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Original article

Caregiver treatment satisfaction is improved together with children's asthma control: Prospective study for budesonide monotherapy in school-aged children with uncontrolled asthma symptoms

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ICS, inhaled corticosteroid; CTS, caregiver treatment satisfaction; JPAC, Pediatric Asthma Control Program; QoL, quality of life; BUD-TBH, budesonide Turbuhaler[®]; LTRA, leukotriene receptor antagonist; %FEV₁, forced expiratory volume in 1 second percent predicted; %PEF, peak expiratory flow percent predicted; %MMF, maximum mid-expiratory flow rate percent predicted

ABSTRACT

Background: If asthmatic children cannot obtain sufficient control of their disease, not only do they suffer from asthma symptoms, but the daily life activities of their caregivers are also disrupted. We investigated the effectiveness of an inhaled corticosteroid (ICS) for symptom control in previously ICS-untreated school-aged asthmatic children as well as caregiver treatment satisfaction (CTS).

Methods: A multicenter, open-label, single-arm study on 12-week ICS (budesonide Turbuhaler[®]) monotherapy was undertaken in subjects aged 5–15 years with bronchial asthma not treated with ICS during the previous 3 months. At 0, 4, 8, and 12 weeks after start of ICS administration, Japanese Pediatric Asthma Control Program (JPAC) scores, and CTS scores were summated and lung function measured. At weeks 0 and 12, questionnaires on caregiver anxiety were also assessed.

Results: Seventy-five patients were enrolled, and 69 assessed. Ninety percent of subjects had been treated with asthma controller medication except ICS before study enrollment. JPAC score and CTS score were improved significantly at weeks 4, 8, and 12 ($p < 0.001$). With regard to CTS, more than half of caregivers showed a perfect score at weeks 8 and 12. There was a significant correlation between JPAC score and CTS score. Lung function and caregiver anxiety were also improved, and good compliance with treatment was observed during the intervention.

Conclusions: If treating ICS-untreated school-aged asthmatic children with uncontrolled symptoms, ICS monotherapy can improve CTS along with improving asthma control.

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Introduction

If asthmatic children cannot obtain sufficient control of their disease, not only do they suffer from asthma symptoms, but the

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daily activities of life of their caregivers are also disrupted. A report on a questionnaire developed to assess the quality of life (QoL) of caregivers of asthma patients¹ showed that caregiver QoL was correlated with asthma control in children.² Whether caregivers feel confident and are satisfied with a child's asthma treatment is an important factor influencing the success or failure of treatment because the assistance of caregivers is essential for long-term management of asthma.³

Inhaled corticosteroids (ICSs) are the first-line treatment of asthma for school-aged and older patients.⁴ In Japan over the past decade, ICSs have been prescribed more commonly, but the prevalence of prescription of ICSs in asthmatic children remains low⁵ (presumably because of anxiety regarding their side effects⁶). Thus, a non-negligible number of asthmatic children are thought to suffer from insufficient control of asthma. ICS administration is likely to improve the asthma control and lung function of patients, as well as caregiver treatment satisfaction (CTS). Several studies have shown the effectiveness of ICS for the treatment of childhood asthma.⁷ However, prospective studies in children with uncontrolled asthma focusing on asthma control and CTS in ICS monotherapy are lacking.

We conducted a 12-week prospective study with budesonide Turbuhaler® (BUD-TBH) monotherapy to elucidate the effectiveness of ICS monotherapy in asthmatic children who did not use an ICS in the previous 3 months, and in whom previous treatment did not enable sufficient control of asthma. Asthma control by patients was measured using the Japanese Pediatric Asthma Control Program (JPAC) score.^{8,9} The relationship between CTS and symptom control by patients was also assessed.

Methods

The present study (UMIN000005155) was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethical Review Board of Dokkyo Medical University (Tochigi, Japan).

This was a multicenter, open-label, single-arm study to evaluate symptomatic improvement, influence on CTS, and safety after 12 weeks of switching to ICS (BUD-TBH) monotherapy in subjects aged 5–15 years with bronchial asthma who had not used an ICS in the previous 3 months. It was conducted between March 2011 and June 2012 at participating institutes.

Subjects

Subjects were enrolled if they satisfied all of the following inclusion criteria: written informed consent could be obtained from the patient and parents/guardians (for patients who were too young to provide written informed consent, verbal assent of the patients confirmed by a parent/guardian could be substituted); outpatients with bronchial asthma aged 5–15 years; patients who were ICS-naïve or not treated during the preceding 3 months; patients who were diagnosed with poorly controlled asthma based on the JPAC questionnaire^{8,9} upon study enrollment; patients who could schedule four visits with same guardian.

Patients were excluded from the study if they: had received systemic corticosteroid therapy within the preceding month; could not use the Turbuhaler® appropriately (as judged by the investigating physician); were contraindicated for the study drug; had any chronic respiratory disease other than asthma; had an acute infection of the lower respiratory tract upon study enrollment; were judged by the investigating physician to be inappropriate for this study.

Treatment and measurements

Subjects were treated with BUD-TBH (400 µg/day) for 12 weeks. Any other controller medications were discontinued before study commencement.

The JPAC score (range, 0–15) was scored as: 15 points, complete control; 12–14, favorable (insufficient) control; and ≤11, poor control. CTS using a “face scale”^{10,11} (five grades scored from 1, extremely dissatisfied to 5, extremely satisfied) designed originally for this study (Fig. 1), spirometry and patient-reported adherence of inhalation (five grades: almost 100%; nearly 75%; nearly 50%; nearly 25%; almost did not) were measured 0, 4, 8, and 12 weeks after the start of ICS administration. Allowance for deviation from a scheduled visit date was set as ±14 days. Standard values of spirometry parameters were calculated using standard formulae provided by the Japanese Society of Pediatric Pulmonology.¹² At week 0 and week 12, a questionnaire on caregiver anxiety was also assessed. The questionnaire contained 14 questions designed originally for this study based on a previous QoL report.¹ Answers were “yes” or “no” and multiple responses were allowed (Table 1). CTS and caregiver anxiety questionnaire constraints had to be answered by the same caregiver.

Q) How satisfied are you with the asthma treatment received by the patient during the past 1 month?
please choose the option that most closely matches your response.



Fig. 1. Caregiver treatment satisfaction (CTS) questionnaire. The face scale has five grades [1 (extremely dissatisfied) to 5 (extremely satisfied)].

Table 1

Questionnaire on caregiver anxiety administered at week 0 and week 12.

- (1) Faced problems within the last 3 months owing to a need to see a doctor outside of regular hospital or clinic hours (including examinations on Sundays and public holidays or visit to acute care facility) for an asthmatic child.
- (2) Faced problems within the last 3 months owing to a need for frequent visits to a hospital or clinic because of an asthmatic child;
- (3) Caused inconvenience in my workplace within the last 3 months owing to lateness or absence due to an asthmatic child;
- (4) Felt anxious about the length of time this lifestyle will continue;
- (5) Felt anxious about the length of time I will have to shoulder the medical costs due to an asthmatic child;
- (6) Wanted to somehow improve the patient's asthma symptoms;
- (7) Experienced family rifts because of an asthmatic child;
- (8) Felt isolated owing to lack of someone to confide in;
- (9) Felt anxious about the effects of my own lack of sleep (e.g., irritability, emotional instability) on daily life;
- (10) Felt deeply concerned about the patient's future owing to asthma;
- (11) Feared that the patient would die during an asthma attack;
- (12) Unable to ask the doctor if I had questions;
- (13) Felt dissatisfied with how the doctor cared for the patient, and have repeatedly changed hospital or clinic;
- (14) Have worried about the side effects of medication.

Answers are "yes" or "no", and multiple responses are allowed.

All adverse events observed during the treatment period were reported.

Statistical analyses

The sample size needed to detect a significant improvement of primary endpoint in the JPAC score was calculated to be 34. This calculation was under the assumption that the mean scores pre-treatment and post-treatment were 10.5 and 12.5, respectively, and that the standard deviation was 4.0 with a significance level of 5% (two-sided) and statistical power of 80%. We set the target number of participants to be 100 by considering correlation analyses and study dropouts.

Baseline parameters are the mean and standard deviation for proportional measurements and as counts for categorical measures. The paired *t*-test, Wilcoxon signed rank test, or McNemar's test were used for comparisons of measures between baseline and after treatment. Correlations between the JPAC score and CTS score were evaluated using Spearman's rank correlation for each visit. Correlation between JPAC scores at all visits and CTS at all visits was also evaluated. Missing data of treatment adherence at the final visit were complemented using the last observation carried forward method. A value of $p < 0.05$ was used for all statistical tests. Statistical analyses were carried out using JMP v10.2 (SAS Institute, Cary, NC, USA) or SPSS v18.3 (IBM, Armonk, NY, USA).

Results

Seventy-five patients were enrolled, and 69 were assessed. Four subjects were excluded because they did not return to the hospital after the first visit, and two cases were excluded because of lack of valid data (all of their visit dates deviated by >14 days from scheduled dates). At week 8, four patients exceeded the visit allowance, and two cases had some unanswered items in the JPAC, so data for six out of 69 patients were excluded. At week 12, nine cases exceeded the visit allowance, and two subjects had unanswered items in the JPAC, so data for 11 out of 69 patients were excluded.

Baseline characteristics are shown in Table 2. Ninety percent of subjects were treated with some type of asthma controller medication except an ICS before study enrollment, and 78% of them used

Table 2

Patient characteristics.

		n = 69
Age (years)		8.8 (2.4)
BMI (kg/m ²)		17.4 (2.9)
Sex	Male	42 (61)
	Female	27 (39)
Previous medication	Any medication	62 (90)
	Leukotriene receptor antagonist	54 (78)
	Theophylline sustained-release formulation	12 (17)
	Sodium cromoglycate	3 (4)
	β ₂ -agonist	34 (49)
	Patch	23 (33)
	Inhaler	11 (16)
	Oral	9 (9)
	None	7 (10)
Disease type	Atopic	64 (93)
	Non-atopic	2 (3)
	Unclear	3 (4)

BMI, body mass index.

Data are the mean (SD) or number (%).

leukotriene receptor antagonists (LTRAs). The JPAC score was improved significantly at weeks 4, 8, and 12 ($p < 0.001$ at each visit) (Fig. 2a). Subjects who achieved complete control had gradually increased JPAC scores until week 12 and, by the end of the study period, 33 (56.9%) had obtained complete control (Fig. 2b). Spirometry parameters such as forced expiratory volume in 1 second percent predicted (%FEV₁), peak expiratory flow rate percent predicted (%PEF), and maximum mid-expiratory flow rate percent predicted (%MMF) were improved significantly at week 4 (Fig. 3). CTS was increased significantly at week 4 ($p < 0.001$), and 27 (39.1%), 32 (50.8%), and 35 (60.3%) were the best scores at weeks 4, 8 and 12, respectively (Fig. 4). Good adherence at the final visit was observed. Fifty patients (72.5%) showed "almost 100%" and 19 (27.5%) demonstrated "nearly 75%". Improvement trends were

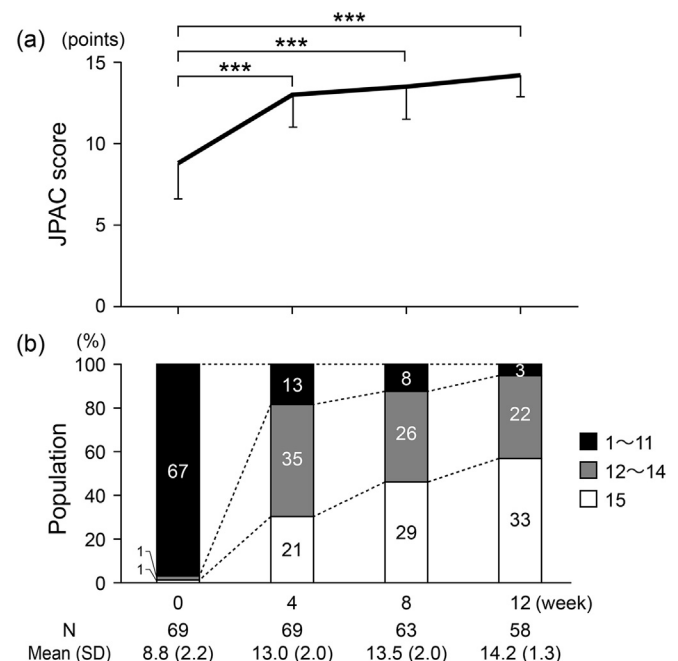


Fig. 2. Changes in JPAC scores. (a) Changes in mean scores; (b) proportion changes of control state (15 points, complete control; 12–14, favorable (insufficient) control; and ≤11, poor control). Numbers of patients are shown in the respective partitions of bars. The Wilcoxon signed rank test was used to compare results at 0–4, 0–8, and 0–12 weeks. *** $p < 0.001$.

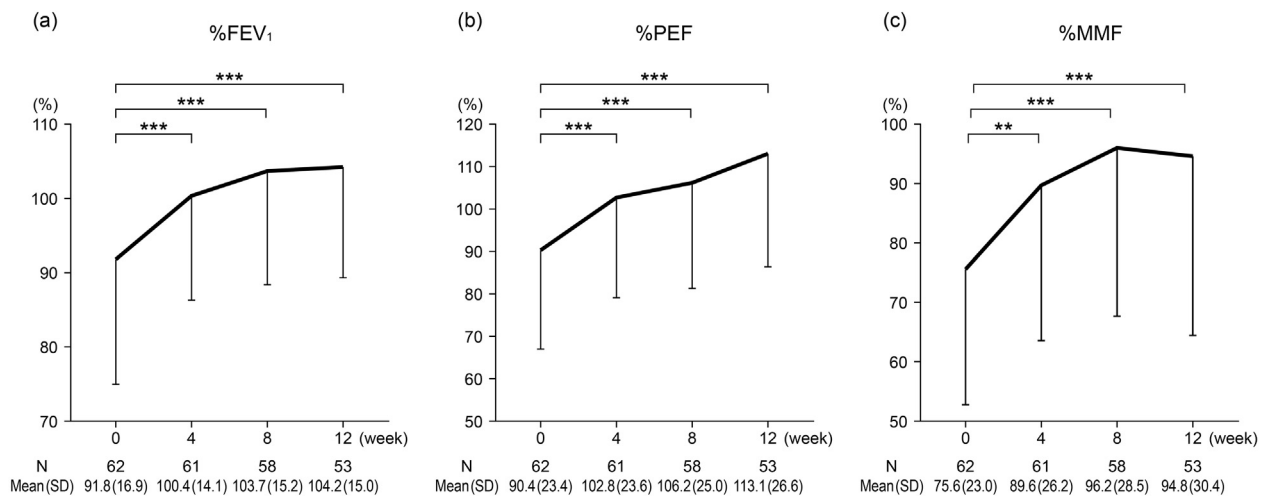


Fig. 3. Changes in lung function. (a) Forced expiratory volume in 1 second (FEV₁) % predicted; (b) peak expiratory flow (PEF) % predicted; (c) maximum mid-expiratory flow rate (MMF) % predicted. The paired *t*-test was used to compare results at 0–4, 0–8, and 0–12 weeks. ***p* < 0.01; ****p* < 0.001.

observed in the JPAC score and satisfaction, as indicated in Fig. 5a, with coordination of patients moving to the upper-right area of the panel according to time course. There was a significant correlation between the JPAC score and CTS ($\rho = 0.420$, $p < 0.001$) (Fig. 5b). In the questionnaire on caregiver anxiety, question 6 (“Wanted to somehow improve the patient’s asthma symptoms”) question 4 (“Felt anxious about the length of time this lifestyle will continue”) and question 14 (“Have worried about the side effects of medication”) were improved significantly at week 12 (Fig. 6). No serious adverse events related with BUD-TBH were reported.

Discussion

We focused on: (i) the effectiveness of ICS monotherapy in a real-life setting; (ii) satisfaction of treatment from the viewpoint of caregivers. The latter has not been investigated sufficiently despite its considerable importance in the long-term management of asthma in children.

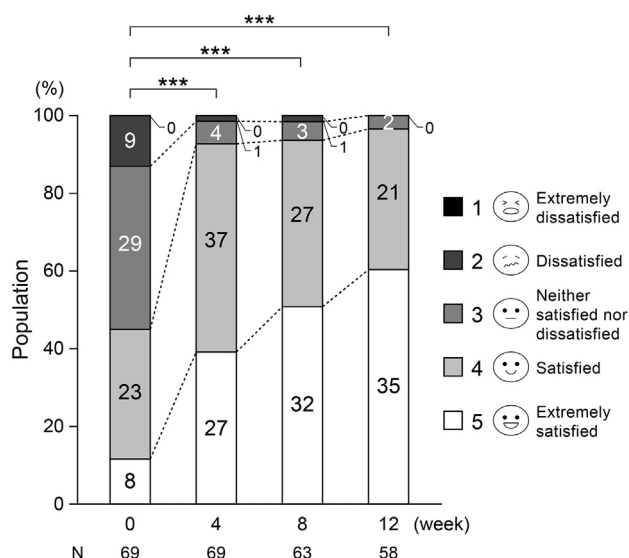


Fig. 4. Changes in the satisfaction of treatment provided by the caregiver. Numbers of patients are shown in the respective partitions of bars. The Wilcoxon signed rank test was used to compare results at 0–4, 0–8, and 0–12 weeks. ****p* < 0.001.

Our results showed that ICS monotherapy improved asthma control in those aged 5–15 years who had not been treated with an ICS during the previous 3 months, and that CTS was correlated with the asthma control of children. After 12-week administration of an ICS, symptom control and lung function in asthmatic children and the CTS of their caregivers improved significantly. Some items of the questionnaire on caregiver anxiety also improved significantly. Murphy *et al.*¹³ showed, in a clinical trial involving asthmatic children (age, 2–6 years) treated with budesonide inhalation suspension, that better health status and asthma management of the child improved the QoL and satisfaction of caregivers. Our results suggested that similar relationships could be extended for school-aged children.

The JPAC score was improved significantly at week 4, and increased gradually until week 12. Moreover, 57% of subjects achieved well-controlled asthma by week 12 despite even though almost all subjects had poorly controlled asthma at baseline. Values of lung function also exhibited significant improvements. Reasons for the drastic improvement in asthma control might be not only the strong suppressive effect of budesonide on airway inflammation, but also because most of the subjects enrolled had received inadequate controller therapy. Most subjects had been treated with LTRAs before study enrollment, presumably because LTRAs are commonly used drugs for pediatric patients with asthma on account of their efficacy and high safety, even in infants aged <1 year.¹⁴ However, some patients have uncontrolled symptoms despite LTRA treatment (as in most of the subjects in the present study). Our results suggested that ICS monotherapy was effective for such patients.

Our results also showed that CTS was correlated with the asthma control of study participants, which was similar to the relationship reported between caregivers’ QoL and children’s asthma control in a study by Stelmach *et al.*² In addition, no serious adverse events caused by BUD-TBH were reported. This finding suggests that CTS improves if the treatment can control symptoms and if its side effects are minimal and well tolerated. Improved CTS is thought to be associated with better compliance with treatment in children, so further improvement in control might be expected. Conversely, if caregivers feel that improvement in symptom control is not sufficient, they might not cooperate with children’s treatment adequately, and such noncompliance can lead to increased morbidity (and even mortality). Thus, if symptoms in asthmatic children are controlled inadequately, controller medication should

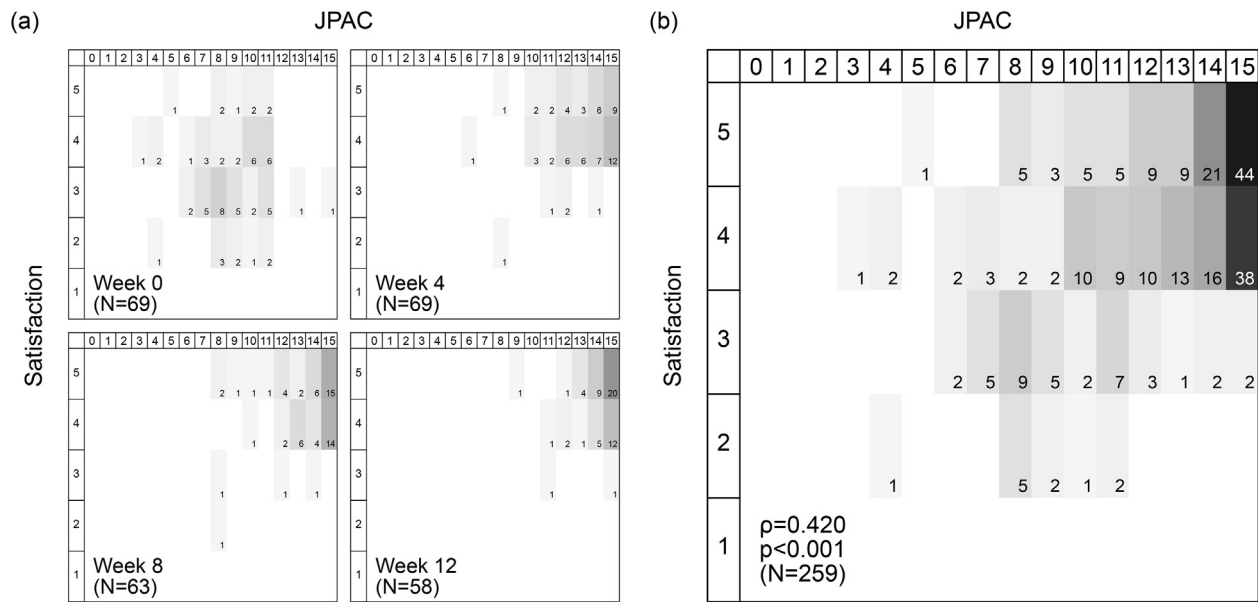


Fig. 5. Relationships between JPAC scores and scores for the satisfaction of treatment provided by the caregiver. Horizontal axes represent JPAC scores, vertical axes represent scores for the satisfaction of treatment provided by the caregiver, and numbers of patients are shown in the respective partitions in diagrams. (a) Relationship at each visit; (b) four-visit total assessment. The Spearman rank correlation coefficient (ρ value) and p value are shown in the total assessment.

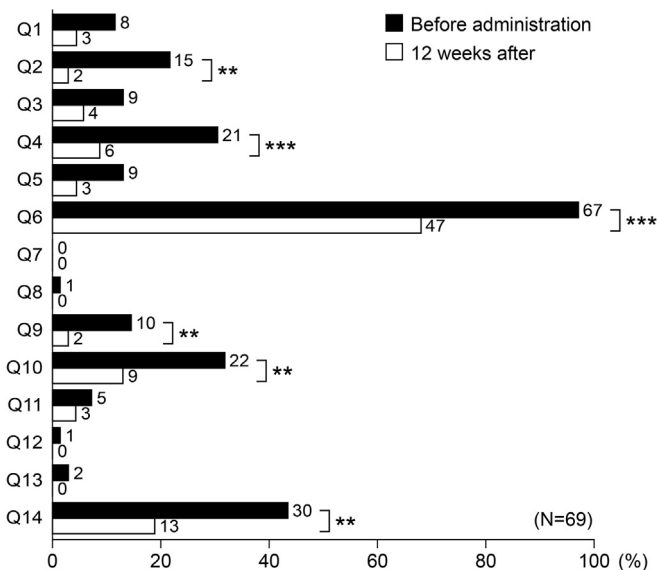


Fig. 6. Changes in responses to questionnaire on caregiver anxiety before and after treatment. Number of “true” answers for each question. McNemar’s test was used to compare results at 0–12 weeks. The questionnaire contained the 14 questions shown in Table 1, and multiple responses were permitted. ** $p < 0.01$; *** $p < 0.001$ (McNemar’s test).

be stepped-up promptly to control asthma symptoms and maintain good compliance with treatment.

With respect to the questionnaire on caregiver anxiety, the proportion of caregivers having fear of side effects at week 12 (18.8%) decreased significantly compared with that at baseline (43.5%). In Japan, the prevalence of prescription of ICSs has been increasing in recent years, but remains at a low level compared with other countries.¹⁵ One reason for the low level could be that caregivers have a fear of side effects such as a reduction in the rate of growth and osteoporosis¹⁶ even though, in fact, growth reduction is within an acceptable level¹⁷ and the incidence of osteoporosis does

not increase in children.⁷ Our study showed that misconceptions about ICSs could be dispelled if children’s asthma symptoms were controlled adequately and side effects were well tolerated. The proportion of caregivers having anxiety about the future of the children and disturbance in daily life was also decreased significantly, which might suggest that caregivers’ QoL improved completely.

Our study had limitations. Usually, this type of before-and-after study design tends to enhance the effectiveness of the medication, especially improvement in patient-reported outcomes, such as the JPAC score in the present study. We did not try to show the effectiveness of ICS in the present study because the effectiveness of ICS for asthmatic children has been shown, especially in randomized parallel-group trials.⁷ A comparatively novel result from the present study is that ICS monotherapy could probably be employed in non-ICS-treated asthmatic children, but this hypothesis should be confirmed in a randomized clinical trial. Another limitation was the lack of validation in our questionnaires except for JPAC. We considered the convenience of the patient/caregiver, and designed an original, simple questionnaire. However, such modifications could cause difficulties for comparison between the present study and previous studies. However, we believe that the results from the present study are useful for analyses of the correlation between symptom control (JPAC) and CTS, which have not been reported previously.

In conclusion, the present study suggests that ICS monotherapy is effective to achieve good control of asthma symptoms in ICS-untreated asthmatic children with uncontrolled symptoms. CTS was shown to be correlated with symptom control in asthmatic children. For ICS-untreated patients with uncontrolled symptoms, our results suggested that ICS monotherapy was likely to aid improvement of CTS as well as asthma control and lung function in patients. Therefore, for asthma control in children, we should also pay attention to CTS to achieve better outcomes.

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Conflict of interest

The authors have no conflicts of interest to disclose.

Authors' contributions

SY, OA designed the study. SY, NK, HF, OA, MA, KS, KY, AT, YY, TW, TS, KN, TN contributed to data collection. SY undertook statistical analyses, interpreted the results and wrote the manuscript. All authors approved the final version of the manuscript.

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