Effects of Budesonide Inhalation Suspension Compared With Cromolyn Sodium Nebulizer Solution on Health Status and Caregiver Quality of Life in Childhood Asthma

Kevin R. Murphy, MD*; Sherahe Fitzpatrick, MD[a]; Mario Cruz-Rivera, PhD, MPH‡; Christopher J. Miller, MStat‡; and Bhash Parasuraman, PhD‡

ABSTRACT. *Objective.* **To compare the effects of 2 nebulizable controller asthma medications on caregiver and pediatric quality of life.**

Methods. **In this 52-week, randomized trial, children aged 2 to 6 years with mild to moderate persistent asthma received budesonide inhalation suspension 0.5 mg (total daily dose) once or twice daily ($n = 168$) or cromolyn sodium nebulizer solution 20 mg 4 times daily ($n = 167$) for 8 weeks, with dosage adjustment thereafter at the investigators' discretion. The Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ), Compliance/Caregiver Satisfaction Questionnaire (CCSQ), Modified Child Health Questionnaire-Parent Form 50 (CHQ-PF50), and Functional Status-II(R) (FS-II[R]) Questionnaire were administered at baseline and weeks 8, 28, and 52. Global assessments of ease of asthma management and child health status were obtained from caregivers and physicians at the end of the study.**

Results. **Improvements from baseline in domain-specific (activities and emotional function) and total PACQLQ scores were greater at each time point (weeks 8, 28, and 52) for caregivers of patients treated with budesonide compared with caregivers of patients receiving cromolyn sodium. Only the budesonide group met the criterion for a clinically important improvement (≥0.5 unit change) in all PACQLQ domains by week 8, which was maintained at weeks 28 and 52. Moreover, improvements surpassed the criterion for moderate clinical importance (1.0 unit change) in all PACQLQ domains for the budesonide group, but this level of improvement was only achieved in the activities domain (at week 28) for the cromolyn sodium group. Based on the CCSQ, budesonide resulted in greater caregiver satisfaction, treatment convenience, ease of use, and compliance compared with cromolyn sodium. Thus, 90.7% of caregivers in the budesonide group were "completely or very satisfied" compared with 53.4% in the cromolyn sodium group. Over half (54.6%) of caregivers in the budesonide group rated budesonide "highly or very convenient" compared with 23% for cromolyn sodium; 77% rated budesonide "extremely or very easy" to use compared with 47% for cromolyn. Adherence with daily medication regimens was reported for 76% of children in the budesonide group compared with 57% in the cromolyn sodium group. Child health status, as indicated by mean FS-II(R) scores, showed improvements from baseline in both groups at weeks 8, 28, and 52. There was a trend for these improvements to be superior in the budesonide group. Additionally, budesonide was superior to cromolyn sodium in caregiver and physician global assessments. At the end of the study, 76% of caregivers of children receiving budesonide reported asthma management to be "a great deal easier" compared with the start of the study, and 74% rated the overall health status of their child as "much better now than 1 year ago." In contrast, only 29% and 37% of caregivers whose children received cromolyn sodium provided these respective ratings.**

Conclusions. **Budesonide inhalation suspension improved the quality of life for caregivers of children with asthma. Caregivers of children treated with budesonide had significantly fewer limitations in daily activities and emotional functioning compared with caregivers of children treated with cromolyn sodium nebulizer solution. The improvements in caregiver quality of life occurred earlier with budesonide compared with cromolyn sodium. Only caregivers in the budesonide group had a clinically important mean change from baseline in all PACQLQ domains by week 8. These benefits were maintained at week 52. Children treated with budesonide inhalation suspension and cromolyn sodium experienced improvements in health status, assessed using the FS-II(R). The greatest differences between treatments were seen in the disease-specific portion of the FS-II(R), which relates impairments in functional status to the child's illness. Caregiver and physician global assessment indicated significantly better overall child health after 1 year of treatment with budesonide, supporting an improvement in health status. Clinical trials in children 4 to 16 years of age with asthma have demonstrated greater effectiveness of inhaled corticosteroids versus cromolyn sodium on several clinical measures of efficacy. Measures of asthma control in this study, reported in detail elsewhere [Leflein et al. *Pediatrics*. 2002;109:866–872], also have shown greater improvements with budesonide therapy. Treatment with budesonide inhalation suspension resulted in a significantly lower mean rate of asthma exacerbations, significantly longer times to first asthma exacerbation, significantly longer times to first additional use of chronic asthma therapy, and significant improvements in asthma symptom scores and breakthrough medication use compared with cromolyn sodium therapy. Additionally, children receiving budesonide inhalation suspension experienced more symptom-free days and episode-free days compared with children receiving cromolyn sodium. Safety profiles**

From the *Midwest Allergy & Asthma Clinic, Midwest Children's Chest Physicians, Omaha, Nebraska; and ‡AstraZeneca LP, Wilmington, Delaware.

Dr. Murphy has served on the Asthma Advisory Board and the Speakers' Bureau of AstraZeneca LP.

[a]Formerly with AstraZeneca LP, Wilmington, Delaware.

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Reprint requests to Kevin R. Murphy, MD, Midwest Allergy & Asthma Clinic, Midwest Children's Chest Physicians, 8552 Cass St, Omaha, NE 68114. E-mail: murphknsc@aol.com

were similar between the 2 treatment groups. Budesonide inhalation suspension was associated with significantly greater caregiver satisfaction, convenience, ease of use, and compliance compared with cromolyn sodium nebulizer solution. This greater caregiver satisfaction and quality of life may be related to the greater asthma control achieved in children treated with budesonide therapy compared with cromolyn sodium. In addition, the convenience of once- or twice-daily dosing with budesonide inhalation suspension, compared with 3- or 4-times-daily dosing of cromolyn sodium, may decrease caregiver burden and enhance the willingness of caregivers to adhere to treatment regimens prescribed for their young children with asthma. This effect on caregiver adherence could further improve treatment effectiveness. This is the first clinical trial comparing the effects of a nebulized corticosteroid with that of an alternative nebulized therapy on quality of life in young children with asthma and their families. Compared with nebulized cromolyn sodium, budesonide inhalation suspension not only provides better overall child health status and asthma management, but greater caregiver quality of life and greater caregiver satisfaction, convenience, ease of use, and compliance. *Pediatrics* 2003;112:e212–e219. URL: http://www.pediatrics.org/cgi/content/full/112/3/e212; ***budesonide inhalation suspension, cromolyn sodium, inhaled corticosteroid therapy, nebulizer therapy, quality of life, pediatric asthma, questionnaire, Pediatric Asthma Caregiver's Quality of Life Questionnaire.***

ABBREVIATIONS. PACQLQ, Pediatric Asthma Caregiver's Quality of Life Questionnaire; CCSQ, Compliance/Caregiver Satisfaction Questionnaire; CHQ-PF50, Modified Child Health Questionnaire-Parent Form 50; FS-II(R), Functional Status-II(R) Questionnaire; ANCOVA, analysis of covariance; CI, confidence interval.

Because it is well-recognized that difficulties, anxieties, and sacrifices in family relationships may be associated with the course of childhood asthma,[1–3] there is substantial interest in the impact of treatment interventions on the quality of life of the parents or caregivers of the child with asthma, as well as the effect of such treatment on the patient's daily functioning.[4–6] Health-related quality-of-life assessments have become recognized in clinical practice as a source of valuable supplemental information that is not accessible through the use of more traditional clinical indices.[5] In terms of functioning and well-being, quality of life is a key outcome in the comprehensive determination of patient benefit.[7] Caregiver quality of life is a key outcome in terms of asthma management, with caregivers of pediatric asthma patients most often citing emotional concerns as having an impact on their quality of life.[8]

Inhaled corticosteroids are fundamental to the long-term management of persistent asthma[9] and are recommended by national guidelines for therapy of young children diagnosed with persistent asthma.[10,11] Numerous clinical trials support their efficacy and relative safety in children.[12] Early corticosteroid intervention is also believed to play a critical role in reduction of permanent lung damage and to alter the chronic, progressive nature of the disease.[13–15]

In the United States, 2 nebulizable controller asthma medications approved by the Food and Drug Administration are available for use in infants and young children. Budesonide inhalation suspension (Pulmicort Respules; AstraZeneca LP, Wilmington, DE) is the first corticosteroid approved for nebulization therapy in pediatric asthma patients as young as 12 months.[16] The efficacy and safety of budesonide inhalation suspension administered once or twice daily by nebulizer have been demonstrated in >1000 infants and young children with mild to moderate persistent asthma.[17–19] Cromolyn sodium nebulizer solution (Intal Nebulizer Solution; Aventis, Bridgewater, NJ) is approved for the treatment of asthma in individuals at least 2 years of age.[20] It has also demonstrated excellent tolerability, although the clinical response to cromolyn sodium is less predictable than that produced by inhaled corticosteroids.[9,10]

This 52-week, open-label, randomized effectiveness study compared the safety and efficacy of the 2 nebulized therapies in young children with persistent asthma. The results showed that budesonide inhalation suspension was as well-tolerated and more effective than nebulized cromolyn sodium based on conventional measures of tolerability, safety, and asthma control (asthma exacerbations, pulmonary function, asthma symptom scores, and breakthrough medication use).[21] In this article we report on the effects of budesonide inhalation suspension compared with cromolyn sodium nebulizer solution on caregiver quality of life and pediatric health status.

METHODS

Patients

Patients 2 to 6 years of age with mild or moderate persistent asthma were eligible for enrollment if they had asthma symptoms more than twice weekly within 6 months of study entry, nighttime asthma symptoms more than twice monthly, at least 1 asthma exacerbation requiring systemic corticosteroids within 6 months of enrollment or at least 2 such exacerbations within 9 months of enrollment, and daily use of at least 1 long-term controller asthma medication (ie, inhaled corticosteroid, nedocromil sodium, cromolyn sodium, or an oral or inhaled bronchodilator) with periodic use of breakthrough medication within 3 months of study entry.

Patients were excluded if they had received intermittent (<14-day courses) or long-term (≥14-day courses) oral corticosteroid treatment within 15 days or 12 weeks of enrollment, respectively. Patients were also excluded if they were born prematurely, had a history of severe or unstable asthma or ventilatory assistance (except at birth), were hospitalized for treatment of airway obstruction within 30 days of study enrollment, had an upper respiratory tract infection and infectious sequelae of the lower respiratory tract within 14 days of study enrollment, or had concomitant lung disease or other significant medical conditions. The study was approved by the institutional review board at each center and was performed according to the principles of the Declaration of Helsinki. Before enrollment, written informed consent was obtained from each patient's legal guardian.

Study Design

This was a randomized, open-label, parallel-group, 52-week effectiveness study conducted from September 1997 to August 1999 at 36 clinical sites in the United States (AstraZeneca LP Study DX-RES-2000). Study design and treatments have been described in detail previously.[21] Briefly, the study began with a 2- to 3-week baseline phase. Patients with asthma symptom severity scores ≥2 (scale: 0 = no symptoms to 3 = severe symptoms) on at least 7 of 14 days before randomization and who used breakthrough medication on at least 5 of these 14 days were randomized 1:1 to

receive budesonide inhalation suspension 0.5 mg (once daily or in divided doses twice daily per investigator judgment) or cromolyn sodium 20 mg 4 times daily for 8 weeks. After 8 weeks and throughout the remainder of the trial, doses of study medication could be titrated up or down at the discretion of the investigator. Budesonide could be titrated to a maximum dose of 1.0 mg twice daily and a minimum dose of 0.25 mg once daily. The dose of cromolyn sodium could be reduced to 20 mg 3 times daily.[20] Patients returned to the clinic 6 times (weeks 2, 8, 16, 28, 40, and 52) for evaluation and data collection.

Concomitant Therapy

Patients discontinued long-term controller asthma medications before randomization. Short-acting β_2-agonists were allowed as breakthrough medication throughout the study, and a 3- to 7-day course of systemic corticosteroids with tapering was allowed, at the discretion of the investigator, to treat asthma exacerbations. Long-term asthma medications other than systemic corticosteroids (eg, methylxanthines, slow-release oral β_2-agonists) were permitted if patients required oral or parenteral corticosteroids for ≥3 asthma exacerbations or required more than the maximum recommended dose of study drug. Patients randomized to either study drug could not receive the other as additional therapy.

Outcome Measures

Caregiver Burden, Satisfaction, and Compliance

The impact of a child's asthma on the caregiver's normal daily activities and emotional functioning was assessed at baseline and weeks 8, 28, and 52 using the self-administered Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ).[22] The PACQLQ is a 13-item questionnaire that assesses caregiver burden with a 1-week recall period. It contains 4 items in an activities domain and 9 items in an emotional function domain. Responses are based on a 7-point scale (1 = all of the time [severe impairment] to 7 = none of the time [no impairment]). Individual items are weighted equally. Total and domain scores range from 1 to 7, with higher scores indicating a more positive response. A change in score of ~0.5 units is the minimal difference that patients and caregivers consider important. Changes of ~1.0 unit are considered of moderate importance.[22–25]

Caregiver satisfaction, treatment convenience, ease of use, and compliance were assessed at baseline and weeks 8, 28, and 52 with a 4-item Compliance/Caregiver Satisfaction Questionnaire (CCSQ), which was developed specifically for this study. Responses to satisfaction, convenience, and ease-of-use questions are based on 7-point Likert-type[26] response scales ranging from "completely satisfied" to "completely dissatisfied," "highly convenient" to "completely inconvenient," and "extremely easy" to "extremely difficult," respectively, with 1 being the most positive response. Responses to the compliance question, which assesses how often patients took their asthma medication in the past 2 weeks, are based on a 5-point scale from 1 (daily) to 5 (not at all).

Child Health Status

Child health status was assessed at randomization and weeks 8, 28, and 52 using the Modified Child Health Questionnaire-Parent Form 50 (CHQ-PF50)[27] and the Functional Status-II(R) Questionnaire (FS-II[R]).[28] The CHQ-PF50 was self-administered by the caregiver and the FS-II(R) was administered via interview.

The CHQ-PF50 is a validated measure of physical and psychosocial well-being of children using 14 multi-item scales and is reported by the caregiver. It is a 50-item generic health status questionnaire with a 4-week recall. Only the General Health Perceptions scale (5 items) was included in this study. Caregivers indicate how true or false the 5 statements in the General Health Perception scale are based on a 5-point Likert-type response scale in which graded responses are scored from 1 = definitely false to 5 = definitely true. Total score for the General Health Perceptions scale was calculated and transformed to a scale of 0 to 100, with higher scores indicating a more favorable response.

The short 14-item form of the FS-II(R) provides a non–disease-specific, concise measure of the health status of a child and determines whether specific behaviors are attributable to illness from the perspective of the caregiver. Part 1 of the questionnaire (FS-II[R] general score) probes the child's eating and sleeping patterns, mood, attention, energy, and behavior. Each question has 3 response options (0 = never or rarely; 1 = some of the time; and 2 = almost always). Part 2 of the questionnaire (FS-II[R] specific score) probes if the dysfunction is attributable to illness. Responses are based on a 3-point scale (0 = not at all; 1 = partly; and 2 = fully). FS-II(R) general and specific scores are transformed to a 0 to 100 scale, with higher scores representing a more positive response.

Global Assessments

Global assessments were conducted at week 52 and included 2 questions for caregivers evaluating their ability to manage the child's asthma and overall child health status since the start of the study. Caregivers were asked to compare their ability to manage the child's asthma at week 52 with their ability at the start of the study. Responses were based on a Likert-type scale ranging from "a great deal easier asthma management" since study start to "a great deal more difficult asthma management." Caregiver perceptions of the child's health were evaluated based on responses to the question of how their child's health was now compared with 1 year ago. Likert-type responses ranged from "a great deal better" to "a great deal worse."

Statistical Analysis

Data were analyzed using an all-patients-treated approach, which included all randomized patients who received at least 1 dose of study medication and who had at least 1 postdose observation. Two approaches were taken to analyze data derived from the PACQLQ, FS-II(R), and CHQ-PF50 questionnaires: first, and primarily, an analysis of all observed data were performed with the last value carried forward to subsequent time points for patients who withdrew early or who had missing data. Second, if a patient took an additional chronic asthma medication in addition to the study medication, data were used only to the point that the additional chronic asthma medication was taken (ie, the data were censored) and, thereafter, were carried forward to subsequent time points. For all other questionnaires, an analysis of all observed data was performed with the last value carried forward to subsequent time points for patients who withdrew early or who had missing data.

Changes from baseline to each time point in total and domain-specific PACQLQ scores, FS-II(R) general and specific scores, and the CHQ-PF50 General Health Perceptions score were compared between treatment groups using an analysis of covariance (ANCOVA) model, adjusted for baseline and the fixed factors of center and treatment.[29,30] Standard model diagnostics were evaluated, including an investigation of the homogeneity of treatment effects across centers and baseline scores. Significant baseline-by-treatment interactions were described by estimating mean treatment effects at several different baseline levels, using an ANCOVA model as described above, but with the inclusion of a baseline-by-treatment interaction term to allow for a different response-versus-baseline slope for each treatment group.

CCSQ responses were summarized descriptively as the number and percentage of patients indicating each response by treatment group and visit and were analyzed by ANCOVA, using an evenly spaced ordinal scoring assignment. Caregiver and physician global assessments were compared between treatment groups using χ^2 tests.

The planned sample size was based on the primary outcome variable—asthma exacerbation rates.[21] No sample size calculations were made for quality-of-life variables.

RESULTS

Patient Population

Of the 426 patients enrolled in this 52-week study, 335 were randomized to receive budesonide inhalation suspension (n = 168) or cromolyn sodium nebulizer solution (n = 167). Baseline demographics, asthma characteristics, and PACQLQ, CHQ-PF50, and FS-II(R) scores were similar between the treatment groups (Table 1). A total of 287 patients completed the study, 154 (92%) in the budesonide group and 133 (80%) in the cromolyn sodium group. Of the 34 patients who discontinued study treatment in the

TABLE 1. Baseline Demographics, Asthma Characteristics, and Quality-of-Life Data

	BIS (n = 168)	CSNS (n = 167)
Mean age ± SD, y	4.2 ± 1.4	4.4 ± 1.5
Male gender, n (%)	104 (61.9)	110 (65.9)
Race, *n* (%)		
White	139 (82.7)	131 (78.4)
Black	19 (11.3)	25 (15.0)
Asian	3 (1.8)	4 (2.4)
Other	7 (4.2)	7 (4.2)
Mean asthma duration ± SD, mo	32.6 ± 17.2	33.5 ± 18.1
Mean asthma symptom severity scores* ± SD		
Nighttime	1.3 ± 0.5	1.3 ± 0.6
Daytime	1.4 ± 0.5	1.4 ± 0.5
Mean days of breakthrough medication use/2 wk ± SD	10.2 ± 3.4	10.2 ± 3.3
Mean PACQLQ scores ± SD		
Total score	4.9 ± 1.2	4.7 ± 1.2
Activities score	4.6 ± 1.4	4.3 ± 1.5
Emotional function score	5.0 ± 1.2	4.9 ± 1.2
Mean CHQ-PF50 General Health Perceptions score ± SD	49.8 ± 9.3	49.5 ± 10.9
Mean FS-II(R) scores ± SD		
General score	74.2 ± 14.7	73.8 ± 13.5
Specific score	78.4 ± 15.0	77.8 ± 14.3

BIS indicates budesonide inhalation suspension; CSNS, cromolyn sodium nebulizer solution.
* Based on a scale of 0–3; 0 = no symptoms to 3 = severe symptoms.

cromolyn sodium group, 3 discontinued because of disease deterioration; 1 because of adverse events; 20 for other reasons (ie, withdrawal of consent, noncompliance with study procedures, randomization error, patient relocation); and 10 were lost to follow-up. There were no discontinuations attributable to disease deterioration or adverse events in the budesonide group, but 8 patients discontinued for other reasons and 6 patients were lost to follow-up.

Caregiver Burden, Satisfaction, and Compliance

Improvements in domain-specific (activities and emotional function) and total PACQLQ scores were significantly greater in the budesonide group than in the cromolyn sodium group at all time points (Fig 1A–1C and Table 2). The benefits of both treatments generally reached a maximum at week 28, and this effect was maintained at the last visit (week 52).

Mean improvements from baseline in total and domain-specific PACQLQ scores were clinically important (≥0.5 unit change) at all time points in caregivers of children receiving budesonide. Improvements surpassed the level of moderate clinical importance (1.0 unit change) by week 8 in the activities domain and by week 28 in both PACQLQ total and emotional function domain scores. In contrast, PACQLQ improvements in caregivers of children receiving cromolyn sodium reached the level of minimal clinical importance by week 8 only in the activities domain. With the exception of week 28 in the activities domain, mean changes did not reach the level of moderate clinical importance with cromolyn sodium.

For both treatments, there was a strong negative correlation between the baseline PACQLQ score and

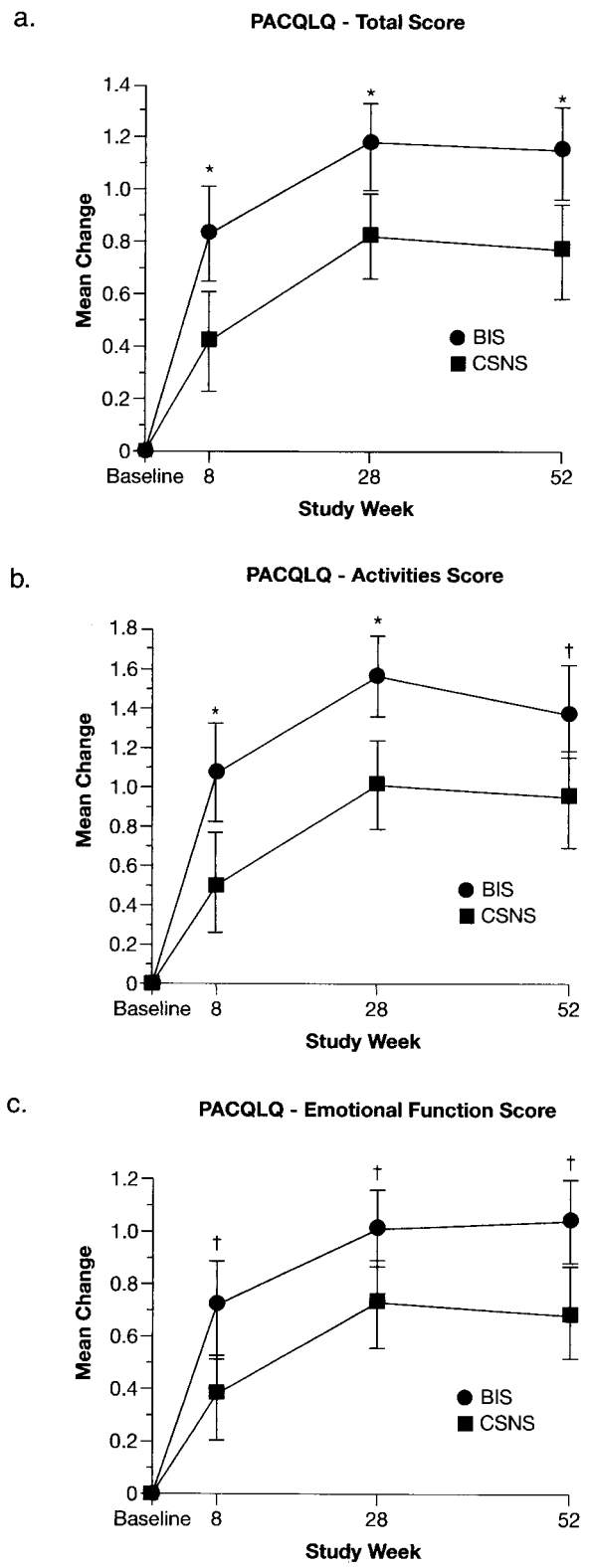

Fig 1. Mean changes from baseline in PACQLQ total (a), activities (b), and emotional function (c) scores. Error bars represent the upper and lower bounds of the 95% CIs for the mean changes. All-patients-treated analysis; last value carried forward. Changes were adjusted for baseline, center, and treatment. BIS indicates budesonide inhalation suspension; CSNS, cromolyn sodium nebulizer solution. *$P \leq .001$ versus CSNS; †$P < .01$ versus CSNS.

degree of improvement, such that caregivers expressing the greatest degree of burden at baseline (ie, a low score) were associated with larger improve-

TABLE 2. Mean Changes From Baseline and Treatment Differences in PACQLQ and FS-II(R) Scores at Week 52

Parameter	Treatment Group	*N*	Mean Score*	Adjusted Mean Change†	Difference from CSNS [95% CI]‡	*P* vs CSNS
PACQLQ primary analysis						
Total score	CSNS	160	5.57	0.77	0.38	.001
	BIS	166	6.0	1.15	[0.15, 0.60]	
Activities score	CSNS	160	5.42	0.95	0.44	.004
	BIS	166	5.92	1.39	[0.14, 0.74]	
Emotional function score	CSNS	160	5.63	0.68	0.35	.002
	BIS	166	6.03	1.04	[0.14, 0.57]	
PACQLQ censored analysis						
Total score	CSNS	140	5.44	0.62	0.47	<.001
	BIS	161	5.97	1.09	[0.23, 0.71]	
Activities score	CSNS	140	5.24	0.72	0.60	<.001
	BIS	161	5.88	1.32	[0.29, 0.91]	
Emotional function score	CSNS	140	5.53	0.57	0.42	.001
	BIS	161	6.0	0.99	[0.18, 0.65]	
FS-II(R) primary analysis						
General score	CSNS	159	81.7	7.87	1.86	.216
	BIS	166	84.1	9.73	[−1.09, 4.81]	
Specific score	CSNS	159	85.9	7.58	3.09	.055
	BIS	166	89.4	10.67	[−0.06, 6.23]	
FS-II(R) censored analysis						
General score	CSNS	139	79.9	5.79	3.75	.022
	BIS	161	84.0	9.54	[0.56, 6.95]	
Specific score	CSNS	139	83.8	4.98	6.0	<.001
	BIS	161	89.8	10.98	[2.72, 9.28]	

CSNS indicates cromolyn sodium nebulizer solution; BIS, budesonide inhalation suspension.
* Higher scores indicate a more positive response.
† Adjusted mean change from baseline from ANCOVA model.
‡ 95% confidence interval of the treatment difference from ANCOVA model.

ments from baseline than those with a lesser degree of burden at baseline. The strength of this relationship differed between the 2 treatments, as evidenced by a significant baseline-by-treatment interaction in the ANCOVA model. When mean changes from baseline in PACQLQ scores were estimated based on the degree of caregiver burden at baseline and compared between treatments, the largest difference between treatment groups was observed in caregivers with the lowest baseline PACQLQ scores (ie, greater burden). For example, the mean difference between the budesonide and cromolyn sodium groups in PACQLQ total score at week 52 was 1.07 (95% confidence interval [CI]: 0.47–1.66), surpassing the threshold for moderate clinical importance, when estimated at a baseline score of 2 (very burdened) compared with 0.08 (95% CI, −0.24–0.41) when estimated at a baseline score of 6 (hardly burdened).

Analysis of PACQLQ data censored at the time of initiation of additional chronic asthma medication led to the same conclusions as the primary analysis, but the effect of this adjustment was to decrease mean changes from baseline in the cromolyn sodium group while not substantially altering responses in the budesonide group. As a result, in this additional analysis, mean differences between budesonide and cromolyn sodium were even larger than in the primary analysis, and they approached or exceeded the threshold for minimal clinical importance. Censored PACQLQ data at week 52 are shown in Table 2.

Mean scores for caregiver satisfaction, convenience, ease of use, and compliance, based on the CCSQ, were significantly ($P \leq .001$) greater for those caregivers whose children received budesonide versus cromolyn sodium. Most caregivers whose children received budesonide (90.7%) were "completely or very satisfied" compared with only about half of those whose children received cromolyn sodium (53.4%) (Fig 2A). Additionally, 54.6% of caregivers rated budesonide "highly or very convenient" compared with only 23% for cromolyn sodium (Fig 2B). Seventy-seven percent of caregivers rated budesonide "extremely easy" or "very easy" to use compared with only 47% for cromolyn sodium. In the budesonide group, 76% of caregivers reported that their children took their medication daily compared with 57% of caregivers in the cromolyn sodium group.

Child Health Status

Child health status, based on mean FS-II(R) scores, improved from baseline to weeks 8, 28, and 52 in both treatment groups (Table 2), but to a somewhat greater extent in children receiving budesonide. Health status generally improved at each successive visit, and improvements were greater for specific versus general scores. Differences between treatment groups in specific scores approached statistical significance at both weeks 8 and 52.

Similar to the PACQLQ, additional analysis of censored data from the FS-II(R) demonstrated greater differences between treatments than in the primary analysis, such that mean differences between treatment groups in both general and specific scores were statistically significant at all time points (Table 2). As in the primary analysis, differences were greater in FS-II(R) specific scores.

Mean CHQ-PF50 scores decreased slightly from

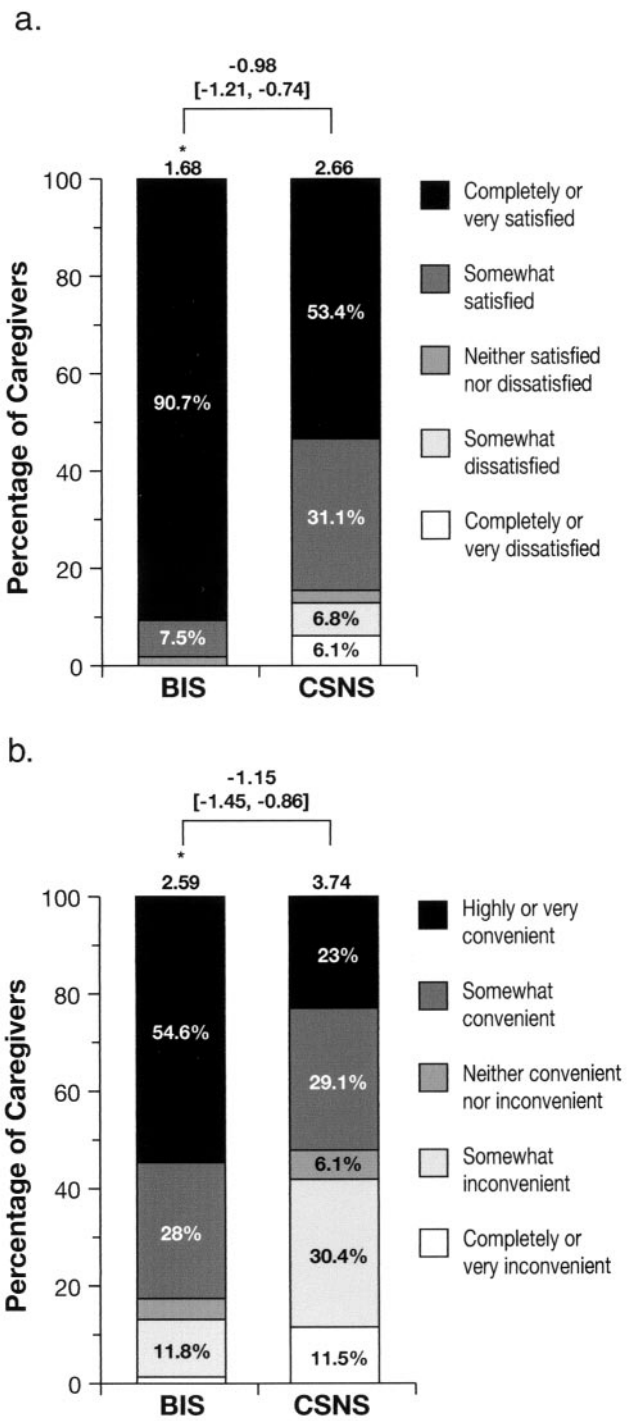

Fig 2. Caregivers' responses to the satisfaction (a) and convenience (b) questions of the CCSQ. The bars depict the percentage of caregivers providing responses in each Likert-type category at week 52 (numbers for percentages <5 are not shown). Categories for "very" and "completely" satisfied/convenient and "very" and "completely" dissatisfied/inconvenient were combined in the figures to reduce the scale from 7 to 5 categories; however, a 7-point scale was used for the ANCOVA analysis of mean results. Mean scores adjusted for center and baseline effect appear on the top of each bar, with lower numbers indicating a more positive response. Estimated mean differences between treatments and associated 95% CIs appear above the brackets. BIS (budesonide inhalation suspension), (n = 161); CSNS (cromolyn sodium nebulizer solution), (n = 148). *$P \leq .001$ versus CSNS.

baseline in the budesonide (−5.5) and cromolyn sodium (−5.1) treatment groups by week 52. Differences between treatments were not significant (P = .635), and unlike PACQLQ and FS-II(R) scores, adjusting for additional asthma medications did not increase treatment differences.

Global Assessments

Global assessment by caregivers demonstrated significantly ($P \leq .001$) easier asthma management with budesonide versus cromolyn sodium at study end (week 52). A majority of caregivers of children receiving budesonide (76%) reported asthma management to be "a great deal easier" at study end compared with fewer caregivers of children receiving cromolyn sodium (29%).

Global assessment of child health status by caregivers also significantly ($P \leq .001$) favored budesonide over cromolyn sodium. Twice as many caregivers of children receiving budesonide (74%) than caregivers of children receiving cromolyn sodium (37%) rated overall child health status as "much better now than 1 year ago."

DISCUSSION

This 52-week study compared the impact of treatment with budesonide inhalation suspension or cromolyn sodium nebulizer solution on the quality of life of caregivers of children with persistent asthma as well as on the children's functional health status and day-to-day activities. The data demonstrate that caregivers of children treated with budesonide inhalation suspension have significantly fewer limitations in PACQLQ-related daily activities and emotional functioning compared with caregivers of children treated with cromolyn sodium nebulizer solution. Treatment with budesonide improved caregivers' quality of life earlier than treatment with cromolyn sodium. Only caregivers of children in the budesonide group had a clinically important mean change from baseline (≥0.5 units) in all PACQLQ domains by week 8 and improvement >1.0 in all PACQLQ domains by week 28; these benefits were maintained at week 52.

For both treatments, there was a strong negative correlation between the baseline PACQLQ score and degree of improvement, such that caregivers expressing the greatest degree of burden at baseline (ie, a low score) were associated with larger improvements from baseline than those with a lesser degree of burden at baseline. It is not certain if this is truly a pharmacologic effect or rather an artifactual "floor effect" of the questionnaire caused by a subgroup of caregivers with relatively high baseline scores who had no room for improvement. This pattern of responses has been reported previously with different therapies and a different quality-of-life instrument.[31]

Budesonide provided significantly greater caregiver satisfaction, treatment convenience, ease of use, and compliance than cromolyn sodium. The results of this study are not unexpected because once- or twice-daily dosing has been previously associated with improved patient compliance and willingness to use controller therapy compared with 4-times-daily dosing.[32,33]

Coincident with this positive impact on caregiver quality of life, the present study has shown improve-

ment in functional status of children receiving both budesonide and cromolyn sodium using the FS-II(R). The greatest differences between treatments were seen in Part II of the FS-II(R), which relates impairments in functional status to the child's illness. Important, was the additional finding of greater between-treatment differences in FS-II(R), as well as PACQLQ, scores when data were censored for additional use of chronic asthma medications. Results of the censored analyses provide a more accurate reflection of differences attributable solely to the study drugs. The fact that improvement in functional status was not seen with the CHQ-PF50 may reflect less sensitivity of the General Health Perceptions scale to treatment effects in asthmatic patients with minimal impairment.

Greater improvements in health status with budesonide versus cromolyn were supported by global assessment indicating significantly better asthma management and overall child health after 1 year of treatment.

In general, clinical trials in children 4 to 16 years of age with asthma have demonstrated greater effectiveness of inhaled corticosteroids versus cromolyn sodium on typical clinical measures of efficacy.[34–36] Efficacy based on the rate of asthma exacerbations, use of additional chronic asthma therapy, asthma symptom scores, and breakthrough medication use by patients in this study has been reported in detail elsewhere.[21] Briefly, compared with cromolyn sodium, treatment with budesonide inhalation suspension resulted in a significantly lower mean rate of asthma exacerbations, significantly longer times to first asthma exacerbation, significantly longer times to first additional use of chronic asthma therapy, and significant improvements in asthma symptom scores and breakthrough medication use ($P \leq .001$ for all variables). Additionally, children receiving budesonide inhalation suspension experienced more symptom-free days (ie, a day and night with no reported asthma symptoms) and episode-free days (ie, a day and night with no reported asthma symptoms, drug-related adverse events, or breakthrough bronchodilator use) compared with children receiving cromolyn sodium ($P = .0001$).[37] Safety profiles were similar between the 2 treatments.[21]

Both improved asthma control and a simplified dosing regimen with budesonide inhalation suspension compared with cromolyn sodium likely contributed to greater caregiver satisfaction and quality of life with budesonide. Compared with dosing of cromolyn sodium 3 or 4 times daily, the convenience of once- or twice-daily dosing with budesonide inhalation suspension likely decreased caregiver burden and enhanced the willingness of caregivers to comply with administering inhalation therapy to their young children with asthma, further improving treatment effectiveness.

This is the first clinical trial comparing the effects of a nebulized corticosteroid with that of an alternative nebulized therapy on quality of life in young children with asthma and their families. Compared with nebulized cromolyn sodium, budesonide inhalation suspension not only provides better overall child health status and asthma management, but greater caregiver quality of life and greater caregiver satisfaction, convenience, ease of use, and compliance.

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REFERENCES

1. Peri G, Molinari E, Taverna A. Parental perceptions of childhood illness. *J Asthma*. 1991;28:91–101
2. Mrazek DA, Klinnert MD, Mrazek P, Macey T. Early asthma onset: consideration of parenting issues. *J Am Acad Child Adolesc Psychiatry*. 1991;30:277–282
3. Mailick MD, Holden G, Walther VN. Coping with childhood asthma: caretakers' views. *Health Soc Work*. 1994;19:103–111
4. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy*. 1991;21:77–83
5. Juniper EF. Quality of life in adults and children with asthma and rhinitis. *Allergy*. 1997;52:971–977
6. Shapiro GG. Management of pediatric asthma. *Pediatr Asthma*. 1998;18:1–23
7. Revicki DA, Frank L. Pharmacoeconomic evaluation in the real world: effectiveness versus efficacy studies. *Pharmacoeconomics*. 1999;15:423–434
8. Townsend M, Feeny DH, Guyatt GH, Furlong WJ, Seip JE, Dolovich J. Evaluation of the burden of illness for pediatric asthmatic patients and their parents. *Ann Allergy*. 1991;67:403–407
9. National Heart, Lung, and Blood Institute, National Institutes of Health. *National Asthma Education and Prevention Program Expert Panel Report. Guidelines for the Diagnosis and Management of Asthma. Expert Panel Report No. 2*. Bethesda, MD: National Institutes of Health; 1997. NIH Publ. No. 97-4051
10. National asthma education and prevention program expert panel report: guidelines for the diagnosis and management of asthma. Update on selected topics—2002. *J Allergy Clin Immunol*. 2002;110:S1–S219
11. American Academy of Allergy, Asthma & Immunology. *Pediatric Asthma: Promoting Best Practice. Guide for Managing Asthma in Children*. Milwaukee, WI: American Academy of Allergy, Asthma & Immunology, Inc; 1999
12. Pedersen S, O'Byrne P. A comparison of the efficacy and safety of inhaled corticosteroids in asthma. *Allergy*. 1997;52:1–34
13. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med*. 1994;88:373–381
14. Haahtela T, Jarvinen M, Kava T, et al. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med*. 1994;331:700–705

15. Selroos O, Pietinalho A, Lofroos AB, Riska H. Effect of early vs late intervention with inhaled corticosteroids in asthma. *Chest*. 1995;108: 1228–1234
16. Szefler SJ. Pharmacodynamics and pharmacokinetics of budesonide: a new nebulized corticosteroid. *J Allergy Clin Immunol*. 1999;104: S175–S183
17. Baker JW, Mellon M, Wald J, Welch M, Cruz-Rivera M, Walton-Bowen K. A multiple-dosing, placebo-controlled study of budesonide inhalation suspension given once or twice daily for treatment of persistent asthma in young children and infants. *Pediatrics*. 1999;103:414–421
18. Kemp JP, Skoner DP, Szefler SJ, Walton-Bowen K, Cruz-Rivera M, Smith JA. Once-daily budesonide inhalation suspension for the treatment of persistent asthma in infants and young children. *Ann Allergy Asthma Immunol*. 1999;83:231–239
19. Shapiro G, Mendelson L, Kraemer MJ, Cruz-Rivera M, Walton-Bowen K, Smith JA. Efficacy and safety of budesonide inhalation suspension (Pulmicort Respules) in young children with inhaled steroid-dependent, persistent asthma. *J Allergy Clin Immunol*. 1998;102:789–796
20. American Society of Health-System Pharmacists. Cromolyn sodium. In: McEvoy GK, ed. *AHFS Drug Information*. Bethesda, MD: American Society of Health-System Pharmacists; 2002:3608–3612
21. Leflein JG, Szefler SJ, Murphy KR, et al. Nebulized budesonide inhalation suspension compared with cromolyn sodium nebulizer solution for asthma in young children: results of a randomized outcomes trial. *Pediatrics*. 2002;109:866–872
22. Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in the parents of children with asthma. *Qual Life Res*. 1996;5:27–34
23. Guyatt G, Juniper E, Walter S, Griffith L, Goldstein R. Interpreting treatment in randomized trials. *BMJ*. 1998;316:690–693
24. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimally important change in a disease-specific quality of life questionnaire. *J Clin Epidemiol*. 1994;47:81–87
25. Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in children with asthma. *Qual Life Res*. 1996; 5:35–46
26. Isaac S, Michael WB. *Handbook in Research and Evaluation*. 3rd ed. San Diego, CA: Educational and Industrial Testing Services; 1997
27. Landgraf JM, Abetz L, Ware JE. *Child Health Questionnaire (CHQ): A User's Manual*. Boston, MA: HealthAct; 1996
28. Stein REK, Jessop DJ. Functional Status II(R). A measure of child health status. *Med Care*. 1990;28:1041–1055
29. Neder J, Wasserman W, Kutner MH. *Applied Linear Statistical Models*. Homewood, IL: Richard D. Irwin, Inc; 1990
30. Wei L, Zhang J. Analysis of imbalance in the clinical trial baseline outcome variable. *Drug Inf J*. 2001;35:1201–1214
31. Jones P, Campbell F, Miller C, Silverman S. Accounting for baseline data in the analysis of quality of life (QoL) in asthma [abstract 514]. *Qual Life Res*. 1999;8:663
32. Mann M, Eliasson O, Patel K, ZuWallack RL. A comparison of the effects of bid and qid dosing on compliance with inhaled flunisolide. *Chest*. 1992;101:496–499
33. Balsbaugh TA, Chambers CV, Diamond JJ. Asthma controller medications: what do patients want? *J Asthma*. 1999;36:591–596
34. Francis RS, McEnery G. Disodium cromoglycate compared with beclomethasone dipropionate in juvenile asthma. *Clin Allergy*. 1984;14: 537–540
35. Edmunds AT, Goldberg RS, Duper B, Devichand P, Follows RMA. A comparison of budesonide 800 μg and 400 μg daily via Turbohaler with disodium cromoglycate via Spinhaler for asthma prophylaxis in children. *Br J Clin Res*. 1994;5:11–23
36. 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
37. Murphy K, Fitzpatrick S, Cruz-Rivera M, Miller C, Parasuraman B. Greater caregiver satisfaction and compliance with budesonide inhalation suspension vs cromolyn sodium [abstract]. *Am J Respir Crit Care Med*. 2002;165:A742

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