

Inhibition of Common Cold-Induced Aggravation of Childhood Asthma by Leukotriene Receptor Antagonists

Shigemi Yoshihara¹, Hironobu Fukuda¹, Toshio Abe¹, Mitsuhiro Nishida¹, Yumi Yamada², Noriko Kanno³ and Osamu Arisaka¹

ABSTRACT

Background: Virus infection is an important risk factor for aggravation of childhood asthma. The objective of this study was to examine the effect of drugs on aggravation of asthma induced by a common cold.

Methods: Asthma control was examined in a survey of 1,014 Japanese pediatric patients with bronchial asthma. The occurrence of common cold, asthma control, and drugs used for asthma control were investigated using a modified Childhood Asthma Control Test (C-ACT) for patients aged <4 years old and 4 to 11 years old, and an Asthma Control Test (ACT) for patients aged 12 to 15 years old.

Results: The status of asthma control did not differ among the age groups. The prevalence of common cold and aggravation of asthma were significantly higher in patients aged <4 years old. Control of asthma following common cold-induced aggravation was significantly less effective in patients aged <4 years old compared to those aged ≥4 years old. In patients aged <4 years old with a common cold, asthma control was significantly more effective for those treated with leukotriene receptor antagonists (LTRAs) compared to treatment without LTRAs. Asthma control did not differ between patients who did or did not take inhaled corticosteroids or long-acting β₂ stimulants.

Conclusions: These findings showed a high prevalence of common cold in younger patients with childhood asthma and indicated that common cold can induce aggravation of asthma. LTRAs are useful for long-term asthma control in very young patients who develop an asthma attack due to a common cold.

KEY WORDS

Asthma Control Test, Japan, long-term control, questionnaire, virus

INTRODUCTION

The basic pathology of childhood asthma is persistent inflammation of the respiratory tract. Respiratory tract infection is an important factor in development and aggravation of asthma, and respiratory syncytial (RS) virus,¹ rhinovirus² and metapneumovirus³ infections are important in young patients. Aggravation of asthma by viruses involves respiratory epithelium injury⁴ caused by direct stimulation of the respiratory tract by viral infection and increased airway hyper-sensitivity accompanying aggravation of respiratory tract inflammation.⁵ Therefore, inhibition of airway in-

flammation using drugs for long-term control such as inhaled corticosteroids (ICS), leukotriene receptor antagonists (LTRAs), and suplatast (a Th2 cytokine inhibitor) and early use of allergen-specific immunotherapy may have preventive and inhibitory effects on aggravation of asthma.

ICS for long-term control of asthma were first recommended in 2008,⁶ but a preventive effect of ICS in the early phase of asthma development in children has not been proven in large-scale clinical trials.⁷⁻⁹ In contrast, Bisgaard *et al.*¹⁰ reported that early use of a LTRA, montelukast, significantly inhibited aggravation of asthma in children. Early use of LTRAs as oral

¹Department of Pediatrics, Dokkyo Medical University, ³Department of Pediatrics, Nishikata Hospital, Tochigi and ²Department of Pediatrics, Tsuchiya Children's Hospital, Saitama, Japan.

Authors' contributions: SY collected data, performed statistical analysis and contributed to writing of the manuscript. HF, TA, MN, YY, NK collected data. OA supervised data collection and analysis.

Conflict of interest: The authors report no conflict of interest regarding the work in the manuscript.

garding the work in the manuscript.

Correspondence: Shigemi Yoshihara, MD, PhD, Department of Pediatrics, Dokkyo Medical University, 880 Kitakobayashi, Mibumachi, Shimotsuga-gun, Tochigi 321-0293, Japan.

Email: shigemi@dokkyomed.ac.jp

Received 18 November 2011. Accepted for publication 22 January 2012.

©0000 Japanese Society of Allergology

antiinflammatory agents is also likely to have a secondary preventive effect. Suplatast can also inhibit asthma development in children with an atopic disposition.¹¹

There are few studies on the effects of drugs for long-term control of pediatric asthma aggravated by a common cold. For appropriate treatment of such cases, it is important to determine the status of control and the drugs used for long-term control. Therefore, the aim of this study was to examine whether ICS, LTRAs and other drugs inhibit common cold-induced aggravation of childhood asthma, based on a survey of patients in Tochigi Prefecture.

METHODS

The subjects were childhood asthma patients who visited 59 pediatric clinics and hospitals in Tochigi Prefecture from August 1 to November 30, 2008. In a questionnaire survey, the patients or their parents were asked about the prevalences of common cold and common cold-induced aggravation of asthma, and the status of asthma control for the previous 4 weeks. Physicians provided information on the patient background and the drugs used by the patients. Long-acting β_2 stimulant was defined as tulobuterol patch, which is approved as a transdermal β_2 stimulant in Japan and has an effect similar to that of salmeterol.¹² Tulobuterol is widely used and is recommended for long-term asthma control in the same manner as a long-acting inhaled β_2 stimulant in the Japanese Pediatric Guideline for the Treatment and Management of Asthma 2005 (JPGL 2005).⁶ Suplatast is a Th2 cytokine inhibitor that is approved as an anti-inflammatory drug and is available only in Japan. In this study, we confirmed good patient compliance orally or using a diary.

The classification of atopy and non-atopy was defined by a physician depending on the presence of predisposing factors for atopic disease (a family history of atopy, a history of allergic disease, or a predisposition to IgE production). During the study period, patients who developed symptoms such as nasal discharge, cough, and sore throat with no fine crackles detected through chest auscultation were diagnosed with a common cold. Patients with other acute symptoms and/or chronic respiratory diseases (e.g. cystic fibrosis, bronchopulmonary dysplasia, and primary dyskinesia) were excluded from this diagnosis. Asthma severity was classified into intermittent, mild persistent, moderate persistent, and severe persistent types according to the JPGL 2005 criteria.⁶ Asthma control was evaluated using a modified version of the Childhood Asthma Control Test (C-ACT) and the Asthma Control Test (ACT). In the original C-ACT, cases scoring ≥ 20 points are classified as "Controlled" or "Partly Controlled" and those with < 20 points as "Uncontrolled". In the modified C-ACT, cases with 26 or 27 points were classified as "Controlled", those

with 20 to 25 points as "Partly Controlled", and those with < 20 points as "Uncontrolled". The modified C-ACT was used for patients aged ≤ 11 years old. The questionnaire was completed by parents for patients aged < 4 years old and by the patient or their parents for patients aged 4 to 11 years old. Patients aged 12 to 15 years old completed the ACT by themselves. In the ACT, cases with a full score (25 points) were considered to be "Controlled", those with 20 to 24 points were "Partly Controlled", and those with < 20 points were "Uncontrolled".¹³

This study was approved by the Regional Ethics Committee for Human Research at Dokkyo Medical University Hospital. The parents of all patients participating in this study gave oral and written informed consent.

Comparison of the prevalences of common cold and common cold-induced aggravation of asthma, and the drugs used for asthma control between age groups was performed by χ^2 test. The status of asthma control and the drugs used for patients aged < 4 years old with a common cold were analyzed by Mann-Whitney U test. A p value < 0.05 was considered to indicate a significant difference.

RESULTS

PATIENT BACKGROUND

Data were collected from 1,047 pediatric patients and 1,014 data were used to the analysis. 33 patients were excluded from the analysis because the ages were more than 16 years or the background data such as age and sex were not obtained. The mean age ($\pm$ SD) was 6.3 ± 3.3 years old and a male: female ratio was 62.2%: 37.8%. The periods of time the children spent with their parents each day were < 8 hours, 8 to 12 hours, 12 to 24 hours, and unknown for 15.6%, 26.9%, 40.4% and 17.1% of the patients, respectively. Asthma was classified as atopic, non-atopic, and unknown in 73.7%, 22.0% and 4.3% of the patients, respectively, and the severity of the disease was intermittent, mild persistent, moderate persistent, severe persistent, and unknown in 18.4%, 50.0%, 23.8%, 1.6% and 6.2%, respectively. The drugs used for long-term control either alone or concomitantly included theophylline (oral), DSCG, oral antiallergic agents, LTRAs, long-acting β_2 stimulants, ICS, and suplatast in 8.4%, 11.3%, 19.4%, 83.2%, 11.6%, 49.5% and 4.6% of the patients, respectively (Table 1).

ASTHMA CONTROL

Evaluations using the modified C-ACT or ACT indicated that asthma control was similar in the age groups of < 4 , 4 to 11, and 12 to 15 years old. The percentage of controlled, partly controlled and uncontrolled cases among patients aged < 4 years old were 42.7%, 40.4% and 11.6%, respectively. These respective rates were 39.8%, 40.4% and 8.8% in patients aged 4 to 11 years old; and 44.4%, 35.8% and 12.3% in those aged

Table 1 Patient background

		<4 years old n = 225	4-11 years old n = 708	12-15 years old n = 81	Overall n = 1014
Sex	Male	155 (68.9)	427 (60.3)	49 (60.5)	631 (62.2)
	Female	70 (31.1)	281 (39.7)	32 (39.5)	383 (37.8)
Respondent	Mother	198 (88.0)	622 (87.9)	69 (85.2)	889 (87.7)
	Father	9 (4.0)	28 (4.0)	5 (6.2)	42 (4.1)
	Grandfather	0 (0.0)	3 (0.4)	0 (0.0)	3 (0.3)
	Grandmother	2 (0.9)	17 (2.4)	1 (1.2)	20 (2.0)
	Others/Unknown	12 (5.3)	23 (3.2)	3 (3.7)	38 (3.7)
	No answer	4 (1.8)	15 (2.1)	3 (3.7)	22 (2.2)
Contact duration	<8 hours	26 (11.6)	106 (15.0)	26 (32.1)	158 (15.6)
	8-12 hours	40 (17.8)	203 (28.7)	30 (37.0)	273 (26.9)
	12-24 hours	116 (51.6)	281 (39.7)	13 (16.0)	410 (40.4)
	No answer	43 (19.1)	118 (16.7)	12 (14.8)	173 (17.1)
Disease type	Atopic	146 (64.9)	534 (75.4)	67 (82.7)	747 (73.7)
	Non-atopic	70 (31.1)	140 (19.8)	13 (16.0)	223 (22.0)
	No answer	9 (4.0)	34 (4.8)	1 (1.2)	44 (4.3)
Severity	Intermittent	32 (14.2)	143 (20.2)	12 (14.8)	187 (18.4)
	Mild persistent	114 (50.7)	355 (50.1)	38 (46.9)	507 (50.0)
	Moderate persistent	66 (29.3)	154 (21.8)	21 (25.9)	241 (23.8)
	Severe persistent	4 (1.8)	8 (1.1)	4 (4.9)	16 (1.6)
	Unknown	9 (4.0)	48 (6.8)	6 (7.4)	63 (6.2)
Drug for long-term control	Theophylline (oral)	8 (3.6)	64 (9.0)	13 (16.0)	85 (8.4)
	DSCG	33 (14.7)	76 (10.7)	6 (7.4)	115 (11.3)
	Oral antiallergic drug	33 (14.7)	142 (20.1)	22 (27.2)	197 (19.4)
	LTRA	202 (89.8)	583 (82.3)	59 (72.8)	844 (83.2)
	Long-acting β 2 stimulant	39 (17.3)	75 (10.6)	4 (4.9)	118 (11.6)
	ICS	111 (49.3)	347 (49.0)	44 (54.3)	502 (49.5)
	Suplatast [†] (Th2 cytokine inhibitor)	7 (3.1)	32 (4.5)	8 (9.9)	47 (4.6)

Percentages are shown in parentheses. [†] Suplatast is available only in Japan.

Table 2 Status of asthma control among the patients

Asthma Control	<4 years old n = 225	4-11 years old n = 708	12-15 years old n = 81
Controlled	96 (42.7)	282 (39.8)	36 (44.4)
Partly Controlled	91 (40.4)	285 (40.4)	29 (35.8)
Uncontrolled	26 (11.6)	62 (8.8)	10 (12.3)
Unknown	12 (5.3)	78 (11.0)	6 (7.4)

Asthma control was evaluated using the modified C-ACT and ACT questionnaires. For patients <4 years old, parents completed the modified C-ACT. For patients aged 4 to 11 years old, the patients or their parents completed the modified C-ACT. Patients aged 12 to 15 years old filled in the ACT themselves.

On the modified C-ACT, 26 or 27 points was considered to indicate asthma that was controlled, 20 to 25 points indicated partly controlled, and <20 points indicated uncontrolled.

On the ACT, 25 points indicated controlled, 20 to 24 points indicated controlled, and <20 points indicated uncontrolled.

Percentages are shown in parentheses.

12 to 15 years old (Table 2).

PREVALENCES OF COMMON COLD AND ASTHMA AGGRAVATED BY COMMON COLD

Among all patients, 46.4% had developed a common cold in the 4 weeks before completion of the survey. These rates were 62.2%, 43.1% and 30.9% in the <4, 4 to 11, and 12 to 15 age groups, respectively, with a significantly higher incidence in patients aged <4 years old ($p < 0.001$). Aggravation of asthma by the common cold occurred in 34.0% of all patients, and in 49.3%, 28.2% and 24.0% in the <4, 4 to 11, and 12 to 15 age groups, respectively. This incidence was also significantly higher in patients aged <4 years old ($p < 0.001$) (Table 3).

ASTHMA CONTROL, COMMON COLD, AND ASTHMA AGGRAVATION IN PATIENTS AGED <4 YEARS OLD

Asthma control in patients aged <4 years old with a common cold was significantly poorer than that in patients in the same age group without a common cold

Table 3 Incidences of common cold and asthma aggravated by common cold over 4 weeks

	<4 years old <i>n</i> = 225	4-11 years old <i>n</i> = 708	12-15 years old <i>n</i> = 81	Overall <i>n</i> = 1014	<i>p</i> value		
					<4 vs 4-11 years old	<4 vs 12-15 years old	12-15 vs 4-11 years old
Common cold	140 (62.2)	305 (43.1)	25 (30.9)	470 (46.4)	<0.001	<0.001	<0.05
Aggravated asthma	69 (49.3)	86 (28.2)	6 (24.0)	161 (34.0)	<0.001	<0.001	N.S.

Percentages are shown in parentheses. N.S., not significantly different.

Table 4 Incidences of common cold and asthma aggravated by common cold and status of asthma control in patients aged younger than 4 years old

	Controlled	Partly Controlled	Uncontrolled	<i>p</i> value		
				Controlled vs Partly Controlled	Controlled vs Uncontrolled	Partly Controlled vs Uncontrolled
Common cold	41/96 (42.7)	67/91 (73.6)	24/26 (92.3)	<0.001	<0.001	<0.05
Asthma aggravated by common cold	2/41 (4.8)	39/69 (56.5)	22/24 (91.6)	<0.001	<0.001	<0.01

Asthma control was evaluated using the modified C-ACT questionnaire, which was completed by parents.

On the modified C-ACT, 26 or 27 points was considered to indicate asthma that was controlled, 20 to 25 points indicated partly controlled, and <20 points indicated uncontrolled.

Percentages are shown in parentheses.

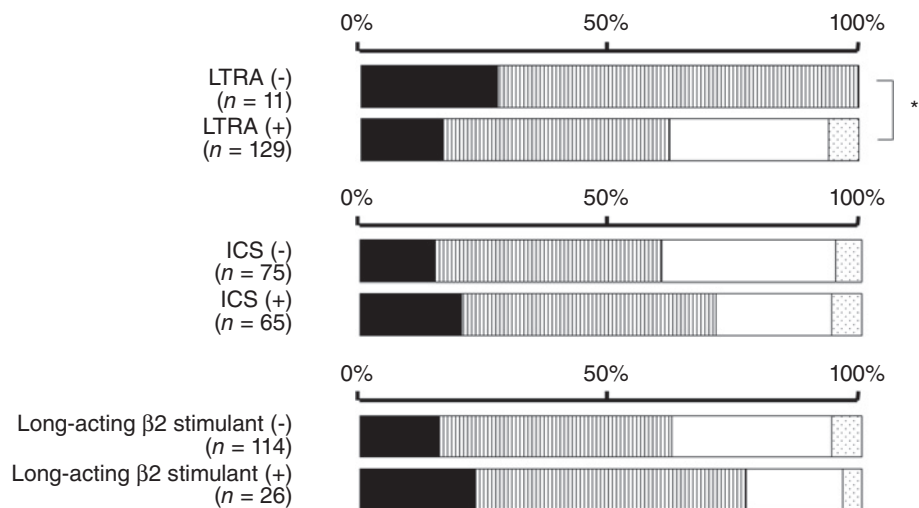


Fig. 1 Effects of drugs for asthma control in asthma patients <4 years old with a common cold. The black, striped, white and dotted bars show cases that were uncontrolled, partly controlled, controlled, and not determined, respectively. **p* < 0.05. Other information is given in the footnote to Table 4.

(*p* < 0.001). Control of asthma aggravated by a common cold in patients aged <4 years old was also significantly poorer than that in patients in the same age group with no aggravation of asthma (*p* < 0.001) (Table 4).

ASTHMA CONTROL AND DRUGS USED IN PATIENTS AGED <4 YEARS OLD WITH A COMMON COLD

The effects of LTRAs, ICS, and long-acting beta2 stimu-

lants, all of which were used at high rates, on asthma control were examined in patients aged <4 years old with a common cold. Asthma control in this age group was significantly better for patients treated with LTRAs compared with those who did not receive LTRAs (*p* < 0.05). In contrast, no significant difference in asthma control was found for patients aged <4 years old who did or did not receive ICS or long-acting beta2 stimulants (Fig. 1).

DISCUSSION

Respiratory infection is an important factor in development and aggravation of pediatric bronchial asthma. The mechanism is thought to involve an increase in airway hypersensitivity accompanied with airway epithelium injury and inflammation aggravated by direct stimulation by virus infection.⁵ Drugs for long-term control such as LTRAs, ICS and long-acting β_2 stimulants are used clinically, but the effects of these drugs on asthma aggravated by a common cold have not been widely examined.

We performed a survey of asthma control in patients with childhood asthma at multiple medical facilities in Tochigi Prefecture to examine whether drugs for long-term control inhibited aggravation of asthma caused by virus infection. The prevalences of common cold and asthma aggravated by common cold were particularly high in younger patients (<4 years old). Asthma symptoms caused by rhinovirus and RS virus infection are especially common in infants, and RS virus infection has been related to successive development of asthma and increased airway hypersensitivity.^{1,2,14} Lung *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* cause acute chronic wheezing.¹⁵ The airway internal diameter is smaller and lung elastic recoil is decreased in infants compared to older children, and thus airway narrowing may easily develop and lead to rapid progression of symptoms.¹⁶ Therefore, it is important to examine whether early use of drugs for long-term control in infants can inhibit progression of asthma.

We evaluated the effects of drugs on asthma control in children using a modified C-ACT, which included two modifications to the original C-ACT. The first was to consider patients with ≥ 26 points on the C-ACT to be "Controlled". In development and validation of the C-ACT, Liu *et al.* compared C-ACT scores by dividing 257 pediatric asthma patients using parameters for respiratory function and asthma control.¹⁷ The favorable groups had %FEV₁ $\geq 100\%$, FEV₁/FVC $\geq 100\%$, a "step down" change in therapy, and completely controlled asthma based on assessment by a specialist. The C-ACT scores for these groups were 20.19 ± 4.11 , 20.14 ± 3.98 , 20.08 ± 4.41 , and 22.27 ± 3.28 , respectively. Therefore, patients with ≥ 26 points (higher than the mean +1 SD for each group) should have very favorable asthma control.

The second modification of the C-ACT was made for evaluation of the current status of asthma control in patients aged <4 years old. Parents of these patients were asked to answer all the questions on the modified C-ACT, but two difficulties were encountered in this approach: it was unclear whether the modified C-ACT score reflected objective asthma symptoms in patients aged <4 years old; and whether the answers given by the parents overestimated or underestimated the asthma symptoms in these pa-

tients. With regard to the validity of the C-ACT score, Yoshihara *et al.* reported that nocturnal sleep disorder in parents of infant asthma patients had a positive correlation with asthma symptoms in the patients.¹⁸ In an investigation of the relationship of the modified C-ACT score with nocturnal sleep disorder in parents induced by an asthmatic attack in the pediatric patients, we found a positive correlation between the modified C-ACT score and nocturnal sleep disorder for parents of pediatric asthma patients aged <4 years old and aged 4-11 years old (data not shown). This suggests that the modified C-ACT score does reflect asthma symptoms in all pediatric patients. Regarding the accuracy of parent answers, we asked ten pediatric patients aged 4-11 years old and their parents to answer questions Q1 to Q4 independently, and calculated the modified C-ACT scores. There was no significant difference in C-ACT score between the patients and their parents (data not shown). These findings suggest that an effective evaluation of the current status of asthma control in patients aged <4 years old can be obtained using the modified C-ACT score.

The effects of LTRAs, ICS, and long-acting β_2 stimulants on control of pediatric asthma in patients aged <4 years old with a common cold were examined using the modified C-ACT. Asthma control in these patients was significantly better in those who received LTRAs compared to those that did not take these drugs. In contrast, use of ICS and long-acting β_2 stimulants did not result in a significant improvement in asthma control compared to patients who did not take the respective drugs. These results suggest that LTRAs inhibit common cold-induced aggravation of asthma in younger children and give favorable asthma control. A secondary preventive effect of ICS in the early phase of asthma development was not found in large-scale trials,⁷⁻⁹ whereas Bisgaard *et al.* found that early use of montelukast in patients aged 2 to 5 years old with mild intermittent asthma significantly inhibited asthma aggravation.¹⁰ These results suggest that LTRAs inhibit common cold-induced aggravation of asthma in younger children and give favorable asthma control, but require confirmation in a prospective comparative study.

LTRAs are oral drugs with high tolerability that can reach the peripheral airway via the blood, and are widely used in treatment of childhood asthma. Our results suggest that LTRAs can contribute to control of an asthma attack accompanied by a common cold. The prevalences of common cold and acute aggravation of childhood asthma by a common cold were particularly high in younger patients (<4 years old), and asthma control in these patients was poor. LTRAs may be particularly useful for long-term control and inhibition of common cold-induced aggravation of asthma in these patients.

REFERENCES

1. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am J Respir Crit Care Med* 2000;**161**:1501-7.
2. Jackson DJ, Gangnon RE, Evans MD *et al*. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med* 2008;**178**:667-72.
3. Van Den Hoogen BG, DeJong JC, Groen J *et al*. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. *Nat Med* 2001;**7**:719-24.
4. Yoshihara S, Yamada Y, Abe T, Linden A, Arisaka O. Association of epithelial damage and signs of neutrophil mobilization in the airways during acute exacerbations of paediatric asthma. *Clin Exp Immunol* 2006;**144**:212-6.
5. Laprise C, Laviolette M, Boutet M, Boulet LP. Asymptomatic airway hyperresponsiveness: relationships with airway inflammation and remodelling. *Eur Respir J* 1999;**14**: 63-73.
6. Nishimuta T, Kondo N, Hamasaki Y, Morikawa A, Nishima S. Japanese guideline for childhood asthma. *Allergol Int* 2011;**60**:147-69.
7. Guilbert TW, Morgan WJ, Zeiger RS *et al*. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006;**354**:1985-97.
8. Bisgaard H, Hermansen MN, Loland L, Halkjaer LB, Buchvald F. Intermittent inhaled corticosteroids in infants with episodic wheezing. *N Engl J Med* 2006;**354**:1998-2005.
9. Murray CS, Woodcock A, Langley SJ, Morris J, Custovic A; IFWIN study team. Secondary prevention of asthma by the use of Inhaled Fluticasone propionate in Wheezy Infants (IFWIN): double-blind, randomised, controlled study. *Lancet* 2006;**368**:754-62.
10. Bisgaard H, Zielen S, Garcia-Garcia ML *et al*. Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. *Am J Respir Crit Care Med* 2005;**171**:315-22.
11. Yoshihara S, Ono M, Yamada Y, Fukuda H, Abe T, Arisaka O. Early intervention with suplatast tosilate for prophylaxis of pediatric atopic asthma: a pilot study. *Pediatr Allergy Immunol* 2009;**20**:486-92.
12. Yoshihara S, Yamada Y, Abe T, Arisaka O. The use of patch formulation of tulobuterol, a long-acting beta 2-adrenoreceptor agonist, in the treatment of severe pediatric asthma. *Ann Allergy Asthma Immunol* 2006;**96**:879-80.
13. Schatz M, Sorkness CA, Li JT *et al*. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. *J Allergy Clin Immunol* 2006;**117**:549-56.
14. Brunetti L, Colazzo D, Francavilla R *et al*. The role of pulmonary infection in pediatric asthma. *Allergy Asthma Proc* 2007;**28**:190-3.
15. Sigurs N, Gustafsson PM, Bjarnason R *et al*. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Respir Crit Care Med* 2005;**171**:137-41.
16. Hershenson MB, Colin AA, Wohl ME, Stark AR. Changes in the contribution of the rib cage to tidal breathing during infancy. *Am Rev Respir Dis* 1990;**141**:922-5.
17. Liu AH, Zeiger R, Sorkness C *et al*. Development and cross-sectional validation of the Childhood Asthma Control Test. *J Allergy Clin Immunol* 2007;**119**:817-25.
18. Kondo N, Inoue R, Matsui E *et al*. [QOL questionnaire version 2001 for pediatric patients with bronchial asthma and parents or caregivers: preparation and evaluation]. *Arerugi* 2001;**50**:667-78(in Japanese).