbation costs would need to be reduced by 58% and 41%, respectively, to reverse the outcome (i.e. negate the cost savings). To reverse the outcome in Spain, the cost estimates for low-dose budesonide and moderate-dose budesonide would need to decrease by 6% or increase by 31%, respectively.

**Discussion**

The extra direct costs of adding the long-acting inhaled β₂-agonist formoterol to the corticosteroid budesonide in asthmatic patients were generally offset by less resource use due to fewer exacerbations. In Sweden and Spain (low-dose...
Fig. 1. (a) Annual total costs per patient—200 μg budesonide. (b) Annual total costs per patient—800 μg budesonide.
budesonide) the extra cost of adding formoterol was more than offset. In the U.K. and in Spain (high-dose budesonide), the extra cost of formoterol was only partially offset. The net costs need to be considered in relation to the significant gains in the various clinical outcome measures found in the FACET study. If indirect costs are included, adding formoterol generates a potential for net savings. The most cost-effective strategy in the FACET study was the moderate dose of budesonide combined with formoterol.

Few health economic studies have previously looked at long-acting $\beta_2$-agonists, and none have investigated the cost-effectiveness of adding a long-acting $\beta_2$-agonist to a corticosteroid. Rutten-van Mólken et al. (7) examined the cost-effectiveness of adding a corticosteroid or an anticholinergic to a short-acting $\beta_2$-agonist in patients with moderately severe obstructive airway disease. They found that anti-cholinergics were not cost-effective whereas inhaled corticosteroids, at a cost of about US$5 per symptom-free day, were considered to be cost-effective. Rutten-van Mólken et al. and Campbell et al. (8,9) compared two long-acting $\beta_2$-agonists, formoterol and salmeterol. Whereas Rutten-van Mólken et al. found no difference in cost-effectiveness, Campbell et al. found that formoterol (supplied with a different device than in the previous study) patients were significantly less expensive and that there was a positive trend in SFDs.

When assessing cost-effectiveness, the ideal is to conduct a prospective study. Information on resource use would then be collected at the same time as the clinical outcomes. As we did not know the frequency of visits to physicians and nurses, other health care contacts, emergency unit visits and absence from work in relation to an exacerbation in the FACET study, we complemented the information we had with expert estimates of likely resource use. This is an accepted method within the health economic community, but only when no other options exist (10). Another possibility for carrying out a retrospective analysis could be to conduct a patient chart review. In the present case, however, this was not possible, since an asthma exacerbation is largely a matter of clinical definition based on use of rescue medication, symptoms and PEF values. Valid and complete data concerning the latter two criteria are most commonly missing in patient charts. Also, the patient may not realise that he/she is experiencing an exacerbation. In the FACET study 18% of those experiencing a fall in PEF of more than 30% did not take the recommended oral corticosteroids (11). Furthermore, there is a risk of underestimation since some of the resource use may take place before the patient actually seeks care, e.g., an increased use of medication and loss in productivity. The effect of severe exacerbations is usually obvious seven or more days before the patient actually seeks medical attention (11).

The number of experts surveyed in each country was large compared to the average of six surveyed in previous studies (10). In addition, we tested the validity of the estimates by conducting demanding threshold analyses. We also surveyed experts from both primary and secondary care, thus reflecting real life clinical practice. The majority of costs (generated from drug consumption and hospitalizations) were obtained directly from the clinical study.

A limitation of this panel expert approach is that the expert estimates may not be accurate or may change over time. Data on the cost of exacerbations is rather sparse. For the U.K., Hoskins et al. (12) found that the average annual health care costs per patient who had an asthma attack were £381 compared with £108 for those who had not had an asthma attack. However, the number of exacerbations per year that these patients experienced was not stated, nor was an asthma attack defined.

International asthma guidelines propose high dose inhaled corticosteroids as an alternative treatment option to adding long-acting $\beta_2$-agonists, for patients not well-controlled on low to moderate doses of corticosteroids. The FACET study did not include such a study arm and hence this option cannot be tested in this analysis. One can only speculate as to the cost-effectiveness of a high dose of inhaled corticosteroids compared to adding a long-acting $\beta_2$-agonist, but there are indications of a relatively poor dose–response when increasing from a moderate to a high dose of corticosteroids (13).

There were major differences between the three countries in the proportions of patients requiring a particular type of resource use. We do know that there are variations in medical practice among countries. Jepson et al. (14) investigated the prescribing of asthma drugs by GPs in eight European areas (Belgium, Ireland, England, Italy, Northern Ireland, Portugal, Scotland and Spain). For adult asthmatics the use of short-acting $\beta_2$-agonists ranged from 24% in Belgium to 44% in England (Spain 40%), and the use of long-acting $\beta_2$-agonists ranged from 1% in Ireland to 9% in Italy (England 2%, Spain 9%). As for inhaled corticosteroids, these were prescribed for only 14% of the Italian asthmatics but for twice as high a percentage in Spain, Scotland and England. The use of oral corticosteroids ranged from 3% in Portugal to 19% in Northern Ireland (Spain 4% and England 14%). To some extent the resource use in connection with an exacerbation was complementary in our study, with some resources being used as substitutes for other.

We conducted the analysis in three European countries with differences in treatment patterns, prices of healthcare and healthcare organization. The clinical results, including the consumption of drugs, were pooled across all patients in the health economic evaluation. Although there were some local variations in the use of specific resource items, the results show reasonable consistency in that adding formoterol to budesonide is cost-effective in each of these three countries.

In conclusion, adding the inhaled long-acting $\beta_2$-agonist formoterol to low to moderate doses of the inhaled corticosteroid budesonide generates significant gains in all core outcome measures, with partial or complete offset of costs. Adding formoterol to budesonide can thus be considered to be cost-effective.

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