Cost-Effectiveness of Fluticasone Propionate Administered Via Metered-Dose Inhaler Plus Babyhaler™ Spacer in the Treatment of Asthma in Preschool-Aged Children*

Hans Bisgaard, MD; Martin J. Price, PhD; Claire Maden, MSc; and Niels A. Olsen, MSc

Study objectives: **To evaluate the cost-effectiveness of inhaled fluticasone propionate (FP) in children aged 12 to 47 months with asthma symptoms.**
Design: **A retrospective economic analysis conducted from the perspective of the Danish health-care system, based on clinical data from a 12-week study.**
Setting: **Thirty-three outpatient centers in nine countries.**
Patients: **Two hundred thirty-seven children aged 12 to 47 months with documented history of recurrent wheeze or asthma symptoms.**
Interventions: **Two dosages of FP, 100 μg/d and 200 μg/d, and placebo administered in two divided doses via a metered-dose inhaler and a Babyhaler (Glaxo Wellcome; Middlesex, UK) spacer device.**
Measurements: **Effectiveness in terms of asthma exacerbations, control of cough and wheeze symptoms, symptom-free days, overall direct costs of asthma management in Danish kroner at 1999 prices, and mean and incremental cost-effectiveness ratios.**
Results: **FP, 200 μg/d, was significantly more effective than placebo treatment in terms of the proportion of exacerbation-free patients (73.7% vs 59.8%; p = 0.025) and patients experiencing a ≥ 25% improvement in cough symptoms (57.9% vs 39.0%; p = 0.018). The costs per exacerbation-free patient, per patient with a ≥ 25% improvement in cough and wheeze symptoms from baseline, and per symptom-free day were lower in the FP groups than in the placebo group. The incremental cost-effectiveness ratios for these end points indicated that the additional benefits of FP, 200 μg/d, were achieved at a lower overall cost compared with placebo treatment.**
Conclusions: **From the perspective of the Danish health-care system, FP, 100 μg bid, administered via the Babyhaler inhalation device was cost-effective relative to standard therapy with bronchodilators alone.** ***(CHEST 2001; 120:1835–1842)***

Key words: asthma; cost effectiveness; fluticasone propionate; preschool children

Abbreviations: CI = confidence interval; DK = Danish kroner; FP = fluticasone propionate; ICER = incremental cost-effectiveness ratio

Inhaled corticosteroids are the most effective long-term control medication for asthma and are therefore the mainstay of treatment for the management of the disease in both adults and children.[1–3] These agents have been shown to improve lung function and reduce symptoms in children with asthma.[4–12] In accordance with these findings, both the British Thoracic Society guidelines[1] and the recent US pediatric asthma guidelines[13] now recommend the use of low-dose inhaled corticosteroids for the treatment of asthma during early childhood.

For editorial comment see page 1762

A randomized, placebo-controlled trial evaluated the efficacy and tolerability of fluticasone propionate (FP) [Flixotide; Glaxo Wellcome; Middlesex, UK]

*From the Copenhagen University Hospital (Dr. Bisgaard), Rigshospitalet, Copenhagen, Denmark; Global Health Outcomes (Dr. Price), Glaxo Wellcome Research and Development, Middlesex, UK; Respiratory Therapeutic Development (Ms. Maden), Glaxo Wellcome Research and Development, Uxbridge, UK; and Glaxo Wellcome (Mr. Olsen), Brondby, Denmark.

This study was sponsored by Glaxo Wellcome (protocol reference FLTB3016).
Manuscript received November 6, 2000; revision accepted July 7, 2001.
Correspondence to: Hans Bisgaard, MD, Professor of Paediatrics, Copenhagen University Hospital, Rigshospitalet, DK-2100 Copenhagen, Denmark; e-mail: Bisgaard@copsac.dk

administered via a metered-dose inhaler using the Babyhaler (Glaxo Wellcome) spacer device in children aged 12 to 47 months.[11] FP, 200 μg/d, produced improvements in terms of asthma exacerbations, symptoms, and parental satisfaction with treatment, providing support for the use of inhaled corticosteroid therapy in young children.

When considering whether to prescribe a new treatment, it is important to identify whether it is an efficient use of health-care resources. This is accomplished by evaluating net changes in both costs and outcomes through economic evaluation. This is particularly important in pediatric asthma because the burden of this condition on the patient, caregiver, and health-care system is high. Childhood asthma can have a profound effect not only on the child but also on the parents/caregivers in terms of distressing respiratory symptoms, sleep disturbance, inability to undertake normal play or social activities, and time lost from school or work.[14] In addition to negative effects on quality of life, childhood asthma can be associated with substantial economic costs.[15,16] Furthermore, Smith et al[15] estimated that preschool asthma accounted for 369,000 bed days in the United States annually, and the associated cost to care for these children was $18.5 million (US dollars); the direct costs of medication and hospitalization in this age group were estimated at $48.1 million and $586.2 million, respectively. The costs for medication and hospitalization represented 6.1% and 74.1% of the total direct costs, respectively. This contrasts with the asthma population as a whole, for which hospital costs typically represent a smaller proportion of overall direct costs than medication costs (20 to 25% and 37%, respectively).[17]

Improving asthma control through effective intervention is desirable from both clinical and economic viewpoints. In Denmark, the rate of hospital admissions for pediatric asthma remained relatively constant between 1978 and 1993, despite a general increase in asthma prevalence.[18] Importantly, during this period, the risk of hospital readmission fell by about one half. These data coincided with an improvement in the treatment of pediatric asthma in Denmark, as a result of the increased emphasis on early treatment with anti-inflammatory drugs.

In light of the burden of pediatric asthma, it is important to assess whether treatment interventions can reduce health-care resource utilization and improve clinical outcomes. The purpose of the present analysis was to evaluate whether adding the inhaled corticosteroid FP to the treatment of asthma in preschool children is a cost-effective treatment intervention.

Materials and Methods

Study Design

This was a retrospective economic analysis based on clinical data from a 12-week, multicenter (33 centers in nine countries), randomized, double-blind, parallel-group, placebo-controlled trial assessing the efficacy and safety of FP in children aged 12 to 47 months.[11] FP, 50 μg (two puffs of 25 μg); FP, 100 μg (two puffs of 50 μg); or placebo were administered twice daily via a metered-dose inhaler delivered through a Babyhaler spacer device. Patients were eligible for inclusion in the clinical trial if they had a documented history of recurrent wheeze or asthma symptoms. Patients were randomized to study treatment if they demonstrated asthma symptoms or required relief salbutamol treatment on at least 7 days of the 14-day run-in period. Those patients who had received treatment with inhaled or systemic corticosteroids or methylxanthine in the 2 weeks prior to the run-in period, or who had required any change to their asthma medication were excluded. Patients were also excluded if they had been hospitalized for asthma or had received a course of antibiotics for a chest infection during this 2-week period.

Salbutamol was used throughout the study as relief medication. Children could continue to receive any regular medication, including sodium cromoglycate, ketotifen, and/or antihistamines throughout the trial, provided the dose remained constant. Inhaled or systemic corticosteroids, anticholinergic medications, nedocromil sodium, β_2-agonists (other than salbutamol rescue medication) and methylxanthines were not permitted during the trial, unless used for the management of an asthma exacerbation.

Patients were assessed for adverse events, asthma exacerbations, and treatment compliance every 3 weeks during the 12-week treatment period. Parents kept daily diary records of their child's symptoms, recording daytime and nighttime scores for wheeze, cough, and shortness of breath on a scale of 0 to 3. Parents were also asked to record daytime and nighttime use of rescue salbutamol and the number of occasions they were awoken at night because of their child's asthma symptoms. Patients were withdrawn from the study if more than one exacerbation occurred that required additional treatment with oral or inhaled corticosteroids, or if symptoms became unacceptable or poorly controlled despite backup medication (short course of oral or inhaled corticosteroids).

The study was conducted in accordance with good clinical practice and the Declaration of Helsinki, and was approved by the local ethics committee at each center. Written informed consent to participate in the study was obtained from the parent/guardian of each patient.

Clinical Effectiveness

A number of outcome measures were used to determine treatment effectiveness for the purpose of the economic analysis. These included the proportion of patients remaining free of asthma exacerbations throughout the study, improvement in cough and wheeze symptoms, and symptom-free days.

An asthma exacerbation was defined as a worsening of the child's asthma symptoms that required either a change in medication (other than relief salbutamol) and/or required the parents to contact their general practitioner or the investigator. The proportions of patients who either experienced an exacerbation, or remained free of exacerbations throughout the trial were calculated for each treatment arm. Patients who withdrew prematurely from the study for reasons other than an asthma exacerbation, and who had not previously experienced an asthma exacerbation, were excluded from the analysis. This was because

it was impossible to predict whether or not the patient would have had an exacerbation if they had remained in the trial.

The proportion of patients achieving a ≥ 25% improvement in the median frequency of cough-free and wheeze-free days compared to baseline was determined. For patients who withdrew early from the study, the percentage of cough-free and wheeze-free days was calculated from the number of days they were in the study. A symptom-free day was defined as a 24-h period during which the patient reported no daytime or nighttime symptoms (score of 0 for cough, wheeze, and shortness of breath during the day and night).

Patients withdrawn from the study were assumed to have experienced no symptom-free days from the time of withdrawal until the end of the study if withdrawn due to asthma-related adverse events or lack of efficacy. Patients withdrawn for other reasons (*eg*, unavailable for follow-up or unrelated adverse events) were assumed to have symptom-free days at the mean rate equivalent to the treatment arm as a whole.

Evaluation of Costs of Asthma Management

The economic analysis was conducted from the perspective of the Danish health-care system. Calculation of the direct costs of asthma management were based on resources consumed by patients in the intent-to-treat population during the 12-week treatment phase of the study. Information on asthma-related direct health-care resource use was collected during the study using serious adverse event forms, concurrent medications forms, exacerbation data, and daily diary card data.

The following resource use data were collected and included in the cost analysis: hospital contacts (emergency department visits, inpatient hospital days), general practitioner contacts, the cost of the Babyhaler device (included in the FP treatment arms only and not the placebo arm) and medications (study drugs, rescue medications, concurrent prescription drugs related to the treatment of asthma, asthma exacerbations, or treatment of adverse effects). All visits included in the cost analysis were "unscheduled." Therefore, health-care contacts related to the study protocol and routine clinic visits associated with regular asthma management were excluded from the cost analysis.

Unit costs of health-care services were derived from published sources and quoted at 1999 prices in Danish kroner (DK).[19–21] Daily costs of medications were calculated using the cost to the pharmacist. Mean direct asthma treatment costs were calculated for all patients in each treatment arm. When patients were withdrawn from the study, they were assigned a constant mean daily cost following withdrawal (*ie*, the mean daily cost for the treatment arm during the study period). For ease of interpretation, key cost data have been converted into approximate dollar and pound values as of November 1999 exchange rates.

Economic Analysis

The mean cost-effectiveness ratio provides an indication of the average cost of achieving a given outcome with each treatment. This was calculated by dividing the mean daily direct cost by the rate of success for each treatment (*eg*, exacerbation-free patients, improvement in wheeze and cough symptoms, and symptom-free days). For example, for exacerbation-free patients, the mean cost-effectiveness ratio was calculated by dividing the mean daily direct cost by the proportion of exacerbation-free patients at the end of treatment. Incremental cost-effectiveness ratios (ICERs) were calculated by dividing the difference in the mean daily direct health-care costs between the treatment groups by the difference in the rate of success for each treatment. ICERs evaluate the net change in both cost and effectiveness between treatments and calculate additional expenditure required to achieve additional health gains with a treatment relative to the comparator. This produces a better understanding of the true value of a new treatment, and so ICERs are more meaningful to health-care decision makers than mean cost-effectiveness ratios as they more accurately reflect the types of treatment decisions that must be undertaken in the real world.

Statistical Analysis

Data from the intent-to-treat population were used in the statistical analysis. Between-treatment differences in the effectiveness parameters were calculated using the van Elteren extension to the Wilcoxon rank sum test. Statistical tests were two sided, and all treatment comparisons were pairwise comparisons. For analyses, $p < 0.05$ was considered to be significant. Confidence intervals for the ICERs were calculated using a nonparametric "bootstrap" method.[22] To achieve this, 1,000 bootstrap resamples of the original cost/effect pairs were generated by taking a random sample from each treatment arm with replacement from the original data, and the ICERs were calculated for all the bootstrap resamples. The 95% confidence intervals (CIs) were calculated by ranking the bootstrap resamples from least cost-effective to most cost-effective and selecting the values corresponding to the 26th and 975th points.

Sensitivity Analysis

A range of sensitivity analyses was used to test underlying assumptions in the economic analysis. For exacerbation-free patients, the impact of differences in effectiveness between the treatment arms was assessed using two scenarios for patients withdrawn from the study (for reasons other than an asthma exacerbation). The first scenario assumed that these patients had not experienced an exacerbation (classified as an exacerbation-free patient), and the second scenario assumed that these patients had experienced an exacerbation. Such an analysis helps to establish the limits that assumptions regarding patient withdrawals will have on the final results. Similarly, the sensitivity analysis for symptom-free days was performed using two scenarios. The first assumed that all days subsequent to premature withdrawal from the study were symptom free; the second assumed that all days subsequent to premature withdrawal were not symptom free. For improvement in cough and wheeze, a sensitivity analysis was conducted by redefining the percentage improvement to ≥ 50% and ≥ 75% (the base-case analysis was ≥ 25%).

Results

A total of 314 patients were recruited to the study, and 237 patients were randomized to treatment (intent-to-treat population). The main reasons for withdrawal prior to randomization were asthma exacerbations or insufficient asthma symptoms. Demographic and baseline characteristics were comparable in the three treatment groups (Table 1).

The clinical results showed that compared with placebo, FP, 200 μg/d, produced a significant improvement from baseline in 8 of 10 diary card parameters (including days without any symptoms [wheeze, cough, shortness of breath], days without

Table 1—*Demographic and Baseline Characteristics

Parameter	FP, 100 μg	FP, 200 μg	Placebo
Patients, No.	80	76	81
Male	53 (66%)	51 (67%)	53 (65%)
Female	27 (34%)	25 (33%)	28 (35%)
Age, mo	29 (11)	29 (12)	27 (10)
Height, cm	89 (9)	90 (10)	90 (8)
Weight, kg	13 (3)	14 (3)	14 (3)
Family history of asthma	56 (70%)	52 (68%)	63 (78%)
No exacerbations in the last year	14 (18%)	9 (12%)	14 (17%)
Use of one or more asthma medications in the month prior to randomization	31 (39%)	26 (34%)	24 (30%)

*Data are presented as mean (SD) or No. (%) unless otherwise indicated.

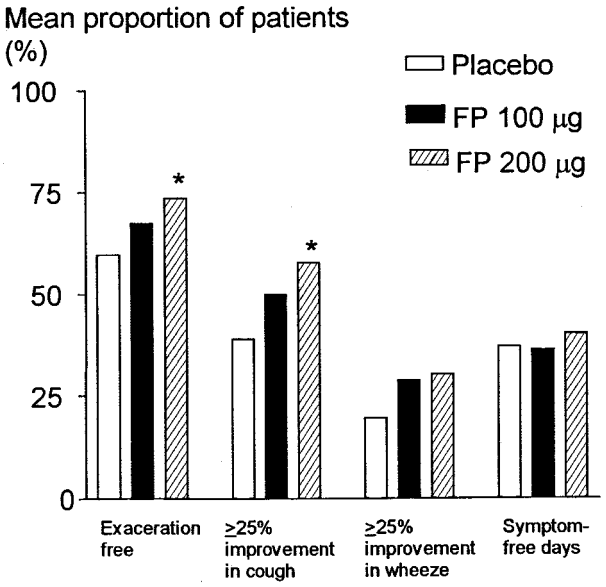

FIGURE 1. Summary of the effectiveness of placebo and both FP dosages, 100 μg/d and 200 μg/d, in preschool children with asthma. *$p < 0.03$ vs placebo.

cough, nights without breathlessness, days and nights without wheeze or salbutamol, and sleep disturbance; $p < 0.05$).[11] There was a significant reduction in 5 of the 10 parameters with FP, 100 μg/d, compared with placebo treatment ($p < 0.05$). There were no significant differences between the two FP groups. FP was well tolerated, with no differences in the safety profile noted between the active treatment and placebo groups.

Clinical Effectiveness

The proportion of exacerbation-free patients was significantly higher in the FP, 200 μg/d, group than in the placebo-treated group ($p = 0.025$), as was the proportion of patients with a ≥ 25% improvement in cough symptoms ($p = 0.018$; Fig 1). The proportion of patients with a ≥ 25% improvement in wheeze symptoms and the proportion of symptom-free days also favored the FP, 200 μg/d, group, but did not reach statistical significance compared with placebo treatment. Although there were trends in favor of FP, 100 μg/d, over placebo treatment for three of the effectiveness end points (exacerbations, cough and wheeze), none of the differences reached the threshold for statistical significance (Fig 1). There were no significant differences in effectiveness end points between the two FP groups, although there were trends in favor of the higher dose (200 μg/d).

Use of Health-Care Resources

Health-care resource utilization (excluding medications) is summarized in Table 2. The number of hospitalizations, emergency department visits, and general practitioner contacts were lower in both the FP groups than in the placebo group. There were no emergency department visits in either FP group compared with six visits in the placebo group. Moreover, there were twice as many general practitioner visits in the placebo group than in the FP, 200 μg/d, group (Table 2).

When drug treatment costs were also considered, the mean total direct health-care costs per patient per day were lower in both FP-treated groups than in the placebo-treated group (Fig 2): 13.85 DK ($1.73 [US]; ≤ 1.17 DK), 14.39 DK ($1.80 [US]; ≤ 1.22 DK), and 20.81 DK ($2.60 [US]; ≤ 1.76 DK) in the FP, 100 μg/d; FP, 200 μg/d; and placebo groups, respectively. Although medication costs were higher in the FP arms than in the placebo-treated group, these costs were more than offset by lower costs for hospital contacts and general practitioner visits in the active treatment arms. Overall costs were slightly higher in the FP, 200 μg/d, group than in the FP, 100 μg/d, group. This was due to higher study drug costs with the higher FP dose.

Table 2—*Summary of Asthma-Related Health-Care Resource Utilization (Excluding Medications) During the 12-wk Treatment Period

Health-Care Resource Utilization	FP, 100 μg (n = 80)	FP, 200 μg (n = 76)	Placebo (n = 82)
Hospital contacts			
Accident and emergency visits	0	0	6
Inpatient visits	2	2	5
General practitioner visits	21	15	30

*Data are presented as No.

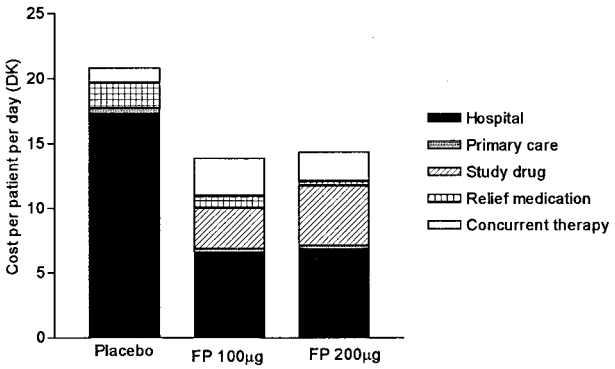

FIGURE 2. Direct asthma treatment costs per patient per day over 12 weeks. Patients withdrawn from the study were assumed to continue to use resources at the same mean rate as those patients still in the trial in their respective treatment arm.

Cost-Effectiveness

The mean costs per exacerbation-free patient, per ≥ 25% improvement in cough or wheeze symptoms, and per symptom-free day were consistently lower for both FP dosages (100 μg/d and 200 μg/d) than for placebo (Table 3), indicating that clinical benefits with FP were consistently achieved at lower mean costs than with placebo (Table 3).

ICERs were calculated to determine the additional health-care costs that must be paid to achieve additional benefits with FP. These are summarized in Table 3. ICERs can only be meaningfully interpreted for end points that have demonstrated a statistically significant difference in effectiveness between treatment groups. In this study, significant differences were found for FP, 200 μg/d, compared with placebo treatment for the exacerbation-free patient and improvement in cough symptoms end points. For both endpoints, the range of the 95% CIs were negative, indicating that the additional benefits with FP were achieved at a lower overall cost compared with the placebo arm with 95% certainty (Table 3). This indicated that using FP, 200 μg/d, in this group of patients not only improved outcomes but also reduced asthma management costs. ICERs for the other comparisons that failed to demonstrate a statistically significant between-group difference in effectiveness are presented for illustrative purposes only, as ICERs are not generally reported for nonsignificant outcomes.

While there were no statistically significant differences between the FP-treatment groups with respect to exacerbations, improvement in cough/wheeze, and symptom-free days, it is clear that from an economic perspective, FP, 200 μg/d, is more cost-effective than FP, 100 μg/d. Although asthma management costs with FP, 100 μg/d, were lower than with placebo treatment and similar to FP, 200 μg/d, there were no significant differences in treatment effectiveness relative to placebo, and so the net health gains demonstrated with the higher dose were not realized with the lower dose. This result is consistent with the clinical findings.[11]

Sensitivity Analysis

The data obtained were robust to changes in underlying assumptions across a range of sensitivity analyses. Effectiveness results for the proportion of

Table 3—*Mean Cost-Effectiveness Ratios and ICERs*

Variables	FP, 100 μg	FP, 200 μg	Placebo
Cost per exacerbation-free patient* (US)	20.5 DK ($2.53)	19.5 DK ($2.40)	34.8 DK ($4.29)
ICER (95% CI)			
Treatment vs placebo	− 89.9	− 46.1 (− 294.0, − 19.0)	
FP 200 μg vs FP 100 μg		8.7	
Cost per ≥ 25% improvement in cough symptoms* (US)	27.7 DK ($3.41)	24.9 DK ($3.07)	53.3 DK ($6.57)
ICER (95% CI)			
Treatment vs placebo	− 63.4	− 34.0 (− 131.6, − 17.9)	
FP 200 μg vs FP 100 μg		10.7	
Cost per ≥ 25% improvement in wheeze symptoms (US)	48.2 DK ($5.94)	47.5 DK ($5.85)	106.7 DK ($13.15)
ICER			
Treatment vs placebo	− 75.3	− 59.7	
FP 200 μg vs FP 100 μg		35.7	
Cost per symptom-free day (US)	6.1 DK ($0.75)	7.2 DK ($0.89)	9.2 DK ($1.13)
ICER			
Treatment vs placebo	1,504.9	− 112.3	
FP 200 μg vs FP 100 μg		8.7	

*Significant differences were found for FP, 200 μg/d, compared with placebo for the exacerbation-free patient and improvement in cough symptoms end points, and therefore CIs calculated around the ICER are reported. ICERs for the other comparisons that failed to demonstrate a between-group difference in effectiveness (improvement in wheeze and symptom-free day) are reported for illustrative purposes only, and CIs for these end points are not presented.

Table 4—*Sensitivity Analyses for Effectiveness Parameters

Parameters	FP, 100 μg	p Value vs Placebo	FP, 200 μg	p Value vs Placebo	Placebo
Exacerbation-free patients					
Dropouts are exacerbation free	59 (73.8)	0.143	61 (80.3)	0.017	51 (62.2)
Dropouts with exacerbation	54 (67.5)	0.356	56 (73.7)	0.080	49 (59.8)
Improvement in cough symptoms					
≥ 50% improvement	17 (21.3)	0.274	20 (26.3)	0.069	12 (14.6)
≥ 75% improvement	5 (6.3)	0.091	5 (6.6)	0.079	1 (1.2)
Improvement in wheeze symptoms					
≥ 50% improvement	7 (8.8)	0.962	10 (13.2)	0.350	7 (8.5)
≥ 75% improvement	0 (0)	0.091	1 (1.3)	0.299	0 (0)
Symptom-free days					
Symptom-free days after study withdrawal	38.1	0.941	42.5	0.285	38.5
No symptom-free days after study withdrawal	34.7	0.759	39.1	0.482	36.5

*Data are expressed as mean proportions of patients (%) except for symptom-free days, which are presented as mean percentage of days.

exacerbation-free patients remained similar to the base-case scenario (patients withdrawn for reasons other than an asthma exacerbation were excluded from the analysis) when patients who were prematurely withdrawn were assumed to be exacerbation-free or to have had an exacerbation (Table 4). Similarly, effectiveness results remained consistently in favor of FP, 200 μg/d, vs placebo treatment when the proportion of patients achieving a ≥ 50% improvement in cough symptoms and wheeze symptoms was calculated. The differences between the three treatment groups became smaller when the proportions of patients achieving a ≥ 75% improvement in wheeze and cough symptoms were determined, owing to a diminished number of patients achieving this level of improvement (Table 4).

Sensitivity analyses performed on the ICERs showed that FP, 200 μg/d, remained consistently cost-saving relative to placebo treatment over a wide range of assumptions. The results demonstrated that the base-case assumption was rigorous, as there was always a trend in favor of the FP groups, regardless of the assumption used. Data from the sensitivity analysis for the ICERs for the exacerbation-free outcome measure are presented in Table 5.

Discussion

This study showed that the improvement in asthma outcomes achieved during treatment with inhaled FP, 200 μg/d (100 μg bid) via a metered-dose inhaler using the Babyhaler spacer device can lead to lower overall asthma management costs. This was primarily the result of a lower proportion of patients experiencing asthma exacerbations, which can be costly to manage. In addition to a higher proportion of exacerbation-free patients, a significantly greater number of patients in the FP, 200 μg/d, group experienced a ≥ 25% improvement in the frequency of asthma cough symptoms. There were no significant improvements in effectiveness in the FP, 100 μg/d (50 μg bid), group compared with the placebo group, although the overall costs of treatment were still lower than in the placebo arm. In both FP groups, health-care resource utilization was lower than that in the placebo arm, both in terms of primary care and secondary care contacts.

In this study, the incremental cost-effectiveness analysis showed that FP, 200 μg/d, resulted in improved asthma control in terms of cough and incidence of exacerbations and was cost-saving relative to placebo treatment (plus treatment with a short-acting β_2-agonist when required). The study

Table 5—*Sensitivity Analysis for ICERs for the Exacerbation-Free Patient Outcome Measure

Variables	FP, 100 μg	FP, 200 μg
Using base-case costs		
Assuming dropouts to be exacerbation-free		
Treatment vs placebo	− 60.2	− 35.5
FP, 200 μg vs FP, 100 μg		8.3
Assuming dropouts to have had an exacerbation		
Treatment vs placebo	− 89.9	− 46.1
FP, 200 μg vs FP, 100 μg		8.7
Using sensitivity analysis costs		
Assuming dropouts to be exacerbation-free		
Treatment vs placebo	− 49.8	− 59.9
FP, 200 μg vs FP, 100 μg		− 77.8
Assuming dropouts to have had an exacerbation		
Treatment vs placebo	− 74.4	− 77.8
FP, 200 μg vs FP, 100 μg		− 82.0

*Data are presented as DK.

did not differentiate explicitly between the two doses, and this was not the primary objective of the economic evaluation. The primary objective was to assess whether adding FP to the treatment of asthma patients aged 12 to 47 months receiving rescue salbutamol and controller medications (regular sodium cromoglycate, ketotifen, and/or antihistamines) is cost-effective. A secondary objective was to evaluate which dose was most cost-effective, although the primary clinical analysis had already demonstrated that FP, 200 μg/d, is more effective than FP, 100 μg/d.[11] The economic analysis supports this finding, with FP, 200 μg/d, demonstrating cost reductions and improved effectiveness. The lack of improved effectiveness with FP, 100 μg/d, despite lower costs indicates that this dose is less cost-effective.

Improvements in the diagnosis of asthma in preschool children and a better understanding of which patients most benefit from inhaled corticosteroid therapy could produce even greater economic benefits with FP. One study[23] reported that children with frequent asthma symptoms (symptoms on ≥ 3 days per week or ≥ 21 days of symptoms over a 4-week period) and those with a family history of asthma showed a greater response to treatment with FP, 200 μg/d, compared with placebo than children with less frequent symptoms or no family history of asthma, in terms of a greater increase in symptom-free days and a greater reduction in exacerbations. Future studies should attempt to characterize those patients who are more likely to respond to treatment. It is possible that pharmacogenetics will enable us to predict which patients are most likely to respond to inhaled corticosteroid therapy.

Because all patients could continue receiving their regular asthma treatment(s), this study demonstrates that adding an inhaled corticosteroid to existing asthma therapy is a cost-effective strategy in preschool children, relative to their usual controller medication alone. This study also illustrates the very high burden of asthma in this age group. During this 12-week study, there were nine hospitalizations, 6 emergency department visits, and 66 unscheduled primary-care visits as a result of the children's asthma. This emphasizes the importance of focusing on reducing asthma exacerbations in children from a health-care system perspective, as well as taking into account the impact of such events on the quality of life of the patients and their families.

There have been few economic analyses of asthma treatments in preschool children. Connett et al[24] concluded that budesonide was cost-effective in terms of improvement in asthma symptom control in children aged 1 to 3 years, although with only 40 subjects, the study was relatively small. Similar findings were also reported in another study in older children (aged 7 to 16 years) in which treatment with an inhaled corticosteroid plus bronchodilator resulted in lower overall costs and better clinical outcomes than treatment with a bronchodilator alone.[25] Both of these studies demonstrate that inhaled corticosteroid therapy improves outcomes and reduces asthma management costs in children. These findings are consistent with those from the current study, which represents the first large-scale economic evaluation of inhaled corticosteroids in this age group.

There are a number of limitations to this study that need to be considered. The clinical study on which the economic analysis was based was of short duration, which may underestimate the true long-term economic consequences of poor asthma control. In particular, the cost of hospitalization, a rare but expensive event, may have been underestimated. Furthermore, this was a retrospective analysis and patients were not followed up after premature withdrawal from the study, so it was necessary to make a number of assumptions about resource use and outcomes during these periods. It is possible that these patients could have been the most severe asthmatics, and therefore the true economic benefits of treatment may have been underestimated. However, despite these limitations, this study provides further evidence of the economic value of inhaled corticosteroid therapy in preschool children. Further large-scale, long-term studies would be beneficial to further validate the findings of this and other economic studies in this age group.

In conclusion, the results of this study suggest that in children aged 12 to 47 months with a history of asthma symptoms, FP, 100 μg bid, administered via the Babyhaler spacer device is a well-tolerated, cost-effective management strategy, from the perspective of the Danish health-care system. Thus, there is both clinical and economic rationale for using inhaled corticosteroids for asthma therapy in this age group.

ACKNOWLEDGMENT: The authors thank the following physicians who participated in and randomized patients into this study: Belgium, Dr. C. de Boeck, Dr. A. Malfroot, Dr. H. Van Bever; Canada, Dr. D. Berube, Dr. S. Feanny, Dr. M. Gold, Dr. S. Lavi, Dr. B. Lyttle, Dr. M. Montgomery; Denmark, Dr. K. Ibsen; Ireland, Dr. P. Greally, Dr. D. Lillis, Dr. M. Taylor; New Zealand, Dr. J. Brown; Poland, Prof. J. Alkiewicz; Prof. D. Chmielewska, Dr. J. Gillies, Prof. R. Kurzawa; South Africa, Dr. C. Bester, Dr. M. Groenewald, Dr. D. Luyt, Dr. A.I. Manjra; Spain, Dr. J. Botey, Dr. A. Escribano, Dr. G. Ferres, Dr. M. Navarro, Dr. E. Gonzalez Perez-Yarza; United Kingdon, Dr. J. Carter, Prof. A. Milner, Dr. A. Speight, Dr. D.A. Spencer. Thanks are also due to Lisa Williams for the statistical analysis.

References

1 British Thoracic Society. The British guidelines on asthma management 1995 review and position statement. Thorax 1997; 52(suppl 1):S1–S21

2 National Asthma Education and Prevention Program. Expert panel report 2: Guidelines for the diagnosis and management of asthma. Bethesda, MD: National Institutes of Health, July 1997; publication No. 97–4051

3 Global Initiative for Asthma (GINA). Pocket guide for asthma management and prevention. National Heart, Lung and Blood Institute. Bethesda, MD: National Institutes of Health, November 1998; publication No. 96–3659B

4 Bisgaard H, Munck SL, Nielsen JP, et al. Inhaled budesonide for treatment of recurrent wheezing in early childhood. Lancet 1990; 336:649–651

5 Connett GJ, Warde C, Wooler E, et al. Use of budesonide in severe asthmatics aged 1–3 years. Arch Dis Child 1993; 69:351–355

6 Gustafsson P, Tsanakas J, Gold M, et al. Comparison of the efficacy and safety of inhaled fluticasone propionate 200 micrograms/day with inhaled beclomethasone dipropionate 400 micrograms/day in mild and moderate asthma. Arch Dis Child 1993; 69:206–211

7 Price JF, Weller PH. Comparison of fluticasone propionate and sodium cromoglycate for the treatment of childhood asthma (an open parallel group study). Respir Med 1995; 89:363–368

8 Hoekstra MO, Grol MH, Bouman K, et al. Fluticasone propionate in children with moderate asthma. Am J Respir Crit Care Med 1996; 154:1039–1044

9 Peden DB, Berger WE, Noonan MJ, et al. Inhaled fluticasone propionate delivered by means of two different multidose powder inhalers is effective and safe in a large pediatric population with persistent asthma. J Allergy Clin Immunol 1998; 102:32–38

10 Shapiro G, Bronsky EA, LaForce CF, et al. Dose-related efficacy of budesonide administered via a dry powder inhaler in the treatment of children with moderate to severe persistent asthma. J Pediatr 1998; 132:976–982

11 Bisgaard H, Gillies J, Groenewald M, et al. The effect of inhaled fluticasone propionate in the treatment of young asthmatic children: a dose comparison study. Am J Respir Crit Care Med 1999; 160:126–131

12 Nielsen KG, Bisgaard H. The effect of inhaled budesonide on symptoms, lung function, cold air and methacholine responsiveness in 2- to 5-year old asthmatic children. Am J Respir Crit Care Med 2001; 162:1500–1506

13 Pediatric asthma: promoting best practice; guide for managing asthma in children. American Academy of Allergy, Asthma and Immunology, National Asthma Education and Prevention Program, National Heart Lung and Blood Institute, and the American Academy of Pediatrics. 2000

14 Lenney W, Wells NEJ, O'Neill BA. The burden of paediatric asthma. Eur Respir Rev 1994; 4:49–62

15 Smith DH, Malone DC, Lawson KA, et al. A national estimate of the economic costs of asthma. Am J Respir Crit Care Med 1997; 156:787–793

16 Lozano P, Sullivan SD, Smith DH, et al. The economic burden of asthma in US children: estimates from the National Medical Expenditure Survey. J Allergy Clin Immunol 1999; 104:957–963

17 Barnes PJ, Jonsson B, Klim JB. The costs of asthma. Eur Respir J 1996; 9:636–642

18 Bisgaard H, Moller H. Changes in risk of hospital readmission among asthmatic children in Denmark, 1978–93. BMJ 1999; 319:229–230

19 Danish Medicines Agency. Danish Pharmaceutical Prices 1999. Available at http://www.medicinpriser.dk; accessed November 11, 1999

20 Danish Health Security. "Takster." Copenhagen, Denmark: Danish National Board of Health 1999

21 National Board of Health. Sundhedsstatistikken. Copenhagen, Denmark: Danish National Board of Health 1997; 4

22 Briggs AH, Wonderling DE, Mooney CZ. Pulling cost-effectiveness analysis up by its bootstraps: a non-parametric approach to confidence interval estimation. Health Econ 1997; 6:327–340

23 Roorda RJ, Mezei G, Bisgaard H, et al. Response of preschool children with asthma symptoms to fluticasone propionate. J Allergy Clin Immunol 2001; 108:540–546

24 Connett GJ, Lenney W, McConchie SM. The cost effectiveness of budesonide in severe asthmatics aged one to three years. Br J Med Econ 1993; 6:127–134

25 Rutten-van Molken MP, Van Doorslaer EK, Jansen MC, et al. Cost effectiveness of inhaled corticosteroid plus bronchodilator therapy versus bronchodilator monotherapy in children with asthma. Pharmacoeconomics 1993; 4:257–270

Cost-Effectiveness of Fluticasone Propionate Administered Via Metered-Dose Inhaler Plus Babyhaler ™ Spacer in the Treatment of Asthma in Preschool-Aged Children*

Hans Bisgaard, Martin J. Price, Claire Maden and Niels A. Olsen

Chest 2001;120; 1835-1842
DOI 10.1378/chest.120.6.1835