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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

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Inhaled corticosteroids are known to be effective in persistent asthma, but their long-term effect in mild persistent disease of recent onset, which is particularly relevant in children, requires clarification. The objective of this study was to determine the long-term efficacy of regular inhaled low-dose budesonide in children aged < 11 yrs with mild persistent asthma with onset within 2 yrs of enrollment. Children aged 5–10 yrs formed part of the population of the inhaled Steroid Treatment As Regular Therapy in early asthma (START) study, and they were randomized in a double-blind manner to treatment with once daily budesonide 200 µg or placebo via Turbuhaler™ in addition to usual clinical care and other asthma medication. The double-blind treatment phase continued for 3 yrs. Of the 1974 children, 1000 in the budesonide group and 974 in the placebo group, were analyzed for efficacy. Addition of once-daily budesonide to usual care was associated with a significant increase in the time to first severe asthma-related event (SARE) and significantly reduced risk of SARE over 3 yrs. The hazard ratio relative to usual care (placebo) was 0.60 (95% confidence interval: 0.40–0.90; $p = 0.012$), with a relative risk reduction of 40%. Children receiving budesonide also needed significantly less intervention with other inhaled corticosteroids (12.3% vs. 22.5% over 3 yrs; $p < 0.01$), with trends towards decreased usage of oral/systemic corticosteroids and inhaled short-acting β_2 -agonists. Budesonide treatment also had a significant beneficial effect on lung function relative to placebo. In conclusion, early intervention adding once-daily budesonide to usual care in children with mild, persistent asthma of recent onset reduces the long-term risk and frequency of SAREs and improves lung function compared with usual care alone.

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Bronchospasm due to smooth muscle contraction was considered in the past to be the major contributor to airway obstruction in patients with asthma, but inflammation is now known to play a critical role (1). Increased microvascular permeability and leakage caused by inflammatory mediators cause airway edema, mucosal

thickening and swelling of the airway, and mucus secretion may eventually lead to chronic mucus plug formation. Remodeling of the airways also appears to take place in mild asthma (2–4).

Inhaled corticosteroids have been shown in controlled clinical studies to decrease pulmonary inflammation, to improve lung function and

alleviate symptoms, and to reduce mortality (5–11), and are now the treatment of choice in patients with chronic persistent asthma (2, 3). Early intervention with inhaled corticosteroids (within 2 yrs of disease onset) has also been shown to confer additional clinical benefit (12, 13), and there is evidence that such intervention may attenuate asthma progression and improves the response to treatment (6, 12–14). These observations have recently received strong support from the findings of 3-yr results from the START (inhaled Steroid Treatment As Regular Therapy in early asthma) study, in which long-term, low dosage, once-daily treatment with inhaled budesonide added to usual care was shown to decrease the risk of severe exacerbation and to improve asthma control relative to placebo in patients with mild persistent disease of recent onset (15).

Early intervention is likely to have particular relevance in younger patients, and long-term data obtained in patients aged 5–12 yrs at enrollment have indicated that inhaled corticosteroid therapy does indeed improve health outcomes in mild to moderate persistent asthma (10). Furthermore, the importance of active treatment of mild disease is underlined by Australian data showing that 33% of 51 asthma-related deaths over a 3-yr period were in patients who had a history of mild or trivial disease (16). The START study divided the study population into three subgroups on the basis of age as follows: children aged 5–10 yrs, adolescents aged 11–17 yrs, and adults aged up to 66 yrs (15). The present article reports findings of the first 3 yrs of START in the youngest age group.

Patients and methods

The START trial consisted of an initial 3-yr double-blind, randomized, placebo-controlled phase, and a subsequent 2-yr open-label extension. This report focuses on the subgroup of children aged 5–10 yrs who were enrolled and who received budesonide at a dosage of 200 μ g once daily. Full details of the 3-yr efficacy data from START have already been published (15), and the following section gives an overview of the methods and procedures used that relate to children.

The START recruited patients who were aged 5–66 yrs from 499 sites in 32 countries and showed symptoms of mild asthma during the 3 months preceding trial entry. Most of the children involved were recruited from centers in the US, and all were confirmed as having reversible airways obstruction as shown by an

increase in forced expiratory volume in 1 s (FEV_1) of $>12\%$ after use of a short-acting bronchodilator, a reduction in FEV_1 of $>15\%$ on exercise testing, or a difference of more than 15% between the two highest and the two lowest expiratory flow rate readings taken across a period of 14 days. Children were excluded if they had shown asthma symptoms or had received treatment for more than 2 yrs before study entry, had been treated with a corticosteroid for more than 30 days, or had received more than one corticosteroid depot injection over the course of 1 yr. Children were also not allowed to participate if a delay in corticosteroid treatment was deemed inappropriate, if they had respective pre- and post-bronchodilator FEV_1 readings of $<60\%$ and 80% of predicted, or if any other clinically significant disease was present. Written and informed consent was required from parents and caregivers before enrollment.

After recording of baseline characteristics, children were randomized to once-daily budesonide 200 μ g or lactose-based placebo delivered via TurbuhalerTM and added to usual clinical care and other asthma medication. Follow-up visits took place 6 and 12 wks after randomization, and then every 3 months for the 3-yr double-blind period.

The primary end-point was the time to the first severe asthma-related event (SARE), which was defined as an event requiring an unscheduled admission to hospital or emergency treatment, or which resulted in death due to asthma. Emergency treatment consisted of acute treatment of airway obstruction with systemic corticosteroids and nebulized or parenteral bronchodilators given under inpatient conditions. Time to introduction of inhaled or oral corticosteroid treatment other than the study medication was also specified as an end-point.

The children and their caregivers recorded asthma-related events and their asthma control details between clinic visits in notebooks, with subsequent assessment and grading by investigators. The participants were also asked at each visit about medication usage, presence of asthma symptoms, and the number of days during the preceding 2 wks on which activities of daily living had been restricted as a result of asthma.

Spirometry was performed at each visit, with post-bronchodilator FEV_1 being measured 30 min after the inhalation of terbutaline 0.5 mg via TurbuhalerTM. Pre-bronchodilator FEV_1 was assessed at randomization and annually thereafter, and height as measured to the nearest centimeter at each visit was used to

express FEV_1 as a proportion of the predicted value.

Adverse reactions and tolerability were assessed on the basis of the children's and caregivers' spontaneous reports and answers to predefined questioning. These are dealt with in greater detail elsewhere (17).

Statistical analyses

Time to first SARE was analyzed by proportional hazards regression. To eliminate confounding effects, FEV_1 values were presented as percentages of predicted normal values; together with the proportion of symptom-free days (SFDs), these were analyzed by the mixed-model method (18) with the underlying assumption of a compound symmetry covariance structure of repeated measurements. Binomial outcomes were compared with chi-square tests. All p-values were two-sided, with no correction for multiple comparisons. Calculations were performed with SAS (version 8.1, SAS Institute Inc., Cary, NC, USA) and StatXact (version 4, Cytel Software Corp., Cambridge, MA, USA) software.

Results

Patient characteristics

A total of 1004 children 5–10 yrs of age were randomized to treatment with budesonide, of whom four were excluded from analysis for administrative reasons. In the usual care (placebo) group, there were 977 children of whom 974 underwent study assessment. Thus, 1974 children were analyzed for efficacy. Mean times on study were 2.63 yrs for budesonide and 2.60 yrs for usual care.

The age distribution of the participating children is illustrated in Fig. 1, from which it can be

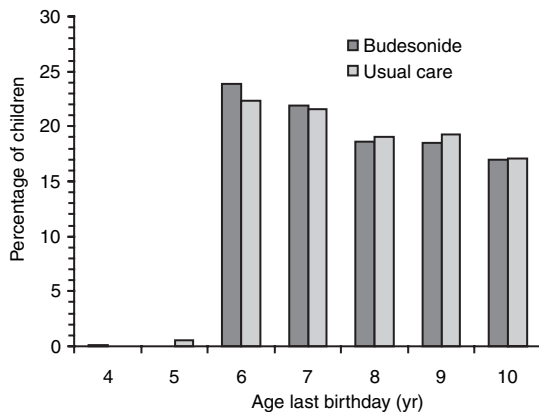


Fig. 1. Age distribution of children participating in START.

seen that the large majority were aged 6 yrs and over. The mean age was approximately 8 yrs. As shown in Table 1, demographic characteristics in each treatment arm were similar, with around two-thirds of children in each group being of Caucasian descent, and approximately 60% male. Duration of asthma before randomization was <12 months in approximately 60% of participants in both groups. During the 2 wks preceding study entry, children had shown symptoms of asthma on 4.9 and 4.6 days on average in the budesonide and usual care arms, respectively. Discontinuation rates in the budesonide and usual care groups were 18.5% and 19.2%, respectively (Table 2).

Table 1. Baseline characteristics of children aged 5–10 yrs at study entry

Characteristic	Treatment	
	Budesonide added to usual care group (n = 1000)	Usual care group (n = 974)
Mean age (yrs) $\pm$ s.d.	8.3 $\pm$ 1.5	8.4 $\pm$ 1.4
Gender (% male)	60.6	59.3
Ethnicity (% of children):		
Caucasian	60.8	60.1
Black	1.6	1.8
Oriental	31.4	31.4
Other	6.2	6.7
Mean duration of asthma before randomization (yrs) $\pm$ s.d.	0.8 $\pm$ 0.7	0.8 $\pm$ 0.6
Duration of asthma before randomization by age (no. of patients)		
<3 months	289	287
3 to <6 months	145	132
6 to <12 months	149	153
12 months or more	417	402
Mean proportion of symptom-free days (%) over the 2 wks preceding visit 1	64.8	67.1
Passive smoker (%)	38.0	43.1
Mean FEV_1 (% predicted) $\pm$ s.d.		
Pre-bronchodilator	85.0 $\pm$ 13.4	85.5 $\pm$ 12.9
Post-bronchodilator	95.8 $\pm$ 14.4	95.9 $\pm$ 13.3

FEV_1 , forced expiratory volume in 1 s; s.d., standard deviation.

Table 2. Discontinuations among children aged 5–10 yrs in START

Reason	Treatment	
	Budesonide added to usual care group (n = 1000)	Usual care group (n = 974)
Adverse event	5	6
Worsened asthma	1	1
Lost to follow-up	18	22
Other	161	158
Total	185	187

Effect of treatment on SARE

Inhaled corticosteroid therapy with budesonide was associated with a statistically significant increase in the time to first SARE and significantly reduced the risk of SARE over the 3 yrs. In the budesonide group there were 52 SAREs in 40 children, which led to 18 emergency department admissions and 34 hospitalizations. Usual care (placebo) was associated with 82 SAREs in 63 children, 29 emergency department admissions and 53 hospitalizations. Children on budesonide accrued a total of 175 hospital days, which was compared with 200 hospital days in the usual care group. The risk of a first SARE was significantly reduced for budesonide, relative to usual care, by 40% (hazard ratio 0.60, 95% confidence interval 0.40–0.90; $p = 0.012$). Children receiving budesonide also had significantly more symptom-free days and less absenteeism from school than did those on placebo; this is discussed in more detail elsewhere (19).

Effect of treatment on use of other medication

In addition to study medication, the children in the budesonide group needed significantly less intervention with other inhaled corticosteroids ($p < 0.001$): across the 3-yr time frame, additional inhaled corticosteroids were needed by 22.7% of patients receiving usual care compared with 12.3% of patients allocated to budesonide. Furthermore, the consumption of oral or systemic corticosteroids and inhaled short-acting β_2 -agonists were lower in the budesonide group compared with children receiving usual care

(Table 3; Fig. 2). Oral or systemic corticosteroids were prescribed for 3.1% of patients receiving usual care and 1.7% of budesonide recipients, and short-acting β_2 -agonists by 68.1% and 63.6%, respectively (Fig. 2).

Effect of treatment on lung function

Pre- and post-bronchodilator FEV₁ values improved considerably in children receiving budesonide compared with those receiving usual care (Fig. 3). Post-bronchodilator FEV₁ fell in both groups over 1 yr and 3 yrs, but to a greater

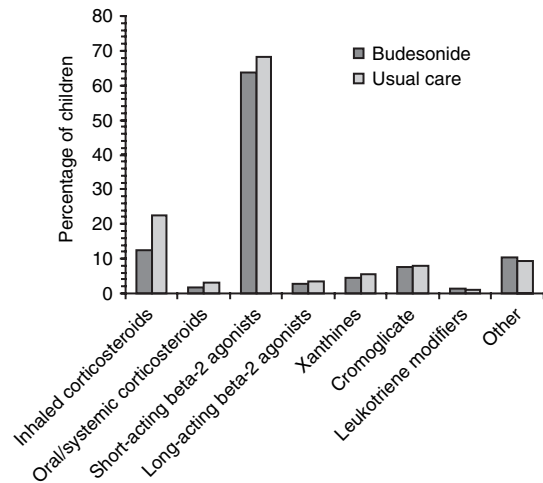


Fig. 2. Concomitant medication consumption by children in START. Percentages of patients receiving medications as listed and expressed as mean values across 6-wk intervals preceding 12, 24 and 36 months of the double-blind study period.

Table 3. Percentages of children receiving additional anti-asthma medication during START. Data were calculated for the 6 wks preceding each time-point

Additional treatment	Group	Time from randomization (months)					p-value (average for months 12, 24 and 36: BUD vs. UC)
		0	3	12	24	36	
Inhaled corticosteroids	UC	6.2	11.7	19.5	23.8	24.8	<0.01
	BUD	4.3	6.5	10.2	13.2	13.6	
Oral/systemic corticosteroids	UC	5.0	4.2	3.6	3.3	2.5	0.08
	BUD	5.2	2.8	2.1	1.9	1.1	
Short-acting β_2 -agonists	UC	64.0	70.6	70.7	67.8	65.9	0.06
	BUD	62.4	65.7	65.8	64.0	60.9	
Long-acting β_2 -agonist	UC	1.3	1.5	2.1	3.5	4.6	0.39
	BUD	1.1	1.3	1.8	2.4	3.7	
Xanthines	UC	10.5	9.3	7.2	5.2	4.6	0.27
	BUD	9.2	7.5	5.9	4.6	2.9	
Cromoglycate	UC	12.3	11.9	9.3	8.0	6.5	0.93
	BUD	13.3	13.0	9.6	7.4	6.2	
Leukotriene modifiers	UC	0.2	0.2	0.6	1.1	1.8	1.00
	BUD	0.1	0.1	0.1	1.7	2.2	
Other	UC	14.4	14.6	11.2	9.1	8.0	0.51
	BUD	15.7	13.9	13.0	10.6	7.6	

BUD, budesonide; UC, usual care (placebo).

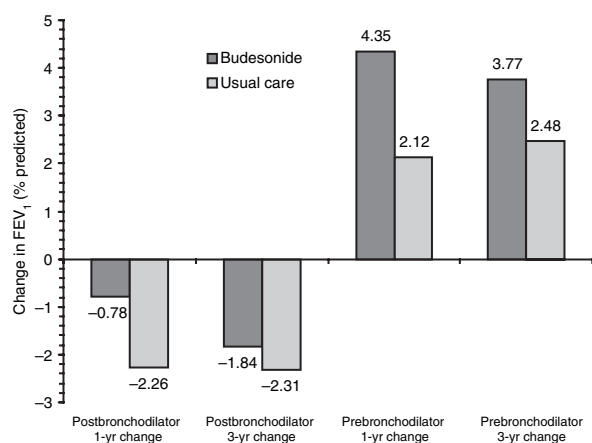


Fig. 3. One- and 3-yr changes in forced expiratory volume in 1 s (FEV_1) after and before administration of a short-acting bronchodilator (terbutaline).

extent with usual care than with budesonide. However, the difference between treatments for the change in FEV_1 expressed as percentage of predicted after 3 yrs was somewhat less in children aged 5–10 yrs [0.47% with standard error (s.e.) 0.46] than in the overall population (0.88%; s.e. 0.25), and adults in particular (1.54%; s.e. 0.34). It should be noted here that age was found to be a significant factor influencing post-bronchodilator response in the overall START population (15). The relative improvement in percent predicted FEV_1 with budesonide was maintained consistently throughout the 3-yr study period (Fig. 4). Correspondingly, pre-bronchodilator FEV_1 values were increased to a greater extent with budesonide than with usual care: the treatment effect in children at 3 yrs (difference 1.29%; s.e. 0.58) was smaller than that

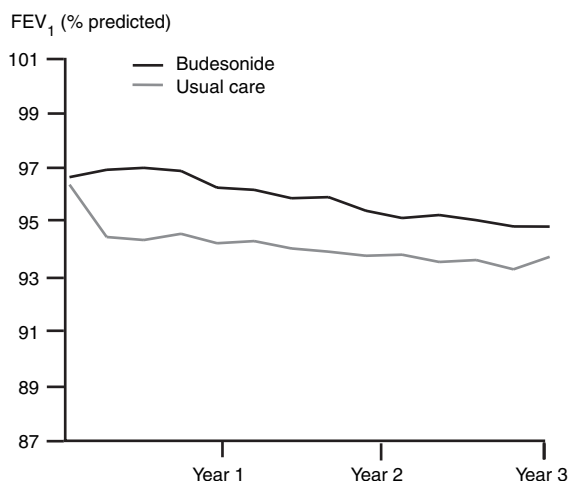


Fig. 4. Post-bronchodilator forced expiratory volume in 1 s (FEV_1) over 3 yrs of START in children aged < 11 yrs.

in adults (2.31%; s.e. 0.44), but greater than that seen in adolescents aged 11–17 yrs (0.43%; s.e. 0.76).

Discussion

This study is the first study which assesses the benefits of early intervention with inhaled corticosteroids in children aged 6–11 yrs. It was found that once-daily treatment with low-dose budesonide reduced the risk of severe exacerbation of asthma by 40%, increased lung functions, number of symptom free days and reduced the need for extra medication and the number of school days lost (19). These effects were seen even if that a large proportion of the patients randomized to placebo received their regular asthma medication with other drugs – including inhaled corticosteroids – and would therefore have been expected to maintain a reasonable degree of asthma control at the very least. The reduction in risk of a severe exacerbation was of the same order as the 44% overall risk reduction seen across all age groups in START even if the remaining patients in the START study received a higher daily budesonide dose (400 μ g). The beneficial effects of budesonide 200 μ g/day via Turbuhaler® on frequency of severe exacerbations of asthma are in agreement with other studies in children. Compared with nedocromil treatment, budesonide reduced the annual exacerbation rate from 2.6 to 1.2 ($p = 0.025$) in 91 children with mild disease (20). Similarly, the Helsinki Early Intervention Childhood Asthma Study (HEICA) in children with newly diagnosed asthma showed respective mean per-patient exacerbation rates of 1.23 and 1.96 in children receiving budesonide induction followed by maintenance therapy and budesonide induction followed by placebo, respectively (21). These were significantly lower than the rate of 2.7 exacerbations per patient reported in children treated with disodium cromoglycate. Finally, Agertoft and Pedersen (12) reported a reduction in the annual rate of hospitalization for acute severe asthma attacks from 0.03 per child in the control group, who did not receive inhaled corticosteroids, to 0.004 per child in children treated with budesonide ($p < 0.001$).

The resource implications of the reductions in the need for additional corticosteroid and other therapies for asthma by early, regular treatment with budesonide are discussed elsewhere in this supplement (19).

The use of systemic and oral corticosteroids (in terms of proportions of children requiring such treatment) was reduced on average by a clinically

relevant 45% over the 3-yr period in children receiving budesonide early. Even if this reduction failed to reach statistical significance it may still be clinically important since even a few courses of systemic steroids may increase the risk of fracture whereas long-term treatment with low doses of inhaled corticosteroids have no adverse effects on bone mineral density or risk of fracture in children (22). Therefore, this finding also lends support to early use of inhaled corticosteroids in children with persistent asthma of recent onset.

The FEV₁ profiles over time were generally similar to those seen across patients of all ages (15). The decrease in difference between the two groups that became evident as the study progressed was expected and likely to be related to the addition of further steroid and bronchodilator therapy to medication regimens in children randomized to placebo. In general the findings in the children were also in agreement with the findings of the Childhood Asthma Management Program (CAMP) Research Group (10). Like START, the CAMP study found that budesonide was superior in most outcomes of asthma control and pre-bronchodilator FEV₁ compared with placebo. However in CAMP, budesonide was not superior to placebo in terms of lung function expressed as post-bronchodilator FEV₁. Moreover, the CAMP study only found a small, non-significant decline of 1% in post-bronchodilator FEV₁ percent predicted and a 1.7% decline in post-bronchodilator FEV₁/FVC ratios over 4 yrs (10). The discrepancy between the findings in CAMP and the findings in START with respect to the post-bronchodilator lung function results are not clear. Some differences may be important:

- 1 Because of the lack of a significant decline in post-bronchodilator FEV₁ per cent predicted in the placebo group in CAMP it was not possible to make firm conclusions on the effects of budesonide on decline in that parameter. The only parameter (FEV₁/FVC ratio) that declined to some extent with time in CAMP was also the one that came closest to a treatment effect ($p = 0.08$).
- 2 All patients in START had a very short duration of asthma at study entry. This was not the case for the patients in CAMP (mean duration of asthma at study entry was 5 yrs). This difference may be important if the decline in lung function is more pronounced early in the disease as suggested by some studies, because it then underlines the potential value of early intervention in mild asthma to prevent loss of lung function as disease progresses.

- 3 The mean age at study entry of the patients in the CAMP study was 9.5 yrs and 14 yrs at the end of the study. So age-wise the CAMP patients resembled the 11–17 yr olds in the START study in whom no significant decline in post-bronchodilator FEV₁ was seen (15). It is not known why the findings in adolescents should be different from other age groups. However, during puberty the relationship between height and lung functions is more complex than in other periods of life and assessment of FEV₁ percent predicted may not be as suitable a measure as in other ages.
- 4 As assessed by pre-treatment lung function, there may also have been some differences in asthma severity between the two studies.

In contrast to CAMP, other randomized prospective studies have reported significant declines in both pre- and post-bronchodilator lung function in patients with mild and moderate asthma (6, 13). In both these studies the decline was modified by budesonide treatment.

In conclusion, the present report shows that adding once-daily low-dose budesonide via TurbuhalerTM to usual care early after the diagnosis of mild persistent is effective over the long-term in the prevention of loss of pulmonary function, extending the time to first SARE, reducing frequency of SAREs, and reducing the rates of usage of other asthma medication in children aged <11 yrs.

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