

Safety and tolerability of inhaled budesonide in children in the Steroid Treatment As Regular Therapy in early asthma (START) trial

Silverman M, Sheffer AL, Díaz PV, Lindberg B. Safety and tolerability of inhaled budesonide in children in the Steroid Treatment As Regular Therapy in early asthma (START) trial.

Pediatr Allergy Immunol 2006; 17 (Suppl. 17): 14–20. © 2006 The Authors. Journal compilation © 2006 Blackwell Munksgaard

The safety and tolerability of asthma medications are still a concern to many asthma patients receiving long-term treatment. Therefore, more safety data from long-term, controlled trials are needed. The aim of this study was to evaluate the safety and tolerability of long-term treatment with once-daily budesonide in children aged 5–10 yrs with mild persistent asthma of recent onset in the inhaled Steroid Treatment As Regular Therapy in early asthma (START) study. Children aged 5–10 yrs with early asthma were randomized to double-blind treatment with budesonide 200 µg or placebo once daily via Turbuhaler™ in addition to usual asthma therapy, for 3 yrs. Adverse events were recorded from both spontaneous reports and responses to standard questions, and asthma-related events and asthma control were recorded between visits and subsequently graded by the blinded investigators. Of the study population of 1981 children (1004 budesonide and 977 usual care), 81% (812 of 1004) in the budesonide group and 82% (797 of 977) in the usual care group experienced a total of 6414 events listed by preferred term (3209 budesonide plus usual care and 3205 placebo plus usual care). The most commonly reported events included respiratory infection, pharyngitis, rhinitis, viral infection and bronchitis, and there were no clinically relevant differences in incidence between treatments. There were no reports of tuberculosis or aspergillosis, and no evidence of increased risk of systemic or ocular adverse events with budesonide relative to placebo. There were 106 serious adverse events in the budesonide group and 128 with usual care. The most frequent, aggravated asthma, was more common with usual care than with budesonide. There were no deaths among children participating in START. In conclusion, the addition of once-daily inhaled budesonide 200 µg via Turbuhaler™ to usual care is safe and well tolerated in children with recent-onset mild persistent asthma.

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Key words: budesonide; pediatric; safety; START; early intervention; asthma

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Chronic inflammation of the airways is now known to be the pathologic mechanism underlying the altered airway physiology and the symptoms seen in people with asthma (1). Airway inflammation develops early in the course of

clinical disease – even when symptoms have been present for <1 yr (2). Inhaled corticosteroid therapy is the key component of treatment regimens for individuals with persistent disease (3, 4). Benefits of early use of inhaled

corticosteroid therapy, ideally within 2 yrs of the onset of symptoms, has been suggested in both children and adults (5–7).

Inhaled corticosteroids are beneficial in mild to moderate persistent asthma (4), and the benefit of such therapy specifically in recent-onset mild persistent disease has recently been confirmed in the inhaled Steroid Treatment As Regular Therapy in early asthma (START) trial, in which over 7000 adults and children were randomized to regular daily therapy with budesonide or placebo delivered via TurbuhalerTM (8, 9). Evidence from clinical studies also suggests that the use of inhaled corticosteroids at recommended dosages over prolonged periods is not associated with long-term clinically relevant adverse effects (10, 11). Overall findings from the 3-yr double-blind (8, 12) and 2-yr open-label extension periods (13) of START concur with this observation.

Systemic exposure to inhaled corticosteroids is very low compared with oral treatment, and the adverse effects of chief concern are local reactions such as throat irritation, oral candidiasis and hoarseness. Allergic reactions, superficial bruising (4, 14, 15) and psychiatric/psychologic disturbances (16–18) have also been reported, although the last-mentioned has been called into question as it appears to be linked with poor adherence and control rather than with the medication itself (19).

The START study is of particular value in clarifying the adverse events associated with long-term low-dosage inhaled corticosteroid therapy in asthma because it is the largest controlled clinical trial performed to date in patients with mild persistent disease. The study design mimics a 'real-world' treatment environment in which study medication was added to existing asthma therapy. In addition, the treatment was given early in the disease and the study used the TurbuhalerTM dry powder inhaler, which compared with the pressurized metered-dose inhaler, has low oropharyngeal deposition (20) and high lung deposition in children (21). The present paper describes the safety and tolerability of low-dose inhaled budesonide, from the 3-yr double-blind treatment period in children aged 5–10 yrs.

Patients and methods

Full details of START have been published elsewhere (8), and safety and tolerability data for the overall study population (all ages: 5–66 yrs) have also been described recently (12). Briefly, the children who are the focus of the present report had mild persistent asthma with a

duration of < 2 yrs at study entry; they presented with wheeze, cough, dyspnea or chest tightening at least once weekly (but not as frequently as daily) and with reversible airways obstruction [see also Chen et al. (9)]. Follow-up visits took place 6 and 12 wks after randomization and at 3-month intervals thereafter. Key exclusion criteria were symptomatic disease or need for regular asthma treatment for more than 2 yrs preceding study entry; treatment for more than 30 days with systemic corticosteroids or more than one depot corticosteroid injection per year; respective pre- and post-bronchodilator values for forced expiratory volume in 1 s (FEV₁) of below 60% and 80% of those predicted; hypersensitivity to budesonide; lactose intolerance; and potential compliance/adherence difficulties. Children were also not randomized if any delay in commencing inhaled corticosteroid therapy was deemed advisable by the treating physician.

Children were randomized to either budesonide 200 µg or to placebo given once daily by inhalation via TurbuhalerTM in addition to their usual asthma medications. The START study protocol was approved by local institutional review boards and ethics committees at all 499 participating centers world-wide, and the study was conducted according to the principles set out in the Declaration of Helsinki. Written and informed consent for all children was provided by parents or guardians before treatment started.

Safety end-points

All adverse and asthma-related events from spontaneous reports from patients and caregivers, together with responses to standard questions, were recorded at all follow-up visits over the 3-yr double-blind study period. The children and their caregivers were asked, 'Have you (i.e. the child) had any health problems or symptoms not usually associated with your asthma since your last visit?' for adverse events, and, 'Have you had any healthcare and/or pharmacy contact due to asthma worsening since your previous visit?' for asthma-related events. Serious asthma-related events were handled in the same way as serious adverse events and were recorded accordingly, and the causal relationship between each event and the study treatment was assessed by the investigator. All events were also monitored by an independent safety committee, which reviewed frequencies of fatal events, serious adverse events and discontinuations due to adverse events or to asthma on a month-by-month basis. The safety committee met twice each year.

Adverse events were coded according to the Astra Adverse Event Directory, a document based on World Health Organization (WHO) adverse reaction terminology. For the purposes of this report, each event is listed by its preferred term and counted once for each child who experienced that event on at least one occasion. Thus, multiple occurrences of the same adverse event in the same patient are not shown. Results were arranged according to the numbers of patients reporting each event and to the frequency of each event (i.e. the percentage of patients reporting each event), with reference in both cases to preferred terms. Adverse events were also recorded by system organ class (SOC), with each child who experienced at least one event in an SOC being counted and results presented according to frequency.

Asthma-related events not considered serious by the safety committee were not recorded as adverse events but were included in the efficacy evaluation, which was in turn overseen by another independent committee. Events that were classified in this way but that nevertheless led to discontinuation of study treatment were recorded separately on study termination forms, and the information was subsequently released to the safety committee on a monthly basis.

Statistical methods

The full START study (overall population) was designed to detect a 35% reduction in risk of having a severe asthma-related event with 95% power and two-sided type I error of 0.05. Drop-out rates of 30%, 10% and 5% were assumed for years 1, 2 and 3, respectively. Children aged from 5 to 10 years comprised a proportion of the study population, so these power calculations must be viewed in that light. Furthermore, descriptive statistics only have been applied to the safety and tolerability data for the children.

Results

Patients

All 1981 children aged under 11 yrs who were randomized to treatment [1004 to budesonide and 977 to usual care (placebo)] received at least one dose of study medication and were therefore eligible for the safety analysis. Baseline age and gender distributions were similar between groups (Table 1). Note that one patient randomized to budesonide was 4 yrs old at the time of recruitment, but was nevertheless included in safety and tolerability assessments. There were also no apparent differences between groups in terms of

Table 1. Baseline age and gender characteristics for the safety population of children aged under 11 yrs at study entry in START

Characteristic	Treatment	
	Budesonide added to usual care group (n = 1004)	Usual care group (n = 977)
Age distribution:		
4 yrs	1	0
5 yrs	0	6
6 yrs	241	218
7 yrs	220	210
8 yrs	186	187
9 yrs	185	188
10 yrs	171	168
Gender:		
Male	609	578
Female	395	399

treatment discontinuations as applied to the pediatric safety population, with five and six patients withdrawing from the budesonide and usual care groups, respectively, because of adverse events. One child in each group discontinued study treatment because of worsening asthma. As shown in Table 2, although 11 patients withdrew, 12 adverse events as listed by SOC were responsible for discontinuation. This is because one child in the placebo group experienced two events: intracranial hemorrhage (SOC: extracardiac vascular disorders) and cerebral edema (SOC: central and peripheral nervous system disorders).

Adverse events

Overall, 81% (812 of 1004) of children in the budesonide group and 82% (797 of 977) in the usual care group reported a total of 6414 adverse

Table 2. Discontinuations among children aged <11 yrs because of adverse events as listed by system organ class (SOC) groupings

SOC name	Treatment	
	Budesonide added to usual care group (n = 1004)	Usual care group (n = 977)
Respiratory system disorders	2	1
Psychiatric disorders	1	2
Central and peripheral nervous system disorders	1	1
Resistance mechanism disorders ^a	1	0
Vascular (extracardiac) disorders	0	1
Gastrointestinal system disorders	0	1
Collagen disorders	0	1
Totals	5	7

^aResistance mechanism disorders comprises viral, bacterial and fungal infections.

events by preferred term (3209 budesonide and 3205 usual care) and 4134 by SOC (2104 budesonide and 2030 usual care). Thus, adverse events were experienced by just over 80% of patients in each group, with no relevant difference in frequency between budesonide and placebo. Grouping of events of special interest relating to corticosteroid therapy by SOC category showed similar rates of reporting of such events in both study arms (Fig. 1).

Infections

Infection constitutes an adverse event category of particular interest in patients receiving treatment with corticosteroids; accordingly, the most commonly reported adverse events in START among children by preferred term were respiratory infection, pharyngitis, rhinitis, viral infection and bronchitis (Table 3). Fever, otitis media, and sinusitis were also reported by more than 8% of patients in both groups.

The reported frequency of cases of pneumonia (5.8% vs. 3.8%), sinusitis (10.1% vs. 8.7%) and bronchitis (18.7% vs. 16.3%) were all higher in the usual care group compared with the budesonide group (Table 3). There were five cases of fungal infection (four with budesonide and one with usual care), and one vaginal infection (usual care group). No cases of tuberculosis or aspergillosis were reported in children, and frequencies of varicella infection were very similar between groups (4.6% with budesonide and 4.1% with usual care).

Local adverse events

Local adverse events were reported by similar proportions of children randomized to

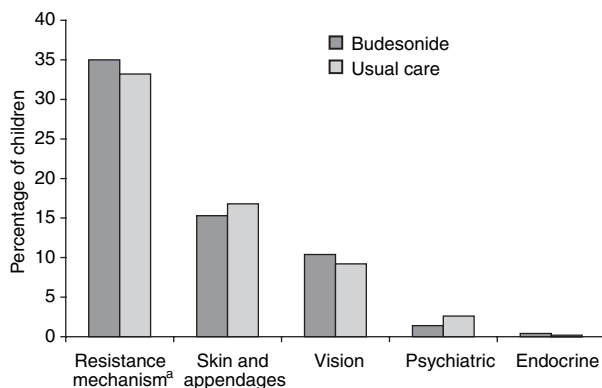


Fig. 1. Adverse events of particular interest reported by children in START, grouped according to system organ class, by treatment. ^aResistance mechanism disorders comprises viral, bacterial and fungal infections.

Table 3. Most commonly reported adverse events (>5% incidence in either group) reported among children less than 11 yrs old in START

Adverse event (preferred term)	Treatment	
	Budesonide added to usual care group (n = 1004)	Usual care group (n = 977)
Respiratory infection	440 (43.8)	428 (43.8)
Pharyngitis	290 (28.9)	304 (31.1)
Rhinitis	285 (28.4)	267 (27.3)
Infection viral	201 (20.0)	184 (18.8)
Bronchitis	164 (16.3)	183 (18.7)
Fever	117 (11.7)	100 (10.2)
Otitis media	112 (11.2)	96 (9.8)
Sinusitis	87 (8.7)	99 (10.1)
Cough	88 (8.8)	81 (8.3)
Conjunctivitis	88 (8.8)	79 (8.1)
Headache	86 (8.6)	72 (7.4)
Accident and/or injury	75 (7.5)	79 (8.1)
Gastroenteritis	81 (8.1)	68 (7.0)
Asthma aggravated	50 (5.0)	73 (7.6)
Pneumonia	38 (3.8)	57 (5.8)

Values given in parentheses are percentages.

budesonide or to usual care (Fig. 2). The most common symptom was coughing, which was reported by 8.8% of budesonide and 8.3% of usual care recipients (Table 3 and Fig. 2). Moniliasis was uncommon, occurring in 0.5% of budesonide and 0.3% of usual care recipients, as was dysphonia (budesonide: 0.5%; usual care: 0.2%). None of the children complained of dryness of the mouth.

Dermatological and allergic events

Skin disorders and allergic reactions were reported by similar proportions of children in both

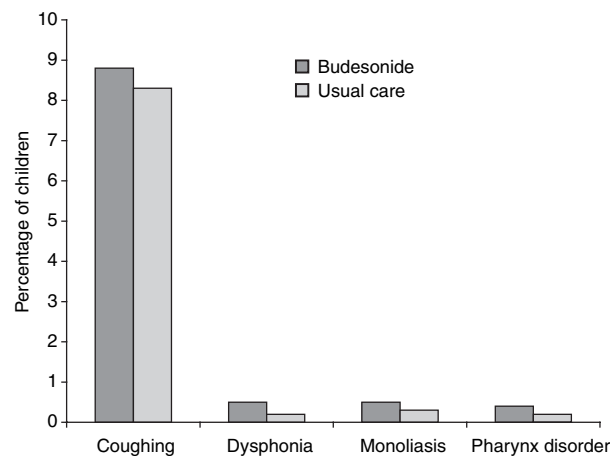


Fig. 2. Local adverse events reported by children in START, by treatment group.

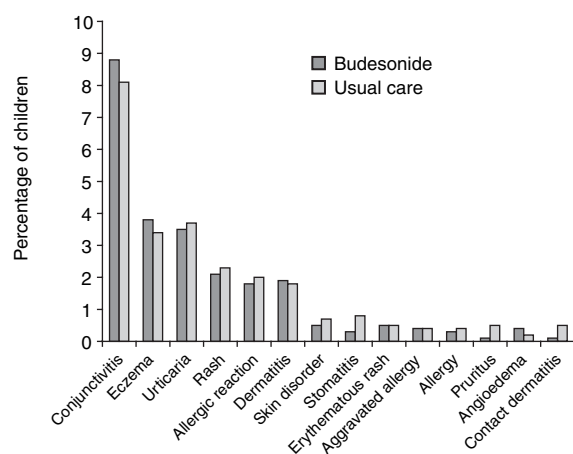


Fig. 3. Skin disorders and allergic reactions reported by children in START, by treatment group.

treatment groups (Fig. 3). The most common, conjunctivitis, was noted in 8.4% of children overall (budesonide: 8.8%; usual care: 8.1%); all other skin and allergic reactions (including eczema, urticaria, rash, pruritus and dermatitis) showed incidences of <4% (Fig. 3). There was an anaphylactic reaction in one child in the usual care group, but there were no reports of anaphylactic shock.

General systemic events

A number of systemic effects, including decreased plasma cortisol levels (a marker of adrenal function suppression), hypokalemia, osteoporosis and hypertension, are associated with the use of oral corticosteroids. Among children aged <11 yrs, there were no reports of decreased levels of circulating cortisol, hypokalemia, hypertension, edema or hypertrichosis. A single report of osteoporosis in this age group was received from the usual care group.

Other events

Except for dizziness, which was reported by 0.5% of children receiving usual care and 0.7% of those randomized to budesonide, psychiatric and behavioral disorders including impaired concentration, depression, somnolence, anxiety, anorexia, agitation, nervousness, attempted suicide and sleep disorders were reported by <0.5% of children in each group. Attempted suicide, nervousness and sleep disorder were each noted in one patient only, all in the usual care group. A similar pattern was seen for ocular disorders, with the most common event by far in this category being conjunctivitis (already discussed

above as an under dermatological and allergic events reaction). Incidences of the second most frequent event, eyelid stye, were 0.4% and 0.6% with usual care and budesonide, respectively. All other ocular events, including eye infections, were reported with incidences at or below 0.5% in both groups, and there were no reports of cataracts or glaucoma. No malignant neoplasms were seen in children during the study.

Serious adverse events

According to verbatim reports, a total of 234 children (106 with budesonide and 128 with usual care) experienced adverse events that were classified as serious. SOC descriptors showed a total of 333 individual serious events, of which the majority was classified as respiratory system disorders (78 with budesonide and 106 with usual care). Classification by preferred term showed aggravated asthma, fracture, pneumonia, accident and/or injury, appendicitis and pharyngitis to be the most common serious adverse events (Fig. 4). The most frequent of these, aggravated asthma, was reported by more children receiving usual care than by budesonide recipients (Fig. 4). There were no deaths among children aged <11 yrs in the START study.

Discussion

The START study showed for the first time in a large number of children that mild persistent asthma of recent onset can be treated successfully (9) in patients aged under 11 yrs with once-daily, low-dosage budesonide via Turbuhaler™ for 3 yrs without any clinically relevant safety or

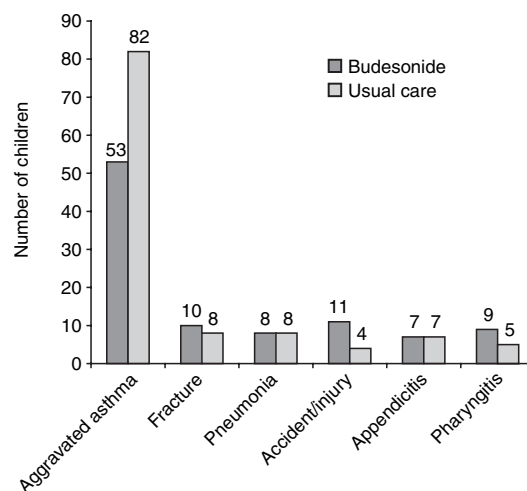


Fig. 4. Serious adverse events among children in START, by treatment group.

tolerability concerns. These findings are particularly relevant to clinical practice because of the 'real-world' design whereby patients were allowed to continue using their other regular asthma medication in addition to their study inhaler.

Overall, the safety and tolerability profile of inhaled budesonide at the dosage used in START in children aged below 11 yrs was similar to that observed with placebo (i.e. continuation of usual care). Results in children from this age group differed from the overall tolerability and safety results for all ages in that the total results showed an overall higher (but still low) frequency of local mouth and upper airway events such as moniliasis/candidiasis with budesonide than with usual care. This difference may have been due to the use of a higher daily dosage of budesonide (400 µg/day) in adolescents and adults than in children. The candidiasis, dysphonia, cough, hoarseness and sore throat associated with the use of inhaled corticosteroid therapy are known to be dose-dependent and can be minimized by the use of an inhaler device such as Turbuhaler™ that reduces oropharyngeal drug deposition relative to pressurized metered-dose inhalers (22).

The lack of any increase in incidence of allergic reactions with budesonide when compared with patients using placebo inhalers matched the findings in the overall START population. Similarly, the pattern of psychiatric and behavioral events in children receiving placebo and budesonide adds further support to the suggestion by Cluley and Cochrane (19) that psychological and psychiatric disturbances are linked to poor asthma control rather than to any particular medication.

Although the immunosuppressant properties of systemically administered corticosteroids can result in increased susceptibility to infection (particularly with high doses), early fears that such effects might be seen with inhaled agents have generally not been borne out in clinical practice. In agreement with this, there was no sign of increased risk of serious systemic infection in children receiving budesonide in START. The upper respiratory tract and other infections documented (including Varicella infection) were typical of those seen in children and were reported with similar frequencies in both treatment groups. There was also no association between budesonide therapy and severe invasive infections such as tuberculosis and aspergillosis. This corroborates the findings of a Turkish group, which found that inhaled corticosteroids were safe in tuberculin-positive children with

asthma (23). These results are of particular interest in light of occasional case reports of tuberculosis in persons receiving inhaled corticosteroid therapy (24, 25).

Low-dose inhaled corticosteroid therapy is not generally associated with the potentially serious metabolic and physiologic effects seen with oral systemic treatment, and the safety results presented here are consistent with this observation. No clinical cases of adrenal insufficiency or any other metabolic disturbance were reported in children in START. These findings are similar to those in the overall study population, and in agreement with the findings of other large, double-blind and placebo-controlled trials with budesonide via Turbuhaler™ at dosages of 100–400 µg twice daily for 12 wks (26) or budesonide 200 µg twice daily for 36 months (10, 27).

Changes in bone metabolism, with consequent increase in fracture risk, are established adverse effects of oral corticosteroids, particularly when these agents are given at high doses. The lack of any increase in fracture risk with budesonide delivered via Turbuhaler™ in the children in START concurs with the overall findings of the START study (8) and with other data obtained in children with mild to moderate asthma (10, 28). The occurrence of reports of glaucoma or cataract in START was not increased either – neither in children or the whole population. This reflects findings in other trials. In one study, children received budesonide for 3–6 yrs at an average daily dose of 500 µg (29), and another followed 176 children aged 5–10 yrs with asthma of recent onset who were randomized to three treatment groups, one of which received inhaled budesonide for 18 months (30). Neither study showed lens abnormalities nor raised intraocular pressure associated with budesonide treatment. The only ocular effects of any note in children in START were minor eye infections and irritations of the type normally seen in infancy and childhood across the general population.

The results from the START study, together with similar results from other well designed studies, suggest strongly that regular long-term budesonide therapy delivered via Turbuhaler™ at a dosage of 200 µg/day does not cause metabolic complications or systemic disturbances in children. A dosage of budesonide of 200 µg once daily in the dry powder inhaler Turbuhaler™ appears to minimize the local upper respiratory effects associated with drug deposition that some patients experience with inhaled corticosteroid therapy, especially when administered by metered-dose inhaler.

Therefore, in conclusion, long-term regular inhaled budesonide therapy via Turbuhaler™ added to usual therapy in children aged < 11 yrs with mild asthma of recent onset was safe and well tolerated.

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