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Review Article

Early intervention with inhaled steroids in childhood asthma

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Abstract

Early introduction of inhaled steroids as a treatment for childhood asthma is recommended in the guidelines to achieve not only early control of symptoms with an improvement in patients' quality of life, but also for the inhibition of airway remodeling. The evidence suggesting clinical usefulness of early intervention with inhaled steroids exists in school-age or older children with asthma. However, further investigations are required to determine the value of early intervention with inhaled steroids in asthmatic infants and very young children, because the disease concept and diagnosis of asthma, as well as clinical usefulness and adverse reactions to inhaled steroids, have not been sufficiently investigated.

Key words: childhood asthma, early intervention, inhaled steroid, remodeling.

Introduction

The pathophysiology of bronchial asthma has been investigated mainly for adult asthma. It has been elucidated that asthma is a chronic inflammatory disorder characterized by recurrent episodes of airway obstruction and hyperresponsiveness to various stimuli. It has also been pointed out that airway remodeling occurs due to sustained airway inflammation and this condition makes the disease intractable and more severe with the progress of irreversible airway lesions. Therefore, an emphasis is placed on the need of treatment aiming for the control of airway inflammation early after the onset of asthma. In particular, the possibility has been suggested that early intervention with inhaled steroids may achieve not only early control of symptoms with an improvement of patients' quality of life (QOL), but also for the inhibition of airway remodeling. However, it still seems difficult to say that sufficient evidence for such a need of early intervention is established in pediatric asthma, even though the clinical usefulness and safety of inhaled steroids have been proven in children. In the present review, we summarize the current issues and possibilities of early intervention with inhaled steroids in childhood asthma by referring to our own data and present the points that should be investigated further in the future.

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Effect of inhaled steroids on respiratory function in childhood asthma

It is confirmed that the prevalence of pediatric asthma has been increasing in recent years.[1] Approximately 20% of adult asthma patients are those who have continuously suffered from asthma from childhood or those who have recurrence after temporary relief of childhood asthma. In consideration of these epidemiological data, it is expected that appropriate early intervention for asthma soon after onset in childhood may alleviate symptoms, normalize respiratory function and eventually increase the spontaneous remission rate of pediatric asthma.

We have investigated the long-term prognosis of severe intractable pediatric asthma and found that many patients at puberty or during adolescence still manifest mild symptoms and obstructive changes in respiratory function tests even though the asthma itself has become milder.[2] We also investigated the effects of inhaled beclomethasone dipropionate (BDP) in adolescent asthmatic out-patients who still showed obstructive changes in respiratory function although their asthma symptoms were relieved after treatment with inhaled disodium cromoglycate (DSCG). That study confirmed that BDP achieved further relief of symptoms and significant improvement of respiratory function (M Kameda *et al.*, unpubl. data, 1993). However, few patients demonstrated complete normalization of respiratory function and many patients were still suggested to have peripheral airway narrowing (Fig. 1). It is inferred that continuous treatment focusing only on the symptoms does not sufficiently inhibit airway inflammation, which results in progression of remodeling and, eventually, fails to achieve normalization of respiratory function.

Agertoft *et al*.[3] investigated the relationship between time from diagnosis of asthma to start of inhaled steroid therapy and the rate of improvement of lung function in asthmatic children. They stressed the need for early intervention with inhaled steroids, suggesting a possibility that failure to use inhaled steroids soon after diagnosis may result in inhibition of normal development of lung function. This is consistent with reports proving the usefulness of early intervention with inhaled steroids in adult asthma.[4,5]

Clinical trial of early intervention with inhaled steroids in childhood asthma

We previously investigated the need and effectiveness of holistic asthma therapy by regarding asthma as a disease with multiple factors and reported that preventive drug therapy is unnecessary in most cases of mild asthma in children.[6] Nevertheless, because airway inflammation is shown to exist even in mild asthma, the influence of airway inflammation on the long-term prognosis should be investigated carefully. Therefore, we evaluated the usefulness of early intervention with BDP and DSCG in children with intermittent or mild persistent asthma aged 3–12 years who had recurrent episodes of relatively mild asthma symptoms soon after the first diagnosis (T Inoue *et al.*, unpubl. data, 2000). After a 1 month run-in period, the patients whose guardians consented to the treatment method were

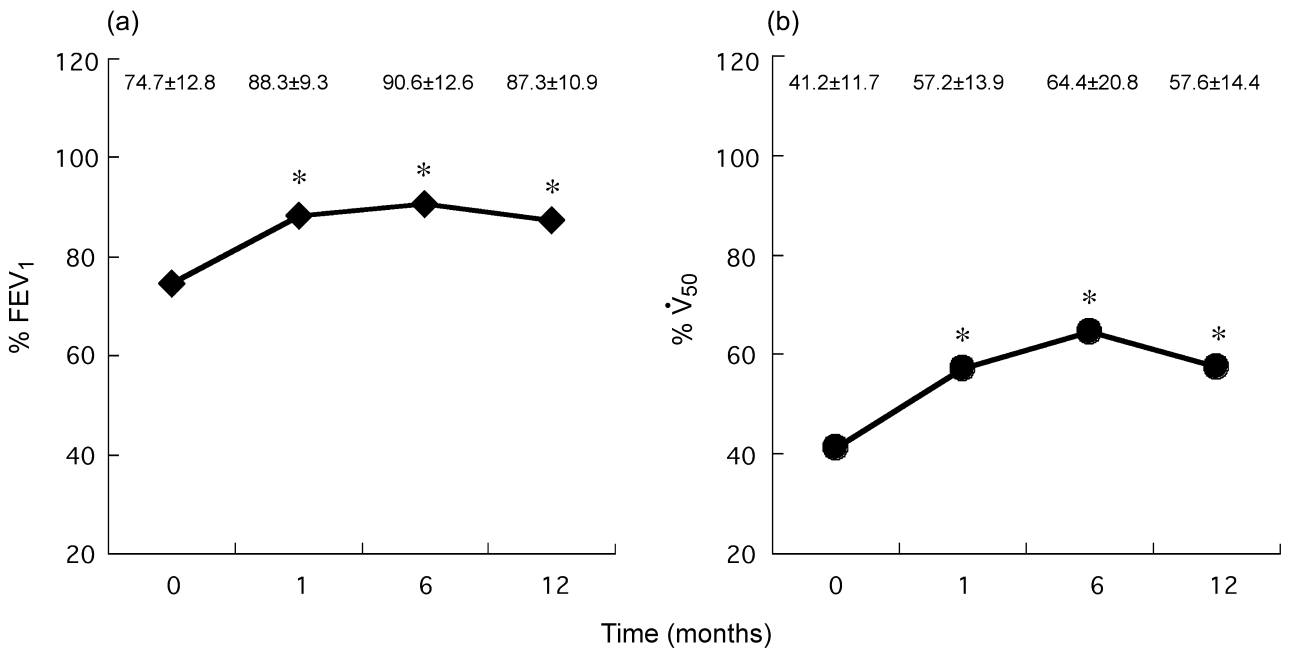

Fig. 1 Effect of beclomethasone dipropionate (BDP) on respiratory function in mild asthmatics with chronic air flow limitation ($n = 17$ cases (11 male, six female); mean age 12.1 ± 2.8 years (range 9–17 years)). The dose of BDP administered was 11.3 ± 4.9 μg/kg per day (range 300–600 μg/kg daily). *$P < 0.01$ (paired *t*-test). FEV_1, forced expiratory volume in 1 s; $\dot{V}_{50}$, expiratory flow at 50% of the forced vital capacity.

randomized to a non-treatment group without any preventive drug therapy, a DSCG group receiving one ampoule (20 mg) of DSCG inhalation solution twice daily via nebulization or a BDP group receiving BDP 200 μg twice daily using an large volume spacer. The clinical courses of the patients were followed at regular visits and by asthma diary cards (including peak flow monitoring at home). Lifestyle guidance, such as improvement of living conditions, was given to all patients whenever necessary. According to asthma symptoms, bronchodilators were concomitantly used as needed or for a short period of time. As shown in Table 1, the number of patients who regularly visited the hospital over 1 year and maintained good compliance was 10 (55.6%), 14 (60.9%) and eight (42.1%) in the non-treatment, DSCG and BDP groups, respectively. In the non-treatment group, many patients stopped visiting the hospital, highlighting the difficulty in managing patients with mild asthma over a long period of time. In the BDP group, there were many cases whose guardians did not give consent and preferred another treatment. This suggests that asthmatic patients and their guardians in Japan are still very cautious about the use of inhaled steroids. In comparison with the symptom scores during the 1 month prior to treatment and over almost the same period after 1 year, no significant change was seen from pre- to post-dose mean scores in the non-treatment group. However, the standard deviation became larger after treatment, indicating that there were both patients with an improvement of asthma symptoms and patients with worsening of asthma symptoms. In contrast, significant improvement in the symptom score was observed in the DSCG and BDP groups. There was no difference in the magnitude of improvement between these two groups (Fig. 2). No symptoms or abnormal laboratory data suggestive of adverse drug reactions were reported in any of the groups. The results demonstrate that introduction of anti-inflammatory inhaled drug therapy in patients with mild asthma early after the onset of asthma can alleviate the symptoms of asthma, but the data did not show that aggressive introduction of BDP is superior to inhalation of DSCG. Further investigations are required to determine the effect on the long-term prognosis. It has also become clear that many aspects remain to be investigated in the future, such as the inclusion criteria of target patients, the types and doses of drugs, treatment period, methods to ensure treatment or inhalation compliance and adverse drug reactions.

König and Shaffer[7] retrospectively reviewed the results of step-wise therapy for each severity of asthma recommended by the International Pediatric Asthma Treatment Guideline announced in 1989.[8] König and Shaffer[7] concluded that it is valuable to start treatment with DSCG in patients with mild asthma earlier than the timing mentioned in the guidelines, but the usefulness of the early introduction of inhaled steroids was not established.

In a report investigating the usefulness of the long-term use of inhaled steroids in mild to moderate pediatric asthma,[9,10] statistical superiority was demonstrated in the population treated with inhaled steroids, but the efficacy gain was small. Further investigations are required to determine whether the early introduction of inhaled steroids should be positively recommended in actual clinical practice.

Inhaled steroid therapy in asthmatic infants and very young children

It has been pointed out that approximately 80% of asthmatic children had the first onset of asthma by the age of 3 years and that the age at first onset of asthma has decreased in recent years.[1] For consideration of early intervention in children, correct diagnosis of asthma shortly after onset is essential in infancy

Table 1 Status of treatment compliance in the early intervention trial (T Inoue *et al.*, unpubl. data, 2000)

	Treatment		
	None	DSCG	BDP
1 year observation	10 (55.6)	14 (60.9)	8 (42.1)
Change of treatment	1 (5.6)	5 (21.7)	1 (5.3)
Change of hospital	–	2 (8.7)	–
Discontinuation of hospital visits	7 (38.9)	2 (8.7)	3 (15.8)
Refusal of treatment	–	–	7 (36.8)
Total	18 (100)	23 (100)	19 (100)

Data show the number of patients in each group, with percentages given in parentheses.

DSCG, disodium cromoglycate; BDP, beclomethasone dipropionate.

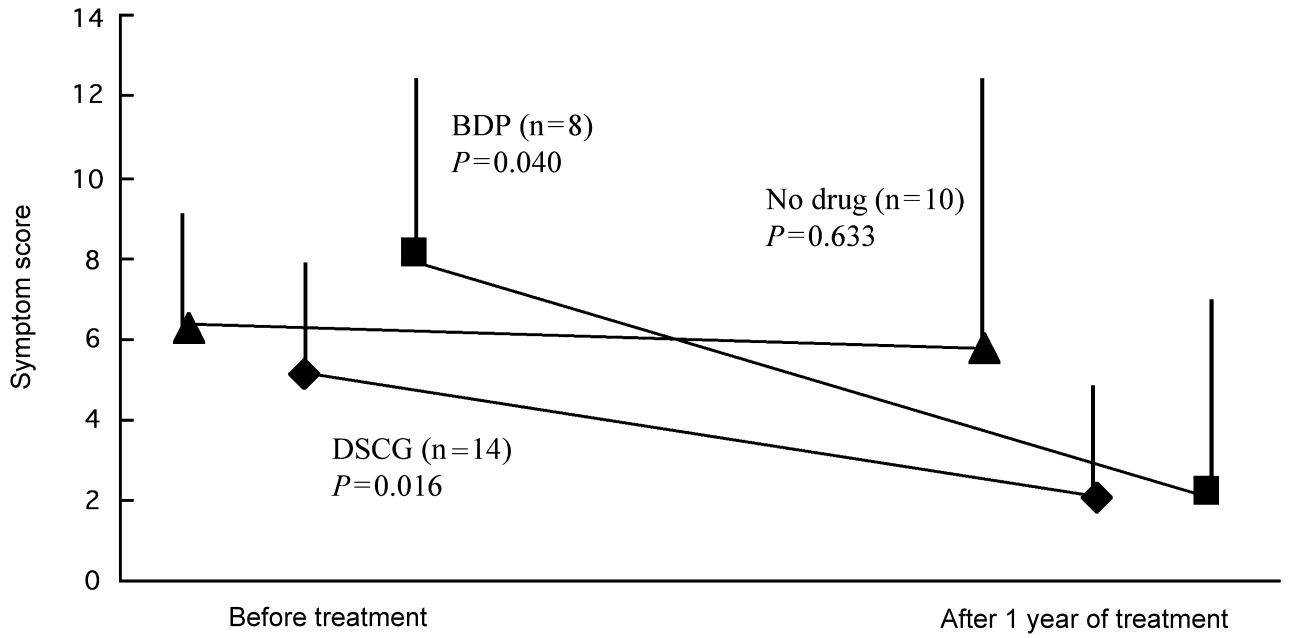

Fig. 2 Clinical effects of anti-inflammatory drugs in an early intervention trial (T Inoue *et al.*, unpubl. data, 2000). The symptom score is expressed as a monthly sum of daily scores (severe attack = 9, moderate attack = 6, mild attack = 3, wheezing = 1, cough = 0.5). DSCG, disodium cromoglycate; BDP, beclomethasone dipropionate.

Table 2 Results of long-term inhaled steroid therapy for young asthmatic children

	At start	5 years later
Change in asthma severity (*n*)		
Severe	10	1
Moderate	6	1
Mild	0	9
No attack	0	5
Change in beclomethasone dipropionate dose (μg/day; *n*)		
600	11	2
400	5	8
300	0	2
200	0	2
None	0	2
Change in the use of concomitant drugs (*n*)		
DSCG + salbutamol	15	8
Slow-release theophylline	16	11
Oral steroid	3	1
None	0	5
Adverse reactions (*n*)		
Oral candidiasis		3
Hoarseness		1
Change in height		
SD score	0.397	0.076
Respiratory function		
$\%FEV_1$		100.0
$\%\dot{V}_{50}$		92.2

Prognosis was investigated in 16 children with asthma younger than 6 years of age (mean age 38.9 months) who started beclomethasone dipropionate (BDP) treatment during the period 1990–1992.

DSCG, disodium cromoglycate; FEV_1, forced expiratory volume in 1 s; $\dot{V}_{50}$, expiratory flow at 50% of the forced vital capacity.

and early childhood. However, infants and very young children are likely to present with wheezing and dyspnea owing to their anatomical and physiological characteristics. Martinez *et al*.[11] performed a prospective cohort study and reported that more than half the patients having wheezing by the age of 3 years outgrew the symptoms by the age of 6 years. They pointed out the difficulty in differentiating transient manifestation of wheezing and typical asthma because of the clinical characteristics of small children.[12] When the cell components of airway secretions from wheezing children were analyzed, an increased number of eosinophils and mast cells involved in allergic inflammation was found in some children, but not in others.[13] In a long-term investigation of respiratory function in wheezing children,[14,15] patients with severe asthma exhibited persistently low values from the start of the observation period, whereas the values in patients with mild asthma were not low but similar to those in healthy children. Because these patients were not treated with inhaled steroids, the results have cast doubt over the value of early intervention with inhaled steroids in cases of mild asthma.

Studying the clinical efficacy of inhaled steroids in infants and very young children can be paraphrased as studying the usefulness of early intervention with inhaled steroids in asthmatic infants and very young children. Randomized double-blind clinical studies have already confirmed clinically significant effects of inhaled steroids, such as an improvement of symptoms and a reduction of the use of reliever medications.[16–18] In contrast, it has been reported that there exist infants and very young children whose asthma cannot be completely controlled with inhaled steroids and that the efficacy of inhaled steroids is poor in mild asthmatic children who have recurrent episodes of wheezing caused by viral infections with few allergic factors.[19,20]

We studied the prognosis of 5 years treatment with inhaled BDP at 600–800 μg/day given with a large volume spacer in severe asthmatic patients younger than 6 years of age (mean age 38.9 months) whose asthma symptoms were not well controlled by the concomitant use of theophylline round the clock (RTC) and regular nebulization of DSCG and salbutamol (M Kameda *et al.*, unpubl. data, 1998). As summarized in Table 2, the severity of asthma became milder and the use of both BDP and concomitant drugs decreased. Oral candidiasis and hoarseness were reported transiently in three and one patient, respectively, as possible adverse reactions with BDP, but these events were resolved by symptomatic treatment. No growth inhibition was observed. Although respiratory function could not be measured before BDP treatment, respiratory function data after 5 years treatment were close to the predictive values. Hence, it is judged that appropriate inhaled steroid therapy can control asthma symptoms in infants and very young children without lowering respiratory function or inhibiting normal growth, even if the treatment is started after the asthma becomes severe.

It is difficult to use simple objective variables, such as lung function tests, in infants and very young children and the asthma control has to depend on the clinical symptoms. Therefore, disease conditions in infants and very young children should be very carefully determined. We have obtained data showing that early intervention with inhaled steroids may be effective not only for the control of asthma symptoms, but also for the inhibition of sensitization by inhaled allergens. We retrospectively investigated the sensitization status by mite allergens 1 year after the start of BDP or DSCG inhalation in asthmatic children aged 2 years or younger who had not been sensitized by mite allergen (N Murayama *et al.*, unpubl. data, 2000). Although the BDP inhalation group (13 patients) seemed to have stronger atopic predispositions than the DSCG inhalation group (22 patients), specific IgE antibody to mite allergens was found to be positive in one patient given BDP inhalation and in five patients given DSCG inhalation. The study was a retrospective study for only 1 year, so the results were inconclusive. However, the results of the study suggest the possibility that early intervention with inhaled steroids may inhibit the establishment of sensitization by inhaled allergens. This point is thought to be an interesting topic that should be investigated further in the future.

Conclusions

With regard to early intervention with inhaled steroids in childhood asthma, evidence suggesting the usefulness of early intervention exists in school-age or older children, so that this population can be regarded in the same manner as the adult population. However, it cannot be denied that the disease concept and the diagnosis of asthma, as well as the clinical usefulness of and adverse reactions to inhaled steroids, have not been investigated sufficiently in infants and very young children. Future investigations from various viewpoints are required to determine the value of early intervention with inhaled steroids in asthmatic infants and very young children.

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