

Inhaled corticosteroid therapy for patients with persistent asthma: Learnings from studies of inhaled budesonide

Bradley E. Chipps, M.D.

ABSTRACT

Inhaled corticosteroids (ICSs) are recommended for patients with asthma who use a short-acting β_2 -adrenergic agonist more than twice weekly—a key indicator of disease persistency. Much knowledge about the long-term benefits of ICSs in persistent asthma stems from studies of the ICS budesonide, which have shaped current asthma guidelines. Results of the 3-year double-blind phase of the inhaled Steroid Treatment As Regular Therapy study indicated that early ICS treatment improves impairment and reduces future risk of severe exacerbations by 44% in adults and children with ICS-naïve, recent-onset persistent asthma. These benefits were maintained or improved during the 2-year open-label phase; however, the benefit of very early versus later introduction of ICS treatment on pulmonary function could not be established. Similarly, in the Childhood Asthma Management Program (CAMP) study, ICS treatment did not alter the progression of asthma. The CAMP study, however, highlighted the need for continued daily ICS treatment, thus providing evidence for the new asthma guidelines' focus on improving asthma control versus altering natural history. In patients not controlled on daily ICSs alone, the Oxis and Pulmicort Turbuhaler in the Management of Asthma (OPTIMA) and Formoterol And Corticosteroids Establishing Therapy (FACET) studies of budesonide showed benefit of ICS combination therapy with a long-acting beta₂-adrenergic agonist (LABA). Taken together, these studies show the efficacy of daily ICS therapy in patients with mild to moderate persistent asthma, support the benefits of initiating ICSs early and continuing treatment, and underscore the need to increase to ICS/LABA in those uncontrolled on ICS alone.

(Allergy Asthma Proc 30:217–228, 2009; doi: 10.2500/aap.2009.30.3201)

Key words: Asthma control, budesonide, combination therapy, formoterol, inhaled corticosteroids, long-acting beta₂-adrenergic agonist, mild persistent asthma, single-controller therapy

When the national guidelines for the diagnosis and management of asthma were first established, severity classification (intermittent or mild persistent, moderate persistent, or severe persistent) was a key determinant of pharmacologic treatment. Although asthma severity remains a relevant indicator of the intrinsic intensity of the disease process, the National Asthma Education and Prevention Program¹ guidelines and the Global Initiative for Asthma guidelines² now emphasize the variable nature of asthma, with treatment based on disease control and treatment response, rather than severity alone.³ The goals of treatment now include achieving and maintaining overall asthma control through reductions in impairment and risk.¹ Impairment takes into consideration the frequency and intensity of symptoms and functional limitations, including lung function, whereas risk includes

the likelihood of exacerbations, medication-related adverse effects, and lung function decline (or reduced lung growth in children).¹

The disadvantage of basing treatment decisions solely on asthma severity stems from the inherent variability in control; loss of asthma control can occur among patients in any severity category. More than one-half of poorly controlled asthma cases occur in patients with intermittent (35%) or mild persistent (26%) disease.⁴ Variability in overall asthma control is further evidenced by studies that show severe exacerbations among patients who report symptoms consistent with intermittent or mild persistent asthma.^{5–7} Therefore, asthma treatment should be initiated based on asthma severity in patients not receiving controller therapy and adjusted based on overall asthma control as measured by impairment and risk in patients receiving therapy.¹

Daily therapy with an inhaled corticosteroid (ICS) is recommended as first-line treatment for persistent asthma.^{1,2} ICSs can be used alone, or when necessary, in combination with a long-acting β_2 -adrenergic agonist (LABA) to maintain overall asthma control. This review focuses on studies of budesonide (Table 1)^{5,8–13} that have contributed to the understanding of the role of ICSs in controlling persistent asthma. The importance of some of these key studies is reflected in the

From the Capital Allergy and Respiratory Disease Center, Sacramento, California (private practice)

Editorial support funded by AstraZeneca LP. B Chipps is a speaker and/or on the advisory board of AstraZeneca

Address correspondence and reprint requests to Bradley E. Chipps, M.D., Capital Allergy and Respiratory Disease Center, 5609 J Street, Suite C, Sacramento, CA 95819

E-mail address: bchipps@capitalallergy.com

Copyright © 2009, OceanSide Publications, Inc., U.S.A.

Table 1 Key findings of budesonide studies

| Study and Study Design | Treatments | Study Population | Key Findings |
|--|--|---|---|
| <p>START^{8,9}</p> <p>R, DB, PBO-controlled 3-yr phase followed by 2-yr OL phase</p> | <p>3 yr DB phase</p> <ul style="list-style-type: none"> • BUD DPI 400 µg (200 µg for those <11 yr) q.d. + usual asthma therapy • PBO + usual asthma therapy | <p>Children and adults aged 5–66 yr with ICS-naive, recent-onset asthma</p> | <p>3-yr results</p> <ul style="list-style-type: none"> • 44% reduced risk of first SARE (HR, 0.56; 95% CI, 0.45–0.71) and longer time to first SARE ($p < 0.0001$ for both) with BUD DPI⁸ • Fewer patients on BUD DPI with ≥ 1 OCS course (OR, 0.59; 95% CI, 0.53–0.67; $p < 0.0001$) vs PBO⁸ |
| <p>CAMP¹⁰</p> <p>4–6-yr, R, DB, PBO-controlled¹⁰</p> | <p>2-yr OL treatment</p> <ul style="list-style-type: none"> • PBO switched to BUD DPI 400 µg (200 µg for those <11 yr) q.d. + usual asthma therapy (late BUD) • Early BUD DPI group continued same BUD DPI dosage <p>4–6-yr, R, DB, PBO-controlled¹⁰</p> <ul style="list-style-type: none"> • BUD DPI 200 µg bid • Nedocromil pMDI 8 mg b.i.d. • PBO b.i.d. | <p>Children aged 5–12 yr with asthma symptoms or inhaled bronchodilator use ≥ 2 times/wk, or who used any daily asthma medication</p> | <p>5-yr results</p> <ul style="list-style-type: none"> • Similar decreases in postbronchodilator FEV₁ percentage-predicted in early and late BUD DPI groups (-2.17 [SE, 0.21] vs -2.27 [SE, 0.21]; $p = 0.74$); in adults, significant difference in favor of early BUD DPI ($p = 0.044$)⁹ • Lower cumulative risk of ≥ 1 SARE with early vs late BUD DPI (OR, 0.61; $p < 0.001$)⁹ <p>43% reduction in hospitalization rate and prednisone courses vs PBO ($p \leq 0.04$)</p> <ul style="list-style-type: none"> • Fewer symptoms (change in symptom score of -0.44) vs PBO (-0.37; $p = 0.005$)¹⁰ • Less albuterol use (change in use of -7.4 puffs/wk) vs PBO (-5.3; $p < 0.001$)¹⁰ • More episode-free days (11.3/mo) vs PBO (9.3/mo)¹⁰ • Improvement in FEV₁/FVC ratio vs PBO ($p < 0.001$)¹⁰ |

DO NOT COPY
 Copyright (c) Oceanside Publications, Inc. All rights reserved

Table 1 Continued

| Study and Study Design | Treatments | Study Population | Key Findings |
|---|--|--|---|
| <p>PAC¹¹</p> <p>3-yr, R, DB, PBO-controlled¹¹</p> <p>IMPACT⁵</p> <p>54-wk, R, DB, PG, PBO-controlled⁵</p> | <ul style="list-style-type: none"> BUD pMDI 400 µg/day or PBO for 2 wk after third day of wheezing episode BUD DPI 200 µg b.i.d. Zafirlukast 20 mg b.i.d. PBO b.i.d. | <p>Newborns aged 1 mo with episodes of wheezing</p> <p>Adults aged 18–65 yr with mild persistent asthma and FEV₁ ≥70% predicted ≥4 hr after bronchodilator</p> | <ul style="list-style-type: none"> After 3 yr, no change in asthma progression with BUD pMDI and no short-term benefit¹¹ Similar increases in morning PEF Greater improvement in prebronchodilator FEV₁ (%) (4.0 ± 1.2) and bronchial reactivity (1.8 ± 0.2) with continuous BUD DPI vs zafirlukast (−1.1 ± 1.0 and 0.3 ± 0.2, respectively) or intermittent treatment (0.7 ± 1.1 and 0.1 ± 0.2, respectively; <i>p</i> ≤ 0.005) Greater improvement in percentage of sputum eosinophils (−0.3) and exhaled nitric oxide (−14.4) with continuous BUD DPI vs zafirlukast (0 and 12.4, respectively) or intermittent treatment (0.2 and 26.6, respectively; <i>p</i> ≤ 0.007)⁵ Improved asthma control scores (−0.4 ± 0.1) vs zafirlukast (−0.2 ± 0.04) or intermittent treatment (−0.3 ± 0.05; <i>p</i> < 0.0001) |
| <p>OPTIMA¹²</p> <p>1-yr, DB, R, PG¹²</p> | <p>Group A</p> <ul style="list-style-type: none"> BUD DPI 100 µg bid BUD DPI 100 µg + F DPI 4.5 µg bid PBO bid | <p>Adults and adolescents ≥12 yr with persistent asthma, ICS free for ≥3 mo with postbronchodilator FEV₁ ≥80% predicted normal (group A) or taking ICSs for ≥3 mo with postbronchodilator FEV₁ ≥70% (group B)¹²</p> | <p>Group A results</p> <ul style="list-style-type: none"> 60% reduced risk of first severe asthma exacerbation with BUD DPI vs PBO, with no significant benefit of added F DPI¹² Improvements for BUD DPI and BUD + F DPI vs PBO in the rate per year of severe exacerbations (0.29 and 0.34 vs 0.77), percentage of days with symptoms (23.1 and 21.5 vs 29.4), and number of rescue inhalations per day (0.51 and 0.51 vs 0.75)¹² |

DO NOT COPY
 Copyright (c) Oceanside Publications, Inc. All rights reserved

Table 1 Continued

| Study and Study Design | Treatments | Study Population | Key Findings |
|--|--|--|--|
| | <p>Group B</p> <ul style="list-style-type: none"> • BUD DPI 100 μg b.i.d. • BUD DPI 100 μg + F DPI 4.5 μg, b.i.d. • BUD DPI 200 μg b.i.d. • BUD DPI 200 μg + F DPI 4.5 μg b.i.d. | | <p>Group B results</p> <ul style="list-style-type: none"> • Addition of F DPI to either BUD DPI dosage reduced the risk of a first severe exacerbation by 43%.¹² • Addition of F DPI to low-dose BUD DPI was more effective than doubling the BUD dose in reducing severe exacerbations (0.56 per patient per year vs 0.96; $p = 0.0001$) and improving percentage–predicted FEV₁ (2.55 vs 0.90) and morning PEF (12.89 vs 1.73; $p < 0.05$)¹² |
| <p>FACET¹³ 1-yr, DB, R, PG¹³</p> | <ul style="list-style-type: none"> • BUD DPI 100 μg bid + PBO b.i.d. • BUD DPI 100 μg + F DPI 12 μg b.i.d. • BUD DPI 400 μg + PBO b.i.d. • BUD DPI 400 μg + F DPI 12 μg b.i.d. | <p>Adults taking ICSs for ≥ 3 mo, with FEV₁ $\geq 50\%$ predicted¹³</p> | <ul style="list-style-type: none"> • ~40% reduction in the rate of mild exacerbations, with higher dose BUD DPI or F DPI addition to low-dose BUD DPI; greater reduction in severe exacerbations with higher dose BUD DPI vs added F DPI ($p = 0.03$)¹³ • More significant symptom and pulmonary function improvements with addition of F DPI¹³ |

START = Steroid Treatment As Regular Therapy; R = randomized; DB = double blind; PBO = placebo; OL = open label; BUD = budesonide; DPI = dry powder inhaler; ICS = inhaled corticosteroid; SARE = severe asthma-related event; HR = hazard ratio; CI = confidence interval; OCS = oral corticosteroid; OR = odds ratio; FEV₁ = forced expiratory volume in 1 s; SE = standard error; CAMPA = Childhood Asthma Management Program; pMDI = pressurized metered-dose inhaler; FVC = forced vital capacity; PAC = Prevention of Asthma in Childhood Trial; IMPACT = Improving Asthma Control Trial; PG = parallel group; PEF = peak expiratory flow; OPTIMA = Oxis and Pulmicort Turbuhaler In the Management of Asthma; F = formoterol; FACET = Formoterol And Corticosteroids Establishing Therapy.

Copyright (c) Oceanside Publications, Inc. All rights reserved. DO NOT COPY

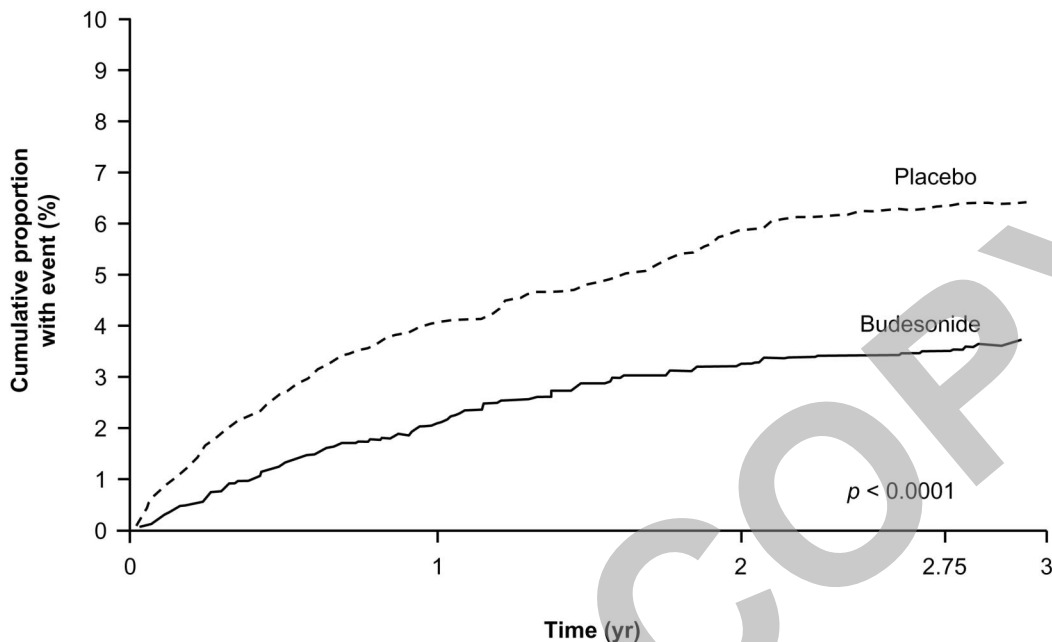


Figure 1. Kaplan-Meier estimate of time to first severe asthma-related event (SARE) for patients receiving budesonide dry powder inhaler (DPI) or placebo. The risk of a first SARE was significantly reduced (44% reduction; $p < 0.0001$) and the time to the first SARE was significantly prolonged ($p < 0.0001$) with budesonide administered via DPI compared with placebo over the initial 3-year double-blind study period. (Reprinted from Pauwels RA, Pedersen S, Busse WW, et al. Early intervention with budesonide in mild persistent asthma: A randomised, double-blind trial. *Lancet* 361: 1071–1076, 2003, with permission from Elsevier.)

number of times they have been cited in other publications (e.g., 3-year inhaled Steroid Treatment As Regular Therapy [START],¹⁴ 184 citations; Childhood Asthma Management Program [CAMP],¹⁰ 475 citations; Oxis and Pulmicort Turbuhaler In the Management of Asthma [OPTIMA],¹² 230 citations; Formoterol And Corticosteroids Establishing Therapy [FACET],¹³ 665 citations).¹⁵ These studies enrolled generally mild to moderate patient populations, some with ICS-naive, recent-onset asthma. The review evaluates the use of ICS therapy in these patients, discussing the benefits of initiating ICSs early in the course of the disease, maintaining long-term treatment with ICSs, and using ICSs on a regular basis. It also discusses patient populations with asthma uncontrolled on ICSs that may benefit from a step up to combination treatment of ICS and LABA.

EARLY INTERVENTION WITH ICS THERAPY: THE START STUDY

Results from early studies of budesonide suggested that improvements in asthma with ICS therapy were greater when the ICS was initiated early in the disease process.^{16–18} However, studies were confounded by inclusion of patients with long-standing disease.⁸ The inhaled START in early asthma study was the largest

randomized, double-blind, placebo-controlled trial to assess the effect of early intervention with ICS therapy. Patients who had mild persistent asthma (defined as cough, wheeze, dyspnea, chest tightness, or nocturnal awakening due to any of these symptoms at least weekly, but not daily) of recent onset (i.e., <2 years) and who had received <30 days of corticosteroid treatment per year were included in the study.¹⁴ Patients with a prebronchodilator forced expiratory volume at 1 second (FEV₁) of <60% of predicted or a postbronchodilator FEV₁ of <80% of predicted were excluded from the study.^{8,14} Overall, 7241 patients were randomized to receive budesonide or placebo in addition to their usual asthma therapy for 3 years.⁸

The results from the START study show the benefits of initiating single-entity ICS therapy early in the course of the disease to reduce the risk of exacerbations and decrease impairment in corticosteroid-naive patients with persistent asthma.⁸ Overall, budesonide administered *via* dry powder inhaler (DPI) significantly reduced the risk of a first severe asthma-related event (SARE; Fig. 1). Additionally, significantly fewer patients in the budesonide DPI group received systemic corticosteroids compared with patients in the placebo group, and earlier use was reported in the placebo group ($p < 0.0001$). Patients treated with budesonide

DPI also had significantly more symptom-free days ($p < 0.0001$) compared with those receiving placebo. Early treatment with budesonide DPI also was shown to significantly reduce the number of hospital days (69% reduction; $p < 0.001$), emergency treatments (67% reduction; $p < 0.05$), and physician visits (36% reduction; $p < 0.001$) compared with placebo.¹⁹

Among 1974 children aged 5–10 years evaluated for efficacy in the START study, budesonide DPI treatment showed a significantly reduced risk of an SARE (reduction of 40%; $p = 0.012$) over 3 years compared with those who received placebo with usual care.²⁰ Moreover, the percentage of children requiring intervention with other ICSs was significantly lower in the budesonide DPI group compared with the placebo with usual care group ($p < 0.001$). As in the overall population, children experienced more symptom-free days with budesonide DPI compared with placebo. Specifically, budesonide DPI treatment resulted in a mean increase of 16 symptom-free days per child over 3 years ($p < 0.001$).²¹ Budesonide DPI treatment also resulted in reductions in the number of hospital days (50% reduction) and the frequency of emergency department visits (34% reduction) compared with placebo.²¹

In the START study, the budesonide DPI safety profile was similar to that of placebo in the overall population and in children aged 5–10 years.^{8,22} Children aged <11 years experienced a 3-year reduction in growth rate of 1.34 cm in the budesonide DPI group compared with the placebo group. The reduction was greatest during the first year of treatment (−0.58 cm) versus years 2 (−0.43 cm) and 3 (−0.33 cm).⁸

After the initial 3-year double-blind phase of the START study, 5146 patients entered a 2-year open-label phase, during which inhaled budesonide DPI therapy was either continued (early budesonide DPI group) or initiated (previous placebo group/late budesonide DPI group).⁹ Over the full 5 years of START, the overall risk of having at least one SARE was significantly lower for patients who began early treatment with budesonide DPI (odds ratio [OR] = 0.61; $p < 0.001$).⁹ For variables associated with impairment (e.g., symptoms), patients maintained improvements achieved during the double-blind phase or continued to improve during the 2-year open-label phase. However, the significant differences observed between the budesonide DPI and placebo groups during the double-blind phase were lost during the open-label phase.

Loss of pulmonary function over time has been shown to be greater in patients with asthma compared with normal subjects in several studies.^{23,24} Results from the first 3 years of the START study suggested that early intervention with single-entity budesonide provides significant benefits in reducing this decline.⁸ Improvements from baseline in prebronchodilator percentage-predicted FEV₁ values were significantly greater with budesonide

DPI compared with placebo after 1 year (4.52 versus 2.28, respectively; $p < 0.0001$) and 3 years (3.49 versus 1.77; $p < 0.0001$) in the overall population.⁸ Children who received budesonide DPI also showed greater improvements in prebronchodilator percentage-predicted FEV₁ values compared with those receiving usual care at 1 year (4.35% versus 2.12%, respectively) and 3 years (3.77 versus 2.48, respectively).²⁰

In the overall population, a decline in postbronchodilator percentage-predicted FEV₁ values was observed in both treatment groups. This decline, however, was significantly attenuated with budesonide DPI compared with placebo at 1 year (−0.63 versus −2.11, respectively; $p < 0.0001$) and 3 years (−1.79 versus −2.68, respectively; $p = 0.0005$).⁸ Age was a significant ($p = 0.004$) factor affecting postbronchodilator response. Children aged 5–10 years who received budesonide DPI also had an attenuated decline in postbronchodilator percentage-predicted FEV₁ values compared with those who received placebo after 3 years of treatment (−1.84 versus −2.31, respectively); the difference between treatments was less pronounced in children than in adults (0.47 versus 1.54, respectively).²⁰ Additional analysis of 3-year START data in patients with less mild asthma (i.e., prebronchodilator FEV₁ value of <80% of predicted normal at baseline or receipt of a corticosteroid dose during the previous 6 weeks) also showed an attenuation of pulmonary function decline with budesonide DPI compared with placebo.²⁵

The full 5-year START study failed to confirm that budesonide might modify the decline in lung function in patients with recent-onset mild persistent asthma.⁹ The 5-year study is limited by the open-label design of the final 2-year phase. Over the entire 5-year treatment period, prebronchodilator percentage-predicted FEV₁ values increased, whereas postbronchodilator percentage-predicted FEV₁ values decreased, regardless of treatment during the double-blind phase. The 5-year change from baseline in prebronchodilator and postbronchodilator percentage-predicted FEV₁ values was not significantly different between the early and late budesonide DPI treatment groups in the overall population. In adults only (aged ≥18 years), early budesonide DPI treatment attenuated the decline in postbronchodilator FEV₁ ($p = 0.044$). This significant difference between early and late budesonide DPI treatment was not observed for children aged 5–10 years or adolescents aged 11–17 years.

Thus, the START study showed that early treatment (i.e., within 2 years of asthma onset) with single-entity ICSs improves overall asthma control by reducing asthma impairment and decreasing the risk of exacerbations, emergency care, and hospitalizations in this population of children and adults with recent-onset, symptomatic asthma not previously receiving routine therapy with ICSs.

LONG-TERM OUTCOMES OF ICS THERAPY: THE CAMP STUDY

The benefits of long-term, continuous treatment with budesonide on asthma control were shown in the CAMP study.¹⁰ This study included 1041 children with persistent asthma, as evidenced by current symptoms or use of inhaled bronchodilators at least twice weekly or other asthma medications daily. Patients were treated with budesonide DPI, nedocromil administered *via* pressurized metered-dose inhaler (pMDI) twice daily, or placebo for 4–6 years. The benefits of single-entity budesonide DPI treatment in the CAMP study were notable for measures of asthma control and resource utilization.

Over the course of treatment, budesonide DPI resulted in significantly fewer symptoms ($p = 0.005$), less albuterol use ($p < 0.001$), and more episode-free days ($p = 0.01$) compared with placebo.¹⁰ Significantly reduced hospitalization rates (43% reduction; $p = 0.04$), urgent care visits (45% reduction; $p < 0.001$), and courses of prednisone (43% reduction; $p < 0.001$) also were observed with budesonide DPI compared with placebo. Treatment with nedocromil pMDI also significantly reduced urgent care visits (27% reduction; $p < 0.02$) and courses of prednisone (16% reduction; $p < 0.01$) compared with placebo. There were no clinically or statistically significant differences, however, between nedocromil pMDI and placebo in symptom scores, use of albuterol, episode-free days, and hospitalization rates.

Similar to the START study, budesonide DPI treatment did not attenuate the decline in pulmonary function as measured by postbronchodilator percentage-predicted FEV₁ values in patients aged 5–12 years.¹⁰ However, budesonide DPI did result in improvements in the FEV₁/forced vital capacity (FVC) ratio compared with placebo (prebronchodilator FEV₁/FVC, -0.2% versus -1.8% , respectively; $p = 0.001$; postbronchodilator FEV₁/FVC, -1.0% versus -1.7% , respectively; $p = 0.08$ [Fig. 2]). In addition, prebronchodilator percentage-predicted FEV₁ increased within 2 months after the start of the study and was significantly higher at the end of the treatment period in children receiving budesonide DPI compared with placebo ($p = 0.02$). In contrast, no differences were observed between nedocromil pMDI and placebo at the end of the treatment period for the FEV₁/FVC ratio or the prebronchodilator percentage-predicted FEV₁.

As with the START study, the mean increase in height at the end of treatment in the CAMP study was significantly ($p = 0.005$) less in the budesonide DPI group (22.7 cm) compared with the placebo group (23.8 cm), but the difference was primarily evident during the first year of treatment, and all groups had similar growth velocity by the end of the treatment period.¹⁰ Notably, a prospective study in children with asthma

showed that despite a reduced rate of growth observed with budesonide (mean dose, 412 $\mu\text{g}/\text{day}$) during the first 3 years of treatment, children attained their final adult height after a mean of 9.2 years of treatment.²⁶

The CAMP study was not an early intervention study because children had a mean duration of asthma of ~ 5 years at baseline. Nonetheless, the study did not support that ICS controller therapy may alter the natural progression of the disease, leading to an important shift in the focus of asthma treatment from long-term disease modification to controlling asthma symptoms and quality of life.^{1,27} The results from the Prevention of Asthma in Childhood (PAC) trial failed to support that ICSs may affect the natural history of asthma in children.¹¹ In the PAC trial, 1-month-old infants ($n = 411$) were treated with 2-week courses of budesonide pMDI (400 $\mu\text{g}/\text{day}$) or placebo after a 3-day episode of wheezing and were followed for the first 3 years of life. Budesonide pMDI treatment during episodes of wheezing did not alter the progression from episodic to persistent wheezing in the first 3 years of life. There also were no short-term benefits of budesonide pMDI therapy in decreasing asthma symptoms during the 2-week treatment periods.

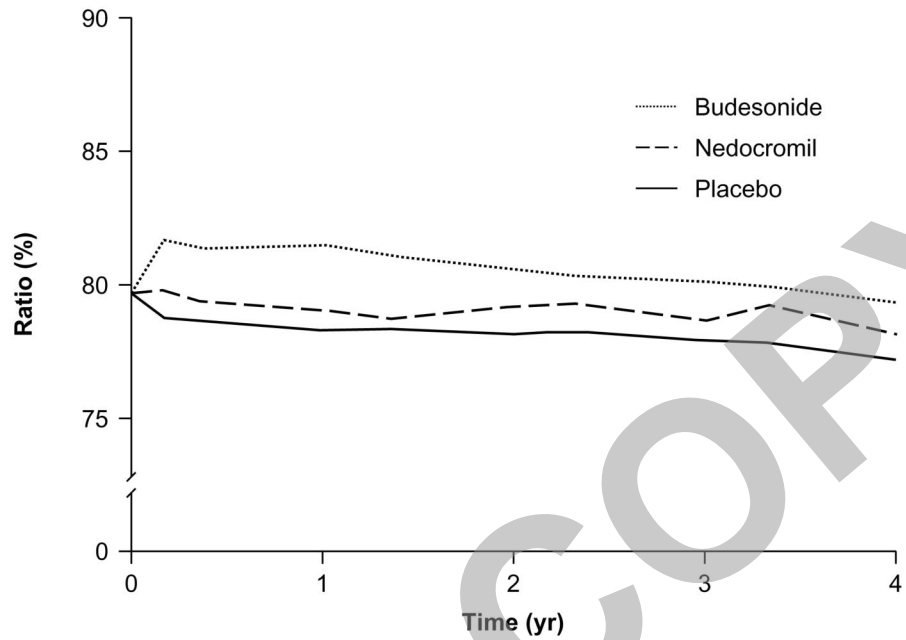
The results from the CAMP study support the use of ICSs as long-term controller therapy for children with symptoms consistent with mild to moderate persistent asthma and reinforce the safety of daily low- to medium-dose ICS therapy in terms of growth and development.²⁷ In the CAMP study, budesonide DPI treatment provided improvements in pulmonary function and morbidity (defined by the number of prednisone courses) that diminished with time but were still present at the end of the treatment period. Airway hyperresponsiveness, however, continued to improve throughout the study period with budesonide DPI compared with placebo ($p < 0.001$).²⁷ A key finding of the CAMP study was the regression of airway hyperresponsiveness to placebo levels within a mean of 0.2 years after discontinuation of budesonide treatment (Fig. 3), further highlighting the importance of continued daily ICS treatment.²⁷

In conclusion, the CAMP study indicated that long-term treatment with the ICS budesonide decreases asthma impairment, evidenced by reduced symptom burden, decreased albuterol use, and improved pulmonary function, and decreases the risk of future exacerbations, evidenced by decreased hospitalizations and urgent care visits, in this population of children with persistent asthma.

DAILY ICS VERSUS AS-NEEDED ICS FOR PATIENTS UNCONTROLLED ON AS-NEEDED BRONCHODILATOR THERAPY: IMPACT

The results of the Improving Asthma Control Trial (IMPACT) showed benefits of daily inhaled budes-

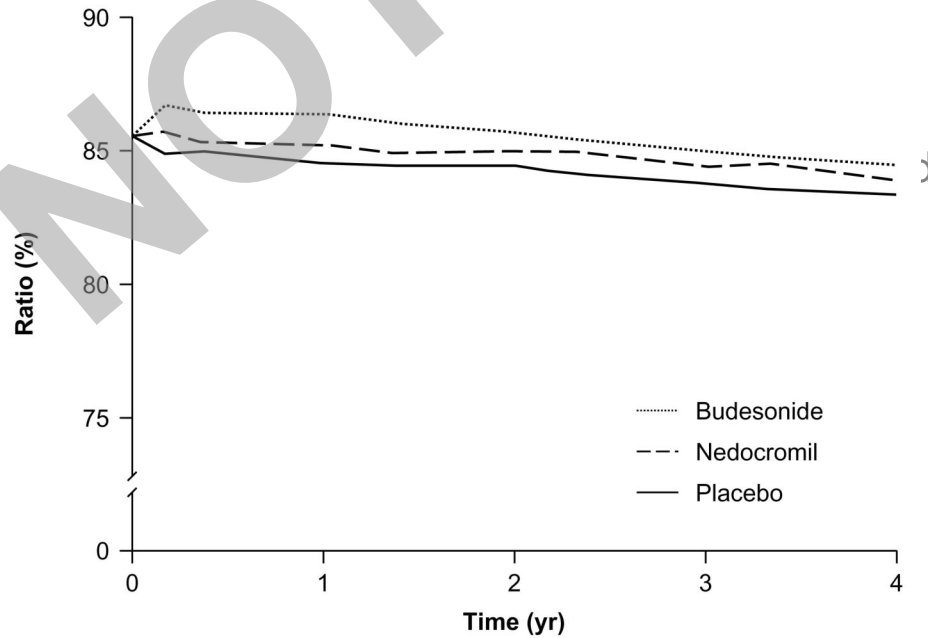
A



Number of observations

| | | | | | |
|------------|-----|-----|-----|-----|-----|
| Budesonide | 311 | 297 | 296 | 291 | 279 |
| Nedocromil | 312 | 305 | 292 | 284 | 268 |
| Placebo | 416 | 396 | 391 | 388 | 374 |

B



Number of observations

| | | | | | |
|------------|-----|-----|-----|-----|-----|
| Budesonide | 311 | 297 | 296 | 291 | 279 |
| Nedocromil | 312 | 305 | 292 | 284 | 267 |
| Placebo | 416 | 396 | 390 | 388 | 374 |

Figure 2. Mean values for (A) prebronchodilator and (B) postbronchodilator forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio over 4 years in patients receiving budesonide dry powder inhaler, nedocromil pressurized metered-dose inhaler, or placebo. (Reprinted with permission, Copyright 2000 Massachusetts Medical Society. All rights reserved.)

onide therapy versus intermittent corticosteroid therapy on measures of asthma control and inflammation in adults ($N = 225$) with uncontrolled asthma on as-

needed rescue therapy.⁵ Patients had symptoms consistent with mild persistent asthma as evidenced by short-acting β_2 -agonist (SABA) use more than twice

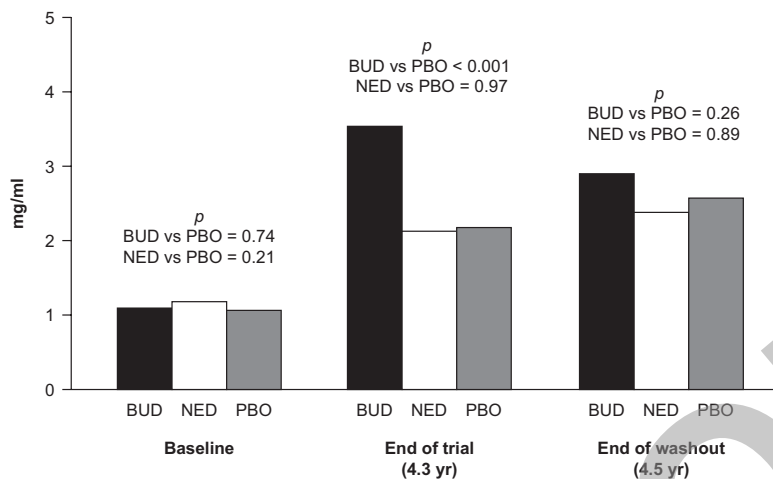


Figure 3. Mean airway responsiveness to methacholine at baseline, end of treatment, and 0.2 years after treatment withdrawal in the Childhood Asthma Management Program (CAMP) study. The *p* values are for differences between treatments in the change from baseline to last follow-up. BUD = budesonide; NED = nedocromil; PBO = placebo. (Reprinted from Strunk RC, and Childhood Asthma Management Program Research Group. Childhood Asthma Management Program: Lessons learned. *J Allergy Clin Immunol* 119: 36–42, 2007, with permission from Elsevier.)

weekly, asthma awakenings more than twice monthly, or peak expiratory flow (PEF) variability of 20–30%. With the exception of accepting a baseline FEV₁ as low as 70% of predicted, patients were excluded who met criteria for moderate persistent asthma.

After a 4-week run-in period, followed by 10–14 days of intense combined therapy (0.5 mg of prednisone per kilogram of body weight per day, 800 µg budesonide DPI twice daily, and 20 mg zafirlukast twice daily), patients received budesonide DPI treatment, oral zafirlukast, or inhaled and oral placebo for 52 weeks.⁵ Patients in all groups used an open-label, short-course of budesonide DPI (800 µg twice daily) or oral prednisone (0.5 mg/kg of body weight per day) for worsening asthma symptoms according to an asthma action plan.⁵ The treatment phase ended with another 10- to 14-day period of intense combination therapy to eliminate any reversible causes of airflow obstruction that would influence measures of PEF or FEV₁.

The study failed to detect a difference among the three treatment groups for morning PEF, postbronchodilator FEV₁, and quality of life.⁵ However, continuous budesonide DPI therapy resulted in significantly greater improvements in pulmonary function (*i.e.*, prebronchodilator FEV₁ [*p* = 0.005] and bronchial reactivity [*p* < 0.001]) and inflammation (*i.e.*, percentage of sputum eosinophils [*p* = 0.007] and exhaled nitric oxide [*p* = 0.006]) compared with intermittent therapy (*i.e.*, as-needed budesonide or prednisone) or continuous zafirlukast therapy. Asthma control scores (*p* < 0.001) and number of symptom-free days (*p* = 0.03) also significantly improved in patients on budesonide compared with intermittent or zafirlukast therapy.⁵

Budesonide DPI is not indicated or recommended for intermittent or as-needed therapy,¹ and the results of the IMPACT study support that continuous daily budesonide therapy provides benefits over intermittent ICS therapy in improving asthma control, bronchial hyperresponsiveness, and inflammation in patients with asthma symptoms that were uncontrolled with as-needed SABA therapy. Daily ICS therapy reduced impairment by improving asthma control scores and prebronchodilator FEV₁. The study was not adequately powered to detect a difference in risk (*i.e.*, exacerbations).²⁸

COMBINATION THERAPY FOR PERSISTENT ASTHMA: THE OPTIMA AND FACET STUDIES

Treatment guidelines recommend combination therapy with an ICS and LABA as a treatment option for children aged ≥5 years and adults who are not well controlled on ICSs alone.¹ The OPTIMA study assessed the effect of adding formoterol to low-dose budesonide therapy for 1 year in patients with persistent asthma uncontrolled on either as-needed SABA or daily ICS.¹² Patients were stratified into two groups. Patients in group A were corticosteroid free (no ICS therapy for ≥3 months), had a postbronchodilator FEV₁ of ≥80% of predicted normal, and were symptomatic during the run-in period on only as-needed SABA. These patients (*n* = 698) were randomized to receive twice-daily treatment with 100 µg of budesonide DPI, 100 µg of budesonide DPI plus 4.5 µg of formoterol DPI, or placebo. Patients in group B had received ≤400 µg/day of inhaled budesonide or its equivalent for ≥3 months, had a postbronchodilator FEV₁ of ≥70% of predicted

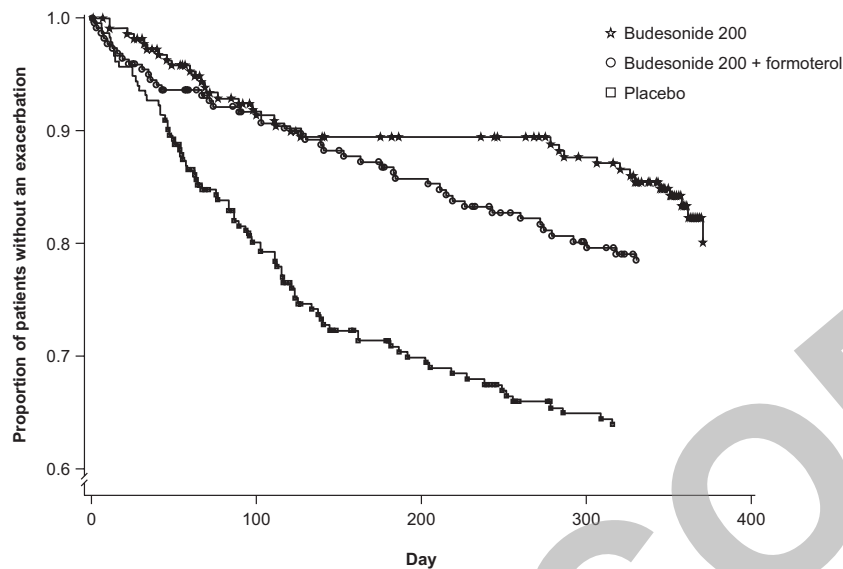


Figure 4. Kaplan-Meier estimate of time to first severe asthma exacerbation in patients receiving twice-daily administration of 100 µg of budesonide dry powder inhaler (DPI; budesonide 200), 100 µg of budesonide DPI plus 4.5 µg of formoterol DPI (budesonide 200 + formoterol), or placebo. (Reprinted with permission. O’Byrne PM, Barnes PJ, Rodriguez-Roisin R, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: The OPTIMA randomized trial. *Am J Respir Crit Care Med* 164:1392–1397, 2001. Copyright 2001 American Thoracic Society.)

normal, and were symptomatic during the run-in period on low-dose daily ICS therapy. These patients ($n = 1272$) were randomized to receive twice-daily treatment with 100 µg of budesonide DPI, 100 µg of budesonide DPI plus 4.5 µg formoterol DPI, 200 µg of budesonide DPI, or 200 µg of budesonide DPI plus 4.5 µg of formoterol DPI.

In group A patients, single-entity budesonide DPI treatment improved asthma control with minimal benefit of added formoterol DPI therapy.¹² Daily budesonide DPI treatment reduced the risk of the first severe asthma exacerbation by 60% (Fig. 4) and the proportion of poorly controlled asthma days by 48% compared with placebo. The addition of formoterol DPI to budesonide DPI therapy did not provide additional significant reductions in these end points. The yearly rate of severe asthma exacerbations was numerically higher ($p = 0.50$) with budesonide DPI and formoterol DPI (0.34) than with budesonide DPI alone (0.29). Improvements in the proportions of days with asthma symptoms or nighttime awakenings, and the number of inhalations of rescue medication per day were significant (all $p < 0.0074$) for single-entity budesonide DPI therapy and budesonide DPI plus formoterol DPI therapy versus placebo but not for monotherapy versus combination therapy. The addition of formoterol DPI to budesonide DPI treatment did result in additional significant benefits for percentage-predicted FEV₁ ($p = 0.023$) and morning PEF ($p = 0.0001$).

In group B patients, the addition of formoterol DPI to either dosage of budesonide DPI (100 or 200 µg twice daily) reduced the risk of the first asthma exacerbation

by 43% and the proportion of poorly controlled days by 30%, whereas doubling the dose of budesonide DPI from 100 µg to 200 µg twice daily improved these end points by only 19% and 13%, respectively.¹² Addition of formoterol DPI to the lower dosage of budesonide DPI was significantly more effective than doubling the dosage of budesonide DPI in reducing the rate of severe exacerbations ($p = 0.0001$) and in improving percentage-predicted FEV₁ ($p = 0.015$) and morning PEF ($p = 0.0015$). The results from the OPTIMA study suggest that patients with persistent asthma who continue to experience symptoms while on single-entity, low-dose ICS therapy benefit from the addition of LABA therapy, whereas those symptomatic on only as-needed SABA therapy can be controlled with ICS therapy alone.

One of the landmark studies examining combination therapy with the ICS budesonide and the LABA formoterol was the FACET study.¹³ A total of 852 adults previously treated with ICS therapy and had a mean baseline FEV₁ of ~76% of predicted normal, which is consistent with moderate to severe persistent asthma, were included in the study. Patients were randomized to treatment with twice-daily administration of 100 µg of budesonide DPI plus placebo, 100 µg of budesonide DPI plus 12 µg of formoterol DPI, 400 µg of budesonide DPI plus placebo, or 400 µg of budesonide DPI plus 12 µg of formoterol DPI. Combination therapy with the lower dose of budesonide DPI plus formoterol and single-entity therapy with the higher dose of budesonide DPI reduced the rates of severe exacerbations by 26% and 49%, respectively, compared with lower

dose budesonide therapy. Thus, the higher dose of budesonide DPI resulted in a greater reduction in the rate of severe exacerbations than the addition of formoterol DPI ($p = 0.03$). The rate of mild exacerbations was reduced by ~40% when either formoterol DPI was added to the lower dose of budesonide DPI or when the higher versus the lower dose of budesonide DPI was given. Although asthma symptoms and pulmonary function improved with the addition of formoterol DPI and with the higher dose of budesonide DPI, significant improvements were more consistent with the addition of formoterol DPI.

In both the OPTIMA¹² and FACET¹³ studies, treatments were well tolerated, with similar frequency of adverse events reported across the different treatment groups. Although the use of LABAs has raised concerns with increases in exacerbations and asthma-related mortality reported in previously conducted studies,²⁹ not all patients in those studies also were taking an ICS.³⁰ These safety concerns did not appear to occur in a long-term safety study of budesonide/formoterol administered *via* one pMDI³¹ or in the OPTIMA¹² and FACET¹³ studies. As described previously, in the OPTIMA study, exacerbation rates in group A patients on budesonide DPI and formoterol DPI combination therapy did not statistically differ from rates in patients on budesonide DPI alone. Exacerbation rates were lower with combination therapy versus monotherapy in group B patients in the OPTIMA study and overall in the FACET study.

Thus, the OPTIMA¹² and FACET¹³ studies defined a population of patients with persistent asthma that might benefit from ICS/LABA combination therapy. The results of the OPTIMA study indicate that in asthma patients with mild impairment who are not currently using ICS therapy, treatment with low-dose budesonide is sufficient to achieve asthma control; however, in patients whose asthma is not controlled on single-entity ICS therapy, the addition of formoterol should be considered. The results of the FACET study further indicate that patients with persistent asthma not adequately controlled on ICSs alone might benefit from combination ICS/LABA therapy.

CONCLUSIONS

Several key studies of budesonide have contributed to our current understanding of the role of ICSs in managing asthma. Together, these studies (START, CAMP, IMPACT, OPTIMA, and FACET) support current recommendations for daily ICSs alone as the first step in pharmacotherapy to reduce asthma impairment and risk in patients with persistent symptoms of asthma that are uncontrolled with as-needed SABA. For optimal control of asthma in patients exhibiting mild impairment while not receiving ICSs, it is impor-

tant to give ICSs as maintenance treatment continuously versus intermittently (IMPACT). Although single-entity ICS therapy is adequate for initiating therapy in recent-onset asthma uncontrolled with as-needed SABA alone, results of the FACET and OPTIMA studies show added benefit of stepping up to combination therapy with a LABA for patients with persistent asthma who may not be controlled with ICSs alone. These studies show the benefit of ICS monotherapy and ICS/LABA combination therapy in improving asthma impairment and reducing future risks of exacerbations. In conclusion, these studies contribute to the recent asthma management concept of treatment based on disease control, through reductions in impairment and risk, and treatment response as outlined in the Global Initiative for Asthma and National Asthma Education and Prevention Program guidelines.^{1,2}

ACKNOWLEDGMENTS

The authors acknowledge Lisa M. Klumpp, Ph.D., and Marissa Buttarò, M.P.H. (Scientific Connexions, Newtown, PA), for writing assistance funded by AstraZeneca LP, the sponsor of the studies.

REFERENCES

1. National Heart, Lung, Blood Institute (NHLBI). National Asthma Education and Prevention Program expert panel report 3: Guidelines for the diagnosis and management of asthma. Full Report 2007, NHLBI publication no. 08-4051. Available online at www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf; last accessed April 2008.
2. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Updated 2007. Available online at www.ginasthma.com; last accessed December 2007.
3. Schatz M, Zeiger RS, Vollmer WM, et al. Determinants of future long-term asthma control. *J Allergy Clin Immunol* 118:1048–1053, 2006.
4. Desfougeres JL, Sohler B, Freedman D, et al. Perception of asthma control by patients: Results of a survey in 5 European countries. *Eur Respir J* 30(suppl):1590, 2007.
5. Boushey HA, Sorkness CA, King TS, et al. Daily versus as-needed corticosteroids for mild persistent asthma. *N Engl J Med* 352:1519–1528, 2005.
6. Salmeron S, Liard R, Elkharrat D, et al. Asthma severity and adequacy of management in accident and emergency departments in France: A prospective study. *Lancet* 358:629–635, 2001.
7. Warman KL, Silver EJ, and Stein REK. Asthma symptoms, morbidity, and antiinflammatory use in inner-city children. *Pediatrics* 108:277–282, 2001.
8. Pauwels RA, Pedersen S, Busse WW, et al. Early intervention with budesonide in mild persistent asthma: A randomised, double-blind trial. *Lancet* 361:1071–1076, 2003.
9. Busse WW, Pedersen S, Pauwels RA, et al. The Inhaled Steroid Treatment As Regular Therapy in Early Asthma (START) study 5-year follow-up: Effectiveness of early intervention with budesonide in mild persistent asthma. *J Allergy Clin Immunol* 121:1167–1174, 2008.
10. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 343:1054–1063, 2000.
11. Bisgaard H, Hermansen MN, Loland L, et al. Intermittent inhaled corticosteroids in infants with episodic wheezing. *N Engl J Med* 354:1998–2005, 2006.

12. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: The OPTIMA randomized trial. *Am J Respir Crit Care Med* 164:1392–1397, 2001.
13. Pauwels RA, Löfdahl C-G, Postma DS, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. *N Engl J Med* 337:1405–1411, 1997.
14. Pauwels RA, Busse WW, O'Byrne PM, et al. The inhaled Steroid Treatment as Regular Therapy in early asthma (START) study: Rationale and design. *Control Clin Trials* 22:405–419, 2001.
15. ISI Web of Knowledge. Web of science. Database search engine. Available online at www.aaps.isisknowledge.com/CitedFullRecor.do?product; last accessed August 2008.
16. Agertoft L, and Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 88:373–381, 1994.
17. Haahtela T, Jarvinen M, Kava T, et al. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med* 331:700–705, 1994.
18. Selroos O, Pietinalho A, Löfroos A-B, and Riska H. Effect of early vs late intervention with inhaled corticosteroids in asthma. *Chest* 108:1228–1234, 1995.
19. Sullivan SD, Buxton M, Andersson LF, et al. Cost-effectiveness analysis of early intervention with budesonide in mild persistent asthma. *J Allergy Clin Immunol* 112:1229–1236, 2003.
20. Chen Y-Z, Busse WW, Pedersen S, et al. Early intervention of recent onset mild persistent asthma in children aged under 11 yrs: The Steroid Treatment As Regular Therapy in early asthma (START) trial. *Pediatr Allergy Immunol* 17:7–13, 2006.
21. Weiss K, Buxton M, Andersson FL, et al. Cost-effectiveness of early intervention with once-daily budesonide in children with mild persistent asthma: Results from the START study. *Pediatr Allergy Immunol* 17:21–27, 2006.
22. Silverman M, Sheffer AL, Díaz PV, et al. Safety and tolerability of inhaled budesonide in children in the Steroid Treatment As Regular Therapy in early asthma (START) trial. *Pediatr Allergy Immunol* 17:14–20, 2006.
23. Lange P, Parner J, Vestbo J, et al. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 339:1194–1200, 1998.
24. Peat JK, Woolcock AJ, and Cullen K. Rate of decline of lung function in subjects with asthma. *Eur J Respir Dis* 70:171–179, 1987.
25. O'Byrne PM, Pedersen S, Busse WW, et al. Effects of early intervention with inhaled budesonide on lung function in newly diagnosed asthma. *Chest* 129:1478–1485, 2006.
26. Agertoft L, and Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *N Engl J Med* 343:1064–1069, 2000.
27. Strunk RC, and Childhood Asthma Management Program Research Group. Childhood Asthma Management Program: Lessons learned. *J Allergy Clin Immunol* 119:36–42, 2007.
28. O'Byrne PM. Daily inhaled corticosteroid treatment should be prescribed for mild persistent asthma. *Pro Am J Respir Crit Care Med* 172:410–412, discussion 415–416, 2005.
29. Mansfield LE. The future of the long-acting beta-adrenergic bronchodilators in the treatment of asthma. *Allergy Asthma Proc* 29:103–108, 2008.
30. Lang DM, and Davis RS. The long-acting beta-agonist controversy: A clinical dilemma. *Allergy Asthma Proc* 28:136–144, 2007.
31. Peters ST, Prenner BM, Mezzanotte WS, et al. Long-term safety and asthma control with budesonide/formoterol versus budesonide pressurized metered-dose inhaler (pMDI) in asthma patients. *Allergy Asthma Proc* 29:499–516, 2008. □

DO NOT COPY
Copyright (c) Oceanside Publications, Inc. All rights reserved