Background: The Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study enrolled 7241 patients aged 5 to 66 years with recent-onset, mild persistent asthma to assess early intervention with the inhaled corticosteroid budesonide on long-term asthma control.

Objective: The open-label phase of the START study was included to determine the effect on lung function and asthma control of adding budesonide to the reference group patients who had not initially received inhaled corticosteroids.

Methods: Patients were randomized to double-blind treatment with budesonide, 200 mg (those aged <11 years) or 400 mg once daily, or placebo plus the usual asthma therapy for 3 years, after which all patients received 2 years of open-label treatment with budesonide once daily.

Results: During the full 5-year study period, postbronchodilator FEV1 percent predicted decreased, irrespective of randomized treatment during the double-blind phase, by an average of 2.22% (SE, 0.15%). However, patients with inhaled budesonide in the double-blind phase had a significantly lower risk (odds ratio, 0.61; P < .001) of a severe asthma-related event during the full 5-year study period than those in the reference group. Moreover, patients in the reference group used more additional asthma medications during both the open-label and double-blind phases.

Conclusions: In mild persistent asthma early intervention with inhaled budesonide was associated with improved asthma control and less additional asthma medication use. (J Allergy Clin Immunol 2008;121:1167-74.)

Key words: Mild persistent asthma, recent-onset asthma, budesonide dry-powder inhaler, inhaled corticosteroid

Asthmatic patients with mild persistent disease can experience considerable asthma-related morbidity1-4 and even mortality.5,6 Guidelines recommend inhaled corticosteroids (ICSs) as the preferred initial choice of anti-inflammatory therapy in patients with persistent asthma7,8 based on gain of greater asthma control (ie, reduced current impairments), decreased exacerbations (diminishing future risks), and improved quality of life.2,3 Previous studies have also suggested that early intervention with ICSs in newly diagnosed asthma might reduce other aspects of future risks, including the degree of progressive loss of lung function that can occur in asthma8 and the influence of the overall treatment response.10-12 The 5-year Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study was designed to determine the potential long-term effectiveness of early intervention with ICSs in adults and children with mild persistent disease of less than 2 years’ duration. In the initial phase of this study, patients were randomized to a 3-year double-blind treatment period with either budesonide, 400 μg (200 μg for children aged <11 years) administered once daily through a dry-powder inhaler (Pulmicort Turbuhaler; AstraZeneca Research and Development, Lund, Sweden), or placebo through a Turbuhaler.1 In addition to the blinded therapy, the managing physician could add other asthma therapy, including the introduction of ICSs to achieve asthma control. This approach to treatment was implemented to ensure asthma control and thus greater patient retention over the duration of the study.13 The primary outcome variable of the double-blind phase of the START study was the time to the first severe asthma-related event (SARE).13 In the double-blind phase of the START study, patients who received budesonide had a significant reduction in asthma exacerbations requiring systemic corticosteroids, a longer time to the first SARE, and less of a decrease in prebronchodilator and postbronchodilator FEV1 values.1

This double-blind phase of the START study was followed by 2 years of open-label treatment, during which all patients received budesonide once daily, as well as continuing their usual asthma therapy received to this point. Throughout the study, the use of this additional asthma therapy was recorded. The primary
outcome variable of the full 5-year study period was the change from baseline in postbronchodilator percent predicted FEV₁. Secondary outcome variables were the change in prebronchodilator percent predicted FEV₁, the number of SAREs, change in asthma-related symptoms, and use of concomitant asthma medication to achieve asthma control. This article reports the results of the full 5-year study period. Some of the findings have been previously reported in the form of an abstract.

METHODS

Study population

The START study (AstraZeneca Study SD-004-0111) has been described in detail elsewhere. Briefly, patients aged 5 to 66 years with recent-onset, mild persistent asthma were enrolled from 499 sites in 32 countries. These patients met the criteria for mild persistent asthma as noted in the US guidelines. Eligible patients had asthma symptoms at least weekly, but not daily, in the 3 months before enrollment. Patients also had reversible airway obstruction, demonstrated by an increase in FEV₁ of greater than 12% after the use of a short-acting β₂-adrenergic agonist, a decrease in FEV₁ of greater than 15% after exercise challenge, or variation of greater than 15% between the 2 highest and 2 lowest peak expiratory flow rates in 14 days. The onset of asthma must have been within 2 years of enrollment, and patients could not have had greater than 30 days of inhaled or oral corticosteroid treatment or more than 1 depot corticosteroid injection per year.

Procedures

Patients completing the 3-year double-blind phase of the study were switched to open-label treatment with once-daily budesonide (200 μg for patients aged <11 years at study entry and 400 μg for patients aged ≥11 years at entry study) plus the usual asthma therapy for the final 2 years of the study. After 3 years, all patients received 2 years of open-label treatment with inhaled budesonide once daily plus usual asthma therapy. The study was performed by the clinical investigators (listed in the Appendix) and monitors, employed by the sponsor, who collected the data. All investigators and the sponsor reviewed the various drafts of the manuscript and made editing suggestions. The authors made final decisions on all aspects of the manuscript. The sponsors of the study had no role in the study design, the planning of the data analysis, and the interpretation of the results, with the exception of the company coauthors, who participated in all aspects of the study.

Role of the funding source

The study was funded through a contract from AstraZeneca Research and Development. The sponsors of the study had no role in the study design, the planning of the data analysis, and the interpretation of the results, with the exception of the company coauthors, who participated in all aspects of the study. The study was performed by the clinical investigators (listed in the Appendix) and monitors, employed by the sponsor, who collected the data. All investigators had free and unlimited access to the raw data and the statistical reports. Staff of the sponsor reviewed the various drafts of the manuscript and made editing suggestions. The authors made final decisions on all aspects of the manuscript.

RESULTS

Study population

In the 2-year open-label phase 5146 patients received regular treatment with budesonide, either as a continuation from the

Abbreviations used

CAMP: Childhood Asthma Management Program
ICS: Inhaled corticosteroid
OR: Odds ratio
PEAK: Prevention of Early Asthma in Kids
SARE: Severe asthma-related event
START: Inhaled Steroid Treatment As Regular Therapy in Early Asthma

FIG 1. Study design. Patients were randomized to double-blind treatment with inhaled budesonide, 200 μg (aged <11 years) or 400 μg once daily through a Turbuhaler, or placebo plus usual asthma therapy for 3 years. After 3 years, all patients received 2 years of open-label treatment with inhaled budesonide once daily plus usual asthma therapy. The study was performed by the clinical investigators (listed in the Appendix) and monitors, employed by the sponsor, who collected the data. All investigators and the sponsor reviewed the various drafts of the manuscript and made editing suggestions. The authors made final decisions on all aspects of the manuscript. The sponsors of the study had no role in the study design, the planning of the data analysis, and the interpretation of the results, with the exception of the company coauthors, who participated in all aspects of the study. The study was performed by the clinical investigators (listed in the Appendix) and monitors, employed by the sponsor, who collected the data. All investigators had free and unlimited access to the raw data and the statistical reports. Staff of the sponsor reviewed the various drafts of the manuscript and made editing suggestions. The authors made final decisions on all aspects of the manuscript. The sponsors of the study had no role in the study design, the planning of the data analysis, and the interpretation of the results, with the exception of the company coauthors, who participated in all aspects of the study. The study was performed by the clinical investigators (listed in the Appendix) and monitors, employed by the sponsor, who collected the data. All investigators had free and unlimited access to the raw data and the statistical reports. Staff of the sponsor reviewed the various drafts of the manuscript and made editing suggestions. The authors made final decisions on all aspects of the manuscript. The sponsors of the study had no role in the study design, the planning of the data analysis, and the interpretation of the results, with the exception of the company coauthors, who participated in all aspects of the study. The study was performed by the clinical investigators (listed in the Appendix) and monitors, employed by the sponsor, who collected the data. All investigators had free and unlimited access to the raw data and the statistical reports. Staff of the sponsor reviewed the various drafts of the manuscript and made editing suggestions. The authors made final decisions on all aspects of the manuscript. The sponsors of the study had no role in the study design, the planning of the data analysis, and the interpretation of the results, with the exception of the company coauthors, who participated in all aspects of the study. The study was performed by the clinical investigators (listed in the Appendix) and monitors, employed by the sponsor, who collected the data. All investigators had free and unlimited access to the raw data and the statistical reports. Staff of the sponsor reviewed the various drafts of the manuscript and made editing suggestions. The authors made final decisions on all aspects of the manuscript. The sponsors of the study had no role in the study design, the planning of the data analysis, and the interpretation of the results, with the exception of the company coauthors, who participated in all aspects of the study. The study was performed by the clinical investigators (listed in the Appendix) and monitors, employed by the sponsor, who collected the data. All investigators had free and unlimited access to the raw data and the statistical reports. Staff of the sponsor reviewed the various drafts of the manuscript and made editing suggestions. The authors made final decisions on all aspects of the manuscript. The sponsors of the study had no role in the study design, the planning of the data analysis, and the interpretation of the results, with the exception of the company coauthors, who participated in all aspects of the study. The study was performed by the clinical investigators (listed in the Appendix) and monitors, employed by the sponsor, who collected the data. All investigators had free and unlimited access to the raw data and the statistical reports. Staff of the sponsor reviewed the various drafts of the manuscript and made editing suggestions. The authors made final decisions on all aspects of the manuscript. The sponsors of the study had no role in the study design, the planning of the data analysis, and the interpretation of the results, with the exception of the company coauthors, who participated in all aspects of the study. The study was performed by the clinical investigators (listed in the Appendix) and monitors, employed by the sponsor, who collected the data. All investigators had free and unlimited access to the raw data and the statistical reports. Staff of the sponsor reviewed the various drafts of the manuscript and made editing suggestions. The authors made final decisions on all aspects of the manuscript.

Statistical analysis

The primary efficacy variable for the full 5-year study period was the change from baseline in postbronchodilator FEV₁ percent predicted. Assuming 1800 patients per treatment group and an SD of change from baseline in postbronchodilator FEV₁ percent predicted of 10%, a difference between treatment groups of 1.2% in this variable would be detected with a power of 95% at a significance level (2-sided) of 5%. Change in postbronchodilator and prebronchodilator FEV₁ percent predicted over the full 5-year study period was estimated by using a linear mixed model, including as covariates the randomized treatment, the baseline value, time since the start of the open-label phase, and the interaction between treatment and time. All data assessed in the open-label phase were used, and therefore results are based on both noncompleters and completers of the open-label phase. For comparability with results on lung function in the START study published earlier, all estimates reported in the tables are adjusted to the overall (for all patients in the START study) mean baseline level of postbronchodilator or prebronchodilator FEV₁ percent predicted. The same analysis model was used for all patients (overall) and separately for each age-by-sex stratum and for the stratum of adults (age ≥18 years) ignoring sex.

Treatment groups were compared regarding the risk of having 1 or more SAREs in terms of odds ratios (ORs) unadjusted for time in study. The OR was computed separately for the full study period, the double-blind phase, and the open-label phase, using all patients available in the study or in a certain study phase. SAS version 8.2 (SAS Institute, Inc, Cary, NC) was the software used for statistical analysis.

FIG 1. Study design. Patients were randomized to double-blind treatment with inhaled budesonide, 200 μg (aged <11 years) or 400 μg once daily through a Turbuhaler, or placebo plus usual asthma therapy for 3 years. After 3 years, all patients received 2 years of open-label treatment with inhaled budesonide once daily plus usual asthma therapy.
double-blind phase or as an addition during the open-label phase. Of these patients, 2604 had been previously randomized to double-blind treatment with budesonide (budesonide group), and 2542 had been randomized to placebo (reference group; Fig 2). Patient demographics at baseline (start of the double-blind phase) were similar in the budesonide and reference groups (Table I).

For patients entering the open-label phase, retention was higher than 90% in both treatment groups (Fig 2). Few patients in either group discontinued participation because of adverse events or worsening asthma. Most patient discontinuations were due to relocation, personal reasons, withdrawn consent, or loss to follow-up.

Lung function measurements

Both the prebronchodilator and postbronchodilator percent predicted FEV₁ values at baseline were similar in the budesonide and reference groups but differed between age-by-sex strata (Tables II and III). In all age groups mean values of percent predicted FEV₁ were higher in female than in male patients. At the end of the open-label phase, the overall (mean values over all patients) significant differences between treatment groups that existed in postbronchodilator and prebronchodilator percent predicted FEV₁ during the double-blind phase were lost, as shown in Fig 3. However, results in different age-by-sex strata were not homogeneous (Table IV and V).

During the full 5-year study period, the postbronchodilator percent predicted FEV₁ decreased, irrespective of randomized treatment during the double-blind phase ($P = .74$), by an average of 2.22%. However, in adults (age ≥18 years), ignoring sex, there was a statistically significant treatment difference of 0.85% ($P = .044$) in favor of budesonide (Table IV).

During the full 5-year study period, prebronchodilator percent predicted FEV₁ increased, irrespective of randomized treatment during the double-blind phase ($P = .20$), by an average of 3.24%. The increase was more pronounced in the pediatric age groups (age <18 years) than in adults. In adults, ignoring sex, a statistically significant treatment difference of 1.21% ($P = .018$) in favor of budesonide was seen between the 2 treatment groups (Table V).
with the risk being similar in the 2 treatment groups (OR, 1.12; experienced 1 or more SAREs during the 2-year open-label phase, patients (16 in the budesonide group and 14 in the reference group) completing all 5 years of the study.

SAREs

The incidence rate of SAREs decreased in each group over the 5-year treatment period (Fig 4). During the 3-year double-blind phase, 315 patients (117 in the budesonide group and 198 in the reference group) entered into the open-label phase, 315 patients (117 in the budesonide group and 198 in the reference group) experienced 1 or more SAREs, with the risk being significantly lower in the budesonide group (OR, 0.61; P < .001). Excluding the 315 patients, 30 differences, which existed during the double-blind phase, were, however, no longer statistically significant during the open-label period (51% on postbronchodilator FEV1 percent predicted and 48% on prebronchodilator FEV1 percent predicted).

In adults, ignoring sex, half the treatment effect of budesonide on lung function (postbronchodilator and prebronchodilator percent predicted FEV1) remained at the end of the 5-year study

Only patients entered into the open-label phase are shown. Data are presented as means (SD) at Bl-1 (ie, the start of the double-blind phase) or Bl-2 (ie, the start of the open-label phase).

FIG 3. Mean postbronchodilator (A) and prebronchodilator (B) percent predicted FEV1 among patients in the budesonide and reference groups completing all 5 years of the study.

TABLE III. Prebronchodilator percent predicted FEV1 at baseline

<table>
<thead>
<tr>
<th>Age-by-sex stratum</th>
<th>Budesonide</th>
<th>Reference</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>86.8 (13.4)</td>
<td>90.2 (13.7)</td>
<td>3.4 (0.8)</td>
</tr>
<tr>
<td>Male 5–10 y, female</td>
<td>85.8 (12.6)</td>
<td>91.6 (12.5)</td>
<td>5.8 (1.0)</td>
</tr>
<tr>
<td>Male 11–17 y, female</td>
<td>89.7 (13.5)</td>
<td>92.8 (13.9)</td>
<td>3.1 (1.0)</td>
</tr>
<tr>
<td>Male 18-66 y, female</td>
<td>88.7 (13.7)</td>
<td>91.7 (14.4)</td>
<td>2.9 (1.0)</td>
</tr>
<tr>
<td>Male</td>
<td>85.3 (13.4)</td>
<td>87.1 (14.6)</td>
<td>1.8 (0.8)</td>
</tr>
</tbody>
</table>

Only patients entered into the open-label phase are shown. Data are presented as means (SD) at Bl-1 (ie, the start of the double-blind phase) or Bl-2 (ie, the start of the open-label phase).

TABLE IV. Change in postbronchodilator percent predicted FEV1 over the study

<table>
<thead>
<tr>
<th>Age-by-sex stratum</th>
<th>Budesonide</th>
<th>Reference</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>−2.17 (0.21)</td>
<td>−2.27 (0.21)</td>
<td>0.10 (0.30), P = .74</td>
</tr>
<tr>
<td>Male 5–10 y, female</td>
<td>−0.84 (0.57)</td>
<td>0.26 (0.56)</td>
<td>−1.10 (0.80), P = .17</td>
</tr>
<tr>
<td>Male 11–17 y, female</td>
<td>−0.42 (0.70)</td>
<td>0.51 (0.74)</td>
<td>−0.93 (1.01), P = .36</td>
</tr>
<tr>
<td>Male 18-66 y, female</td>
<td>−1.89 (0.38)</td>
<td>−3.04 (0.39)</td>
<td>1.15 (0.54), P = .034</td>
</tr>
<tr>
<td>Male</td>
<td>−4.73 (0.49)</td>
<td>−4.91 (0.47)</td>
<td>0.18 (0.67), P = .79</td>
</tr>
</tbody>
</table>

Only patients entered into the open-label phase are shown. Data are presented as means (SEs) of the 5-year change estimated by means of mixed model analysis.

TABLE V. Change in prebronchodilator percent predicted FEV1 over the study

<table>
<thead>
<tr>
<th>Age-by-sex stratum</th>
<th>Budesonide</th>
<th>Reference</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>3.47 (0.25)</td>
<td>3.01 (0.25)</td>
<td>0.46 (0.35), P = .20</td>
</tr>
<tr>
<td>Male 5–10 y, female</td>
<td>5.21 (0.64)</td>
<td>5.32 (0.64)</td>
<td>−0.12 (0.90), P = .90</td>
</tr>
<tr>
<td>Male 11–17 y, female</td>
<td>4.27 (0.79)</td>
<td>4.30 (0.78)</td>
<td>−0.03 (1.10), P = .98</td>
</tr>
<tr>
<td>Male 18-66 y, female</td>
<td>4.60 (0.81)</td>
<td>4.92 (0.85)</td>
<td>−0.32 (1.17), P = .79</td>
</tr>
<tr>
<td>Male</td>
<td>0.80 (0.60)</td>
<td>−0.09 (0.58)</td>
<td>0.90 (0.84), P = .29</td>
</tr>
</tbody>
</table>

Only patients entered into the open-label phase are shown. Data are presented as means (SEs) of the 5-year change estimated by means of mixed model analysis.

FIG 4. Cumulative probability of having a first SARE. The curves are based on life-table estimates (interval width, 0.25 years) by using all patients entered into the study. The number of patients at risk in the budesonide group is 3597 (3568) at time 0, 2613 (2486) at time 2.50 years, and 2337 (2195) at time 4.50 years.

P = .76. The cumulative risk of having 1 or more SAREs during the full 5 years of START was significantly lower in the budesonide group than in the reference group (OR, 0.61; P < .001).

Asthma control and use of additional therapy

The reductions in the percentages of patients with symptoms, restrictions in normal activities, and sleep problems caused by asthma from baseline to the end of the double-blind treatment phase were maintained or further improved during the subsequent 2 years of open-label budesonide treatment. Between-group differences, which existed during the double-blind phase, were, however, no longer statistically significant during the open-label
phase. The percentage of symptom-free days increased among patients in both treatment groups throughout the 5-year study period (Fig 5), and the differences between groups were no longer significant during the open-label phase. Patients who received budesonide during the double-blind treatment phase used significantly less additional asthma medication during the open-label treatment phase. Significantly fewer patients in the budesonide group required additional ICSs (10.4% vs 14.6%, \( P < .001 \)) than those in the reference group. Third, a greater proportion of patients in the reference group required significantly more additional asthma medication (ICSs other than budesonide, long-acting \( \beta_2 \)-adrenergic agonists, and cromones) to achieve the same level of asthma control during years 4 and 5 of the study.

During both the double-blind and open-label phases of the START study, physicians were instructed to constantly tailor additional asthma medications to achieve clinical control of the disease, which was assessed based on symptoms, medication use, the number of asthma-free days, and the number of days in the previous 2 weeks their lives had been restricted by asthma symptoms. The use of additional medications was evaluated, and it appeared that these instructions were followed. Thus the use of cromones decreased and the use of long-acting \( \beta_2 \)-adrenergic agonists increased with time in both treatment groups. Moreover, the use of inhaled and oral corticosteroids was reduced in both groups during open-label treatment. These findings make it unlikely that differences in the use of additional asthma medications between the groups were merely due to a lack of treatment tailoring during the open-label phase.

A diminished response to ICS therapy in the patients with a delayed initiation of budesonide could be another possible explanation for our findings. This has been reported in a previous study, which evaluated the benefit of early versus late intervention with budesonide administered over 5 years in patients with mild or moderate persistent asthma. In this study patients with asthma of less than 2 years’ duration had their symptoms controlled on a lower dose of budesonide and used less additional asthma medications, including long-acting \( \beta_2 \)-adrenergic agonists, to maintain asthma control than patients with a median asthma duration of more than 5 years before treatment initiation.

The clinical benefits of regular treatment with low-dose ICSs in patients with mild persistent asthma have also been assessed in the Childhood Asthma Management Program (CAMP) study. However, this study was not an early-intervention study because patients in the CAMP study had a mean asthma duration of more than 5 years. The CAMP study treated children from 5 to 12 years of age with low-dose inhaled budesonide, nedocromil, or placebo for at least 4 years. The results from the CAMP study did not demonstrate any difference in the postbronchodilator FEV\(_1\) between treatments but did demonstrate that treatment with ICSs significantly improved airway responsiveness to methacholine, as well as resulting in fewer hospitalizations, fewer urgent visits to a caregiver, fewer courses of prednisone, and a smaller percentage of days on which additional asthma medications were needed. This study is consistent with the results of the START study and suggests an important clinical benefit of low-dose ICSs for patients with mild persistent asthma.

Guilbert et al recently reported on their observations in the Prevention of Early Asthma in Kids (PEAK) study, which was designed to determine whether early introduction of ICSs for

In the 3-year double-blind phase of the START study, treatment with budesonide significantly improved asthma control, as demonstrated by a reduction in SAREs, breakthrough symptoms, sleep disturbances, and activity limitations. The effects on asthma control in the open-label phase of the START study yielded 3 important findings. First, asthma control, as reflected in features of current impairments, was maintained or improved in patients randomized to early budesonide intervention. Second, the introduction of open-label budesonide after 3 years of usual asthma therapy resulted in a “catch-up” in asthma control in the reference group. Third, a greater proportion of patients in the reference group required significantly more additional asthma medication (ICSs other than budesonide, long-acting \( \beta_2 \)-adrenergic agonists, and cromones) to achieve the same level of asthma control during years 4 and 5 of the study.

Serious adverse events

Budesonide was well tolerated throughout the study, with no new or unexpected safety findings evident at 5 versus 3 years of budesonide treatment. Worsening asthma, accident, fracture, appendicitis, and pneumonia were the most frequently reported serious adverse events during both the double-blind and open-label treatment phases. Fewer serious adverse events and discontinuations caused by adverse events were reported during the 2-year open-label phase compared with during the 3-year double-blind phase.

DISCUSSION

Because of a rapid catch-up in lung function values in the reference group during the open-label phase of the START study, there was no significant overall difference between treatment groups in the 5-year change from baseline, either in the postbronchodilator or prebronchodilator FEV\(_1\) percent predicted values. However, in adults (age \( \geq 18 \) years) nearly half the treatment effect of budesonide on lung function attained in the double-blind phase of the START study still remained at the end of the 5-year study period. This finding in adults is consistent with a number of observational studies that have indicated that a delay in the initiation of ICSs in asthmatic patients is associated with a lower postbronchodilator FEV\(_1\). Moreover, some studies also reported this benefit in children. The latter was not seen in the present study. The reasons for this difference are not obvious, but the severity of asthma in the children in the study by Agertoft and Pedersen seemed to be somewhat greater than that of the children in the present study.

In the 3-year double-blind phase of the START study, treatment with budesonide significantly improved asthma control, as demonstrated by a reduction in SAREs, breakthrough symptoms, sleep disturbances, and activity limitations. The effects on asthma control in the open-label phase of the START study yielded 3 important findings. First, asthma control, as reflected in features of current impairments, was maintained or improved in patients randomized to early budesonide intervention. Second, the introduction of open-label budesonide after 3 years of usual asthma therapy resulted in a “catch-up” in asthma control in the reference group. Third, a greater proportion of patients in the reference group required significantly more additional asthma medication (ICSs other than budesonide, long-acting \( \beta_2 \)-adrenergic agonists, and cromones) to achieve the same level of asthma control during years 4 and 5 of the study.

During both the double-blind and open-label phases of the START study, physicians were instructed to constantly tailor additional asthma medications to achieve clinical control of the disease, which was assessed based on symptoms, medication use, the number of asthma-free days, and the number of days in the previous 2 weeks their lives had been restricted by asthma symptoms. When the use of additional medications was evaluated, it appeared that these instructions were followed. Thus the use of cromones decreased and the use of long-acting \( \beta_2 \)-adrenergic agonists increased with time in both treatment groups. Moreover, the use of inhaled and oral corticosteroids was reduced in both groups during open-label treatment. These findings make it unlikely that differences in the use of additional asthma medications between the groups were merely due to a lack of treatment tailoring during the open-label phase.

A diminished response to ICS therapy in the patients with a delayed initiation of budesonide could be another possible explanation for our findings. This has been reported in a previous study, which evaluated the benefit of early versus late intervention with budesonide administered over 5 years in patients with mild or moderate persistent asthma. In this study patients with asthma of less than 2 years’ duration had their symptoms controlled on a lower dose of budesonide and used less additional asthma medications, including long-acting \( \beta_2 \)-adrenergic agonists, to maintain asthma control than patients with a median asthma duration of more than 5 years before treatment initiation.

The clinical benefits of regular treatment with low-dose ICSs in patients with mild persistent asthma have also been assessed in the Childhood Asthma Management Program (CAMP) study. However, this study was not an early-intervention study because patients in the CAMP study had a mean asthma duration of more than 5 years. The CAMP study treated children from 5 to 12 years of age with low-dose inhaled budesonide, nedocromil, or placebo for at least 4 years. The results from the CAMP study did not demonstrate any difference in the postbronchodilator FEV\(_1\) between treatments but did demonstrate that treatment with ICSs significantly improved airway responsiveness to methacholine, as well as resulting in fewer hospitalizations, fewer urgent visits to a caregiver, fewer courses of prednisone, and a smaller percentage of days on which additional asthma medications were needed. This study is consistent with the results of the START study and suggests an important clinical benefit of low-dose ICSs for patients with mild persistent asthma.

Guilbert et al recently reported on their observations in the Prevention of Early Asthma in Kids (PEAK) study, which was designed to determine whether early introduction of ICSs for

In the 3-year double-blind phase of the START study, treatment with budesonide significantly improved asthma control, as demonstrated by a reduction in SAREs, breakthrough symptoms, sleep disturbances, and activity limitations. The effects on asthma control in the open-label phase of the START study yielded 3 important findings. First, asthma control, as reflected in features of current impairments, was maintained or improved in patients randomized to early budesonide intervention. Second, the introduction of open-label budesonide after 3 years of usual asthma therapy resulted in a “catch-up” in asthma control in the reference group. Third, a greater proportion of patients in the reference group required significantly more additional asthma medication (ICSs other than budesonide, long-acting \( \beta_2 \)-adrenergic agonists, and cromones) to achieve the same level of asthma control during years 4 and 5 of the study.

During both the double-blind and open-label phases of the START study, physicians were instructed to constantly tailor additional asthma medications to achieve clinical control of the disease, which was assessed based on symptoms, medication use, the number of asthma-free days, and the number of days in the previous 2 weeks their lives had been restricted by asthma symptoms. When the use of additional medications was evaluated, it appeared that these instructions were followed. Thus the use of cromones decreased and the use of long-acting \( \beta_2 \)-adrenergic agonists increased with time in both treatment groups. Moreover, the use of inhaled and oral corticosteroids was reduced in both groups during open-label treatment. These findings make it unlikely that differences in the use of additional asthma medications between the groups were merely due to a lack of treatment tailoring during the open-label phase.

A diminished response to ICS therapy in the patients with a delayed initiation of budesonide could be another possible explanation for our findings. This has been reported in a previous study, which evaluated the benefit of early versus late intervention with budesonide administered over 5 years in patients with mild or moderate persistent asthma. In this study patients with asthma of less than 2 years’ duration had their symptoms controlled on a lower dose of budesonide and used less additional asthma medications, including long-acting \( \beta_2 \)-adrenergic agonists, to maintain asthma control than patients with a median asthma duration of more than 5 years before treatment initiation.

The clinical benefits of regular treatment with low-dose ICSs in patients with mild persistent asthma have also been assessed in the Childhood Asthma Management Program (CAMP) study. However, this study was not an early-intervention study because patients in the CAMP study had a mean asthma duration of more than 5 years. The CAMP study treated children from 5 to 12 years of age with low-dose inhaled budesonide, nedocromil, or placebo for at least 4 years. The results from the CAMP study did not demonstrate any difference in the postbronchodilator FEV\(_1\) between treatments but did demonstrate that treatment with ICSs significantly improved airway responsiveness to methacholine, as well as resulting in fewer hospitalizations, fewer urgent visits to a caregiver, fewer courses of prednisone, and a smaller percentage of days on which additional asthma medications were needed. This study is consistent with the results of the START study and suggests an important clinical benefit of low-dose ICSs for patients with mild persistent asthma.

Guilbert et al recently reported on their observations in the Prevention of Early Asthma in Kids (PEAK) study, which was designed to determine whether early introduction of ICSs for
Inhaled corticosteroids†

<table>
<thead>
<tr>
<th></th>
<th>Budesonide (n = 2604)</th>
<th>Reference (n = 2542)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 4</td>
<td>Year 5</td>
<td>Year 4</td>
<td>Year 5</td>
</tr>
<tr>
<td>11.1</td>
<td>10.4</td>
<td>16.3</td>
<td>14.6</td>
</tr>
<tr>
<td>1.5</td>
<td>0.9</td>
<td>1.5</td>
<td>0.7</td>
</tr>
<tr>
<td>61.8</td>
<td>60.3</td>
<td>63.8</td>
<td>62.2</td>
</tr>
<tr>
<td>5.4</td>
<td>6.3</td>
<td>8.5</td>
<td>9.3</td>
</tr>
<tr>
<td>2.9</td>
<td>2.5</td>
<td>3.3</td>
<td>2.2</td>
</tr>
<tr>
<td>1.5</td>
<td>0.9</td>
<td>2.6</td>
<td>2.1</td>
</tr>
<tr>
<td>1.3</td>
<td>1.4</td>
<td>1.5</td>
<td>1.4</td>
</tr>
<tr>
<td>5.2</td>
<td>5.3</td>
<td>5.4</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Only patients entered into the open-label phase are shown. Data are calculated for the 6 weeks before each time point.

*Budesonide versus reference therapy. P values refer to the average percentages for years 4 and 5.

†Includes inhaled corticosteroids other than budesonide, as well as budesonide over the prescribed dose.

2 years would have a sustained effect on asthma control after discontinuation of treatment. In contrast to the START cohort, which had early onset but well-defined characteristics of asthma, the PEAK population was younger, 2 to 3 years of age, and two thirds had 1 or more visits to an emergency department for an asthma exacerbation. The 285 enrolled participants received either placebo or inhaled fluticasone, 88 μg twice daily, for 2 years. After 2 years of treatment, there was no change in the development of asthma symptoms in the following 12-month period. However, during the 2 years of active treatment, inhaled fluticasone reduced the need for systemic corticosteroids for an exacerbation, decreased montelukast use for greater than 2 months, and resulted in less supplemental use of fluticasone. Although the design, objective, and ages of treatment were distinct from the population in the START study, participants in the PEAK study had improved asthma control while taking corticosteroids and, in this sense, parallel the benefits associated with ICS use.

In conclusion, results from the START study support current guideline recommendations for the daily use of ICS therapy in adults and children with mild persistent asthma. The results from the START study also indicate that early intervention with ICSs improves overall treatment effectiveness and reduces the need for additional medication required to maintain asthma control. These findings thus support the recommendations of the recently released “US guidelines for the diagnosis and management of asthma” that ICS use in patients with recent-onset, mild persistent asthma will achieve control of features of current impairment and future risks.7

We thank Leslie Sell, PhD, for her assistance in the preparation of this manuscript.

**Clinical implications: Although early intervention with ICSs did not affect lung function, this approach can lead to improved asthma control and result in the need for less additional medication.**

REFERENCES


APPENDIX

START Safety Committee

A. Sheffer (Boston, Mass [Chairman]); A. Woolcock (Sydney, Australia); P. Díaz (Santiago, Chile); M. Silverman, (Leicester, United Kingdom); B. Lindmark (Lund, Sweden [nonvoting member]).

START investigators (and numbers of patients recruited) by country

Western and Central Europe

Austria (88)—Josef Eckmayr, Josef Riedler, Gert Wurzinger, Günter Ott, Jasminka Zarkovic, Andrea Schulheim, Manfred Götz, Herwig Schinko, Ingrid Thömiller.

Belgium (225)—Wilfried de Backer, Hugo van Bever, Geert Verleden, Christiane de Boeck, Joseph Aumann, Walter Vincen, Isidor Dab, Paul de Vuyyst, Marc de Jonghe, Georges Casimir, Guy Jooos, Frans de Baets, Yves Bogaerts, Jean-Luc Halloreve, Pierre Bartsch, Georges Casimir, Jacques Thiriaux.

Czech Republic (226)—Petr Pohnouek, Ondřej Rybníček, Olga Škopková, Ludmila Pavelková, Pavel Brož, Eva Ohnutková, Irenna Novotná, Jiří Baly, Irena Krčmová, Zuzana Kuralová, Tomáš Kocí, Helena Honomichlovká, Viktor Kasiáš, Petr Panzer, Vladimír Vondra, Jaroslava Německová, Ester Seberová, Tomáš Šykora, Vit Petruš, Jarmila Turzíková.

Denmark (97)—Torben Sörensen, Steen Neldam, Jürgen Peter Jensenius, Ulrik Bo Hansen, Thorkild Knudsen, Paul Jörgen Schultz, Dan Rost, Flemming Jensen.


France (121)—Philippe Godard, Patrick Rufin, Michel Anton, Jean-Pierre Aubert, Martine Grosclaude, Christian Brambilla, Patrick Archaud, Jean-Louis Racineux, Jean-Francois Muir, Paul Kourkoulis, Jérôme Bari, Alain Deybach, Christine de Boeck, Christine de Boeck, Alexandre de Vaux, Frédéric de Vaux, Yves de Vaux, Yves de Vaux, Yves de Vaux.


Hungary (226)—Marta Orosz, Agnes Devai, Gabor Uherczky, Katalin Rajkay, Ferenc Gönczi, Erzsébet Győri, Gergely Dobra, Katalin Puha, Zsuzsanna Sztańciski, Katalin Gomöri, Tamás Dolinay, Istvan Bittera, Szvetlana Palinkasi, Zsuzsanna Cseké, Marta Bisits.

Norway (128)—Ditlef Bjämer, Jan Ivar Holme, Arnulf Langhammer, Kristin Hunstad, Jens Harald Holmboe, Erling Grangård, Dag Asting Solberg, Thor Arne Grønnerød, May-Britt Salkowski, Knut Øymar, Knut Iversen.


Sweden (120)—Ulf L. Eriksson, Halina Wahlestedt, Mia Selsingberg, Ronny Larsson, Karin Rignér, Bernt Alm, Mikael Aронsson, Inger Winnerård, Mats Lagerwall, Ulla Martinsson, Lucy Berlin, Barbro Rydberg.

United Kingdom (39)—David Weston, M. E. Johnson, Colin Barrett.

Southern Europe


Italy (129)—Andrea Rossi, Antonio Foresti, Carlo Giuntini, Alberto Bisetti, Sergio Scoditti, Carmelindo Tranfo, Franco Zaccuelli, Marcello Giovanni, Attilio Boner, Maurizio Miraglia del Giudice, Leonardo M Fabbi, Giuseppe Giribio, Giovanni Barberio, Emanuele Cacciari.

Malta (12)—Stephen Montefort, Raymond Parascandalo.

Portugal (234)—Rui Pato, Maria de Lourdes Vieira, Celso Moreira, D Santos Vieira, Ulisses Brito, Fernando Drummond Borges, Ana Carvalho Marques, Maria Manuel Figueiredo, Felicidade Dias, Antonio Bugalho de Almeida, Jose Cesar-Ramos, Jose Maria Valente, Jose Dias Pereira, Carlos Nunes, Maria Felicia Riberio, Agostinho Marques, Mario Queirós Rebelo Carvalho, Marianela Vaz de Azevedo, Antonio Ramalho de Almeida, Jose Augusto Figueiredo Pinto, Maria De Fatima Mónica Matias, Abel Afonso, Jose Manuel Lopes Dos Santos.

Spain (291)—Carlos Villasante Fernandez, Isabel Cifuentes Agustín, Jose Maria Lobos Bejarano, Alejandro Abon Santos, Eva María, Corina Corina, Corina Corina, Corina Corina, Corina Corina, Corina Corina, Corina Corina, Corina Corina, Corina Corina, Corina Corina, Corina Corina, Corina Corina.
North America

Canada (114)—John H. S. Li, Daniel Landry, Dennis O’Keefe, Bhanu F. Muram, Howard S. Conter, Douglas Tweel, Sharon D. Peters.


Other countries

Argentina (235)—Alberto Dolmann, Ricardo Gene, Juan Carlos Figueroa Casas, Carlos Piovano, Edgardo Segal, Ana Maria Balanzat, Jorge Taborda, Angel Truganti, Alejandro Teper.

Australia (85)—Jason Garrood, Marjorie J. E. Patel, Chris Hogan, Grant Russel.

China (389)—Yuan Jue Zhu, Ling Cao, Shi-Ying Liu, Jing-Zhi Miao, Dong-Jie Ding, Wan-zhen Yao, You-Ning Liu, Ping Chen, Shu-Qing Kong, Lee Pang, Bin Sun, Zhong Min Li, Guo-Shun Li, Pei Li Chen, Qin Zhu, Ting-Xi Zhang, Xing-Hai Wang, Songhua Wei, Wei-Wu Deng, Xin Zhou, Yan Yan Ji, Wen-Tong Luo, Qiang Li, Hui-Ru Zhu, Jin-Yun Sheng, Jia-Yong Ma, De-Ping Zhang, Chun-Zhen Ji, Xi-Rong Xia, Zu Yi Zhang, Kai-Sheng Yin, Jiong Yang, Yuan Gui Li, Pei-Wen Tang, Fu-Guang Liu, He-Ping Wang, Nan-Shan Zhong, Zhong-Sheng Rong, Ying-Chun Tang, Cai-Yuan Lin, Jiu-Shan Liu, Han-Zhang Liu, Ding-Min Cai, Jia-Cheng Yang, Qiong-Feng Ma.

Indonesia (196)—Hadiarto Mangunnegoro, Caecilia Arimah Wijono, Nancy Hutabarot Tobing, Nastiti N. Rahajoe, Sugito, Eddy Surjanto, Barmawi Hisyam, Hood Alsagaff, Gunadi Santosa.

Korea (88)—You-Young Kim, Choon-Sik Park, Mi-Kyeong Kim, Young-Joo Cho, Dong-Chull Choi, Young-Koo Lee.

Malaysia (109)—Jai Mohan, S. Yogeswery, Swee Lan Wong, Geok Lan Kuan, Chong Tuan Koh, Ban Seng Quah, Jessica de Bruyne, C. K. Lian.

Mexico (310)—Mayra Mejia Avila, Francisco Cuevas, Nicolas Chavaje, Luz Audina Mendoza Topete, Isaia Badillo, Miguel Ponce, Javier Chan Merida, Yolanda Gonzalez Espinosa, Jose Mario Ledezma, Jose Arturo Galindo Garcia, Guadalupe Gonzalez, Luis Mendez Martínez, Jesus Enrique Reyes Ramos, Jorge Rodriguez Dorantes, Carlos Cansecos Gonzalez, Javier Gomez Vera, Ricardo Guido Bayardo, Alvaro Pedroza Melendez, Carlos Baez Loyola, Miguel Angel Cruz Suarez.


Singapore (76)—Lee Bee Wah, Yoon Kam Hon, Ong Yong Yau, Chay Oh Moh, Wang Yee Tang.


Taiwan (78)—Sow-Hsong Kuo, Han-Pin Kuo, Jui-Long Wang, Tzuwen-Hsiue, Jia-Horng Wang, Chi-Der Ching.