

Tiotropium as an add-on treatment to inhaled corticosteroids in children with severe and mild symptomatic asthma: Multi-center observational study for efficacy and safety analysis

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Abstract. Children aged 6-11 years with uncontrolled asthma are treated with low-dose inhaled corticosteroid (ICS) with stepwise increase in ICS dosage and/or add-on maintenance treatment, as necessary. The objective of the present study was to evaluate the efficacy and safety of tiotropium add-on treatment in children with severe and mild symptomatic asthma. The present prospective cohort study included 144 children with severe and mild asthma (age, 6-11 years) who received ICS (budesonide) with ≥ 1 controller treatment combination therapies for ≥ 1 month and score ≥ 1.5 based on Asthma Control Questionnaire-Interviewer-Administered. In addition to ICS with ≥ 1 controller treatment, children received 5 μg once-daily tiotropium (treatment group; $n=72$) or did not receive tiotropium (control group; $n=72$). The peak forced expiratory volume in 1-sec change from the baseline 3 h post-administration of tiotropium was significantly improved in the treatment group compared with the control group (384 ± 31 vs. 248 ± 28 ml; $P<0.0001$). The trough forced expiratory volume in 1-sec (224 ± 28 vs. 140 ± 31 ml; $P<0.0001$) and forced expiratory flow at 25-75% of forced vital capacity (389 ± 36 vs. 116 ± 27 ml/sec; $P<0.0001$) showed significant

improvement following treatment with tiotropium. Significant differences were noted for trough forced vital capacity (153 ± 29 vs. 139 ± 30 ml/sec; $P<0.0001$), mean weekly rescue treatment usage (0.29 ± 0.08 vs. 0.36 ± 0.09 ; $P<0.0001$), mean weekly peak expiratory flow measurement (4.12 ± 3.56 vs. 7.46 ± 3.29 l/min; $P<0.0001$) and mean weekly symptom-free time (0.19 ± 0.04 vs. 0.16 ± 0.04 days; $P<0.0001$) between both cohorts. Children of both groups tolerated any adverse effects. Tiotropium 5 μg administered once/day as an add-on treatment to ICS with ≥ 1 controller treatments in children (6-11 years of age) with severe and mild symptomatic asthma was found to be efficacious and safe (level of evidence 2; technical efficacy stage 4).

Introduction

Asthma is a prevalent chronic disease in children (1). Increased prevalence of pediatric asthma has been observed in a number of studies conducted in China (2,3). The management goals of asthma in children include improved control of symptoms, normal activity maintenance, decreased risk of lung growth impairment and symptom exacerbation and decreased treatment-associated adverse effects (4).

According to the World Health Organization 2019 report (5), ~262 million individuals globally have chronic airway inflammation and asthma. Among these, ~5.1 million are children younger than 18 years old. Patients with asthma experience regular symptom exacerbations that affect quality of life. The first-line medication for treatment of asthma is inhaled corticosteroids (ICSs); however, these do not prevent symptoms in ~40% of patients (5).

The long-acting anticholinergic bronchodilator drug tiotropium taken once a day has shown to be efficacious as an add-on treatment to ICS in adolescents as well as adults (6). The Global Initiative for Asthma guidelines recommend tiotropium as an additional therapy under steps 4 and 5 as part of the stepwise methodology for patients with asthma aged ≥ 12 years (4).

In children aged 6-11 years, the Global Initiative for Asthma guideline advises therapy with low dose ICS followed by stepwise increase in ICS dosage and/or add-on maintenance treatment, such as long-acting β -agonist (LABA) or

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Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting β -agonist; LTRA, leukotriene receptor antagonist; ACQ-IA, Asthma Control Questionnaire-Interviewer-Administered; FEV₁, forced expiratory volume; FVC, forced vital capacity; PEF, peak expiratory flow; FEF, forced expiratory flow; df, degree of freedom

Key words: add-on treatment, anticholinergic drug, inhaled corticosteroid, lung function, pediatric asthma, tiotropium

leukotriene receptor antagonist (LTRA), as necessary to treat uncontrolled asthma (4). China released its first children's asthma action plan in 2017 to improve asthma control (7). In China, children with asthma exhibit poorer compliance than adults with asthma. Moreover, the prescribing doctor may not show consistent adherence to therapy guidelines or provide proper treatment or enough education to pediatric patients with asthma, worsening the problem of poor asthma control (8,9).

Exacerbations of asthma symptoms are associated with higher morbidity and mortality risk, as well as greater treatment cost. The exacerbation risk is raised with decreased lung function and frequent exacerbations may result in persistent asthma in pediatric patients and increased chronic obstructive pulmonary disease risk during adulthood (6,9,10). Children with asthma exhibit increased comorbidity rates, including depression and behavioral problems, that increase with severity of the asthma (11). Moreover, poor control of asthma increases the risk of sleep interference, such as awakening at night, resulting in missed school days. Therefore, it is necessary to increase patient adherence by improved communication and scrutinizing add-on treatment choices for treating asthma that are controlled sub-optimally (9). It is important to ensure potential new treatments are effective and safe. Although the Global Initiative for Asthma guidelines included tiotropium as one of the add-on therapies under step 4, available evidence for efficacy and safety is insufficient (4,9).

The present prospective study aimed to assess the efficacy and safety of tiotropium add-on treatment administered at 5 μ g dose for 12 weeks in children (age, 6-11 years old) with severe and mild symptomatic asthma.

Materials and methods

Inclusion/exclusion criteria. The patients enrolled in the present study were children with severe and mild symptomatic asthma aged 6-11 years. Children received ICS (200 μ g budesonide; Budecort; Cipla Ltd.), ICS + LABA (formoterol fumarate at standard pediatric dose; Perforomist[®]; Viatrix Inc.), ICS + LTRA (5 mg montelukast; Almont; Dr. Reddy Laboratories) or ICS (400 μ g budesonide; Budecort; Cipla Ltd.) + >2 controllers (LABA, LTRA and/or theophylline; Alergin[®]; Cipla Ltd.) for ≥ 1 month and had a score of ≥ 1.5 based on Asthma Control Questionnaire-Interviewer-Administered (ACQ-IA) (12). Moreover, participants exhibited pre-bronchodilator tested forced expiratory volume in 1 sec (FEV₁) at 60-90% of predicted normal logs in addition to $\geq 12\%$ FEV₁ reversibility 15-30 min post-administration of 200 μ g salbutamol (Ventolin[®] HFA; GlaxoSmithKline PLC).

Children with recent respiratory infection or any significant disorder other than asthma were excluded.

Intervention. The present study divided 144 children were into treatment groups and control group (n=72/) based on whether they received tiotropium or not, respectively. In addition to ICS with ≥ 1 controller treatment, children in treatment group received tiotropium (5 μ g once daily; 2 doses of 2.5 μ g each; Tiova Inhaler; Cipla Ltd.) for 12 weeks with 3-week follow-up (13). The children in the control group received ICS with ≥ 1 controller treatment for 12 weeks and did not

receive tiotropium. These participants were also followed-up for 3 weeks. Salbutamol was used as a rescue treatment as necessary.

Clinical characteristics and outcome measurement. Asthma monitoring devices (e-diaries with integrated peak flow meters; Smart Peak Flow; BMedical Pvt. Ltd.) were utilized for measurement of lung function. Demographic and clinical data were gathered from medical records.

The primary outcome was peak FEV₁ change from the baseline 3 h post-administration of tiotropium [FEV_{1(0-3 h)}]. Secondary outcomes were trough FEV₁ change from the baseline (10 min before next dose administration of tiotropium, i.e. at the dosing interval end), peak forced vital capacity (FVC) change from baseline 3 h post-administration [FVC_(0-3 h)], trough FVC change, mean ACQ-IA score and weekly mean rescue treatment usage, peak expiratory flow (PEF) and symptom-free days.

Other outcomes were mean forced expiratory flow (FEF) at 25-75% of FVC (FEF_{25-75%}) for every time-point (during the morning) during 12 weeks of treatment, peak FEV_{1(0-3 h)}, as well as trough of FEV change % and predicted response at week 12.

Respiratory system-associated adverse effects. Time to first asthma exacerbation (unusual increase in ≥ 1 asthma symptom for ≥ 2 days and/or $\geq 30\%$ decrease in morning PEF for ≥ 2 days) and first severe exacerbation (asthma deterioration requiring systemic CS therapy for ≥ 3 days) were recorded. All outcome measures were evaluated in the morning (unless required to monitor in the evening) using spirometry lung function measurements. The same method was used in both centers at which the patients enrolled. Adverse and side effects were noted for 30 days following final administration of tiotropium for assessment of safety.

Statistical analysis. Categorical variables are expressed as frequency (%) and continuous variables are expressed as the mean \pm standard deviation (mean of 3 repeats). Distribution of continuous and ordinal data were checked for normality using Kolmogorov-Smirnov test. Mann-Whitney U-test was used for non-normal data. The Student's t-test (Unpaired test for between groups and paired test for within groups) was used for continuous and ordinal variables and χ^2 -test was used for categorical variables for statistical analysis. Analysis of all data was performed using IBM SPSS Statistics (version 21.0; IBM Corp.). P<0.05 was considered to indicate a statistically significant difference. Dunnett's multiple comparisons test was used for post hoc analysis; q>2.233 was considered to indicate significance.

Results

Study population. In this study, 144 children were enrolled in the Department of Pediatrics of the First Affiliated Hospital of Xinjiang Medical University (Urumqi, China), and the First People's Hospital of Kashi (Kashi, China) from February 12, 2017, to August 16, 2019. Among these children, 72 were in the tiotropium therapy group (treatment group) and 72 in the control group (Fig. 1).

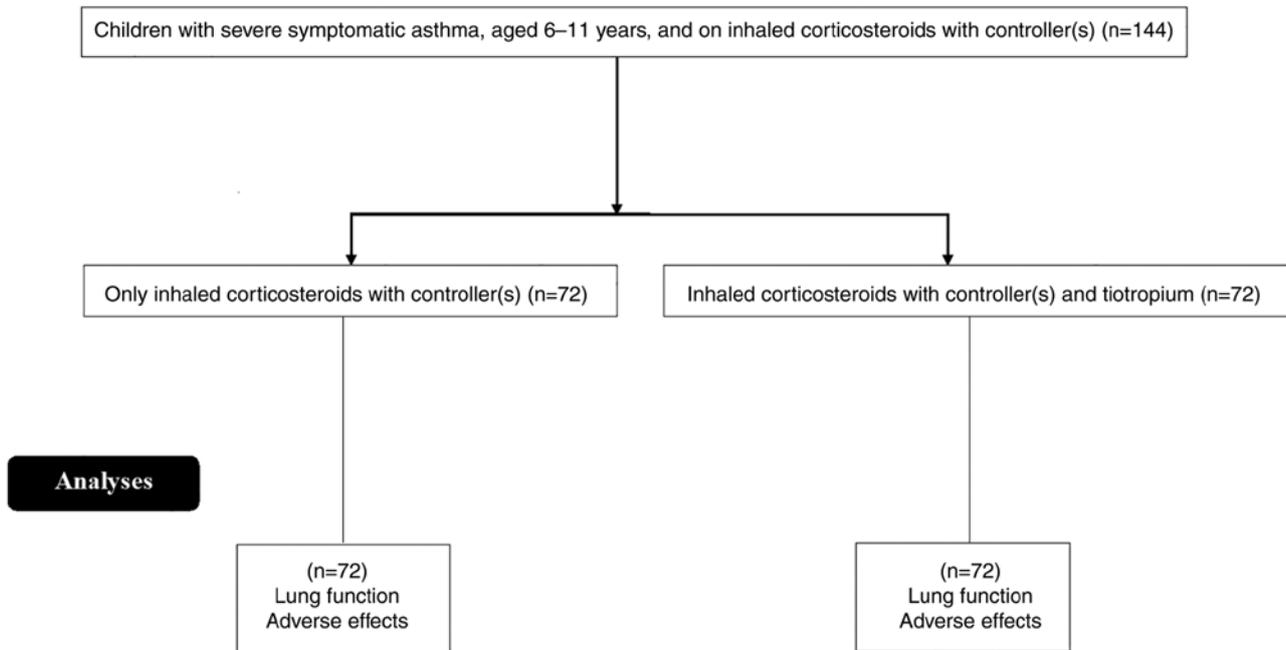


Figure 1. Flow chart of study.

Baseline characteristics. The demographic and clinical characteristics were not significantly different between the two groups (Table I). The majority of children were male (63%) and aged 9-11 years old (69%), with a mean age of 8.90 ± 1.80 years. All subjects in the treatment groups and control group started and ended the study at the same time.

Outcome measures. The primary outcome, $FEV_{1(0-3\text{ h})}$, was significantly improved at week 12 in the treatment group compared with that of the control group (Table II; $P < 0.0001$; df, 71; t-test). Regarding secondary outcomes, trough FEV_1 showed significant improvement with tiotropium compared with control group (Table II; $P < 0.0001$; df, 71; t-test). Moreover, significant differences were noted for peak $FVC_{(0-3\text{ h})}$ (Table II; $P < 0.0001$; df, 71; t-test), as well as trough FVC (Table II; $P = 0.0051$; df, 71; t-test) at week 12 between the treatment group and control group. ACQ-IA scores demonstrated similar improvement in asthma control [decreased from baseline in both groups (Table II; $P < 0.0001$; Mann-Whitney U-test)] with significant differences between treatment group and control group at week 12 (Table II; $P = 0.1159$; Mann-Whitney U-test). The mean weekly rescue treatment usage, PEF measurement and symptom-free days (Table II; all $P < 0.0001$; all df, 71; t-test) showed significant improvements in treatment group compared with control group.

$FEF_{25-75\%}$ showed significant improvement in the treatment group compared with control group at week 12 (Table II; $P < 0.0001$; df, 71; t-test). At week 12, peak $FVC_{(0-3\text{ h})}$ % predicted response and trough FEV_1 % predicted response (Table II; both $P < 0.0001$; both df, 71; t-test), were statistically different between the two groups.

Respiratory system-associated adverse effects. A total of 3 children (4%) in the treatment group and 4 children (6%) in

the control group experienced severe exacerbation of asthma during the study period ($P = 0.6984$; df, 1; χ^2 -test). During the study period, ≥ 1 episode of exacerbation was seen in 17 children (24%) in the treatment group and 23 children (32%) in the control group ($P = 0.3522$; df, 1; χ^2 -test) (data not shown).

Side effects. The number of children reporting side effects in the treatment group ($n = 30$; 42%) was less than that in the control group ($n = 35$; 49%; Table III). The number of serious side effects requiring hospitalization was 2 (3%; asthma and respiratory tract infection) in the treatment group and 1 (1%; asthma) in the control group, which was comparable between the groups. There was no discontinuation of treatment and no fatal events occurred in either group. Side effects on the cardiovascular and digestive systems in the treatment group were not reported.

Discussion

In the present prospective study enrolling 6-11-year-old children with severe and mild asthma, tiotropium ($5\ \mu\text{g}$) add-on to ICS with ≥ 1 controller treatment demonstrated improvement in lung function. Significant improvement in peak $FEV_{1(0-3\text{ h})}$ primary outcome was observed in the treatment group compared with the control. The secondary outcomes, such as trough FEV_1 change, peak $FEV_{1(0-3\text{ h})}$ % predicted response and trough FEV_1 % predicted response, as well as $FEF_{25-75\%}$, showed significant statistical differences between the two groups (all $P < 0.0001$). Children who received tiotropium add-on to ICS with ≥ 1 controller treatment showed notable efficacy profiles for the management of asthma. The positive effect of tiotropium as an add-on therapy to ICS was shown in clinical trials performed in adults and children by Kerstjens *et al* (14) and Hamelmann *et al* (15), respectively. The United States Food and Drug Administration has approved

Table I. Baseline demographic and clinical characteristics.

| Characteristic | Group | | P-value | 95% CI | Df |
|--|---------------------------------|-------------------------|------------------------------|----------------------|-----|
| | Treatment group (5 µg; n=72) | Control group (n=72) | | | |
| Median age (range), years | 9.30 (6.00-10.90) | 9.20 (6.00-11.00) | 0.2146 (Mann-Whitney U-test) | N/A | N/A |
| Age in years, n (%) | | | | | |
| 6-<9 | 21 (29) | 24.00 (33.00) | 0.7192 (χ^2 -test) | 0.6281 to 1.3070 | 1 |
| 9-11 | 51 (71) | 48.00 (67.00) | | | |
| Sex, n (%) | | | | | |
| Male | 46 (64) | 45.00 (63.00) | 0.6828 (χ^2 -test) | 0.7323 to 1.4500 | 1 |
| Female | 26 (36) | 27.00 (37.00) | | | |
| Body mass index, kg/m ² | 18.21±4.11 | 17.61±3.89 | 0.3698 (t-test) | -1.9180 to 0.7184 | 71 |
| Asthma duration, years | 5.11±2.48 | 4.92±2.32 | 0.6357 (t-test) | -0.9812 to 0.6012 | 71 |
| FEV ₁ , ml | 1584.00±366.00 | 1546.00±348.00 | 0.5242 (t-test) | -155.6600 to 79.6570 | 71 |
| FEV ₁ , % predicted | 79.11±12.59 | 78.81±12.11 | 0.8843 (t-test) | -4.3700 to 3.7700 | 71 |
| FEV ₁ , % reversibility | 27.21±13.81 | 26.81±13.91 | 0.8628 (t-test) | -4.9660 to 4.1660 | 71 |
| FVC, ml | 2081.00±483.00 | 2008.00±451.00 | 0.3502 (t-test) | -226.9500 to 80.9520 | 71 |
| FVC, % predicted | 91.69±14.61 | 90.10±13.81 | 0.5033 (t-test) | -6.2740 to 3.0940 | 71 |
| FEF _{25-75%} , l/s | 1.30±0.69 | 1.31±0.71 | 0.9318 (t-test) | -0.2207 to 0.2407 | 71 |
| FEF _{25-75%} , % predicted | 59.79±22.11 | 61.31±24.61 | 0.6972 (t-test) | -6.1870 to 9.2270 | 71 |
| Mean weekly evening PEF, l/min | 232.00±68.00 | 228.00±69.00 | 0.7266 (t-test) | -26.5690 to 18.5690 | 71 |
| Median ACQ-IA score (range) | 2.08 (1.55-2.62) | 2.14 (1.59-2.58) | 0.3903 (Mann-Whitney U-test) | N/A | N/A |
| ICS dosage, µg | 457.00±246.00 | 474.00±243.00 | 0.6772 (t-test) | -63.5560 to 97.5560 | 71 |
| Add-on maintenance treatment prior to study, n (%) | | | | | |
| LABA | 53 (74) | 54.00 (75) | 0.8487 (χ^2 -test) | 0.6680 to 1.3930 | 1 |
| LTRA | 61 (85) | 61.00 (85) | 0.9999 (χ^2 -test) | 0.6350 to 1.5750 | 1 |
| Add-on maintenance treatment during study, n (%) | | | | | |
| LABA | 51 (71) | 54 (75) | 0.7076 (χ^2 -test) | 0.6350 to 1.2810 | 1 |
| LTRA | 60 (83) | 61 (85) | 0.8201 (χ^2 -test) | 0.6178 to 1.4620 | 1 |

Df, degree of freedom; FEV₁, forced expiratory volume in 1 sec; FVC, peak forced vital capacity; FEF_{25-75%}, forced expiratory flow at 25-75% of peak forced vital capacity; PEF, peak expiratory flow; ACQ-IA, The Asthma Control Questionnaire-Interviewer-Administered; ICS, inhaled corticosteroid; LABA, long-acting β -agonist; LTRA, leukotriene receptor antagonist; N/A, not applicable.

tiotropium for children >6 years old with asthma. The present study observed children in China aged 6-11 years with severe and mild asthma treated with tiotropium add-on to standard therapy. The present study supports evidence from randomized trials in children and adolescents in demonstrating the safety and efficacy of tiotropium in severe asthma in a real-world setting (6,16).

The peak and trough FEV₁ change showed significant improvement following tiotropium treatment in children with severe and mild asthma. The outcomes of the present study are in line with those of randomized control trial conducted on children (9) and adolescents (15). However, the improvement of primary outcome is not in line with another study performed on adolescents (15). Here, tiotropium add-on to ICS with ≥ 1

controller treatment improved lung function of 6-11-year-old children with severe and mild asthma.

ACQ-IA score after 12 weeks was not improved among children who received tiotropium (treatment group) compared with the control group, but >70% of children in both groups demonstrated improvement compared with baseline. These results are in agreement with studies of children and adolescents (9,15). Although similar improvement in control of asthma in both groups was observed, the number of respiratory system-associated adverse events and side effects (asthma and PEF rate decrease) were found to be lower in the tiotropium group. The results of respiratory system-associated adverse events and side effects are in agreement with studies of children and adolescents (9,15). Tiotropium add-on to ICS with

Table II. Primary and secondary outcome measures at week 12.

| Outcome measure | Group | | P-value | 95% CI | Df |
|--|------------------------------|----------------------|---------|--------------------------|----|
| | Treatment group (5 µg; n=72) | Control group (n=72) | | | |
| Peak FEV _{1(0-3 h)} , ml | 384.00±31.00 | 248.00±28.00 | <0.0001 | -145.73000 to -126.20000 | 71 |
| Peak FEV _{1(0-3 h)} , % predicted | 17.40±7.30 | 11.50±5.80 | <0.0001 | -8.07200 to -3.72800 | 71 |
| Trough FEV ₁ , ml | 224.00±28.00 | 140.00±31.00 | <0.0001 | -93.73200 to -74.26800 | 71 |
| Trough FEV ₁ , % predicted | 9.30±4.20 | 5.80±3.40 | <0.0001 | -4.75900 to -2.24100 | 71 |
| Peak FVC _{1(0-3 h)} , ml | 268.00±34.00 | 241.00±32.00 | <0.0001 | -37.87700 to -16.12300 | 71 |
| Trough FVC, ml | 153.00±29.00 | 139.00±30.00 | 0.0051 | -23.72100 to -4.27900 | 71 |
| FEF _{25-75%} , ml/sec | 389.00±36.00 | 116.00±27.00 | <0.0001 | -283.48000 to -262.52000 | 71 |
| ACQ-IA score | 0.95±0.04 | 1.02±0.04 | <0.0001 | 0.05682 to 0.08318 | 71 |
| Mean weekly rescue treatment usage | 0.29±0.08 | 0.36±0.09 | <0.0001 | 0.04195 to 0.09805 | 71 |
| Mean weekly peak PEF (evening), l/min | 4.12±3.56 | 7.46±3.29 | <0.0001 | 2.21100 to 4.46900 | 71 |
| Mean weekly symptom-free days | 0.19±0.04 | 0.16±0.04 | <0.0001 | -0.04318 to -0.01682 | 71 |

Df, Degree of freedom; FEV_{1(0-3 h)}, forced expiratory volume in 1 sec change from the baseline 3 h post-administration; peak FVC_{1(0-3 h)}, peak forced vital capacity change from the baseline 3 h post-administration, FEF_{25-75%}, forced expiratory flow at 25-75% of peak FVC; ACQ-IA, Asthma Control Questionnaire-Interviewer-Administered; PEF, peak expiratory flow.

Table III. Side effects reported <30 days after last dosage administration.

| Side effect | Total (n=144) | Group | | P-value | 95% CI | Df |
|------------------------------------|---------------|------------------------------|----------------------|---------|---------------|----|
| | | Treatment group (5 µg; n=72) | Control group (n=72) | | | |
| Any, n (%) | 65 (45) | 30 (42) | 35 (49) | 0.5030 | 0.6214-1.2130 | 1 |
| Serious, n (%) | 3 (2) | 2 (3) | 1 (1) | 0.5596 | 0.5930-3.0410 | 1 |
| Asthma, n (%) | 27 (19) | 12 (17) | 15 (21) | 0.6694 | 0.5486-1.3690 | 1 |
| Decreased PEF rate, n (%) | 18 (13) | 8 (11) | 10 (14) | 0.8011 | 0.5076-1.5080 | 1 |
| Respiratory tract infection, n (%) | 10 (7) | 5 (7) | 5 (7) | 0.9999 | 0.5259-1.9020 | 1 |
| Nasopharyngitis, n (%) | 7 (5) | 3 (4) | 4 (6) | 0.6984 | 0.3559-2.0340 | 1 |
| Xerostomia, n (%) | 1 (1) | 1 (1) | 0 (0) | 0.3156 | 1.7080-2.3760 | 1 |
| Oropharyngeal candidiasis, n (%) | 2 (1) | 1 (1) | 1 (1) | 0.9999 | 0.2476-4.0390 | 1 |

Serious side effects were those requiring hospitalization. PEF, peak expiratory flow; CI, confidence interval; df, degree of freedom.

≥1 controller treatment demonstrated improvement in asthma control in 6-11-year-old children with severe and mild asthma.

Improvement of FEF_{25-75%} in the group treated with tiotropium add-on to ICS was statistically significant compared with control. FEF_{25-75%} associated with small airways and is a sensitive indicator of symptomatic asthma (13,17); the aforementioned improvement in FEV₁ showed the efficacy of tiotropium add-on to ICS with ≥1 controller treatment in 6-11-year-old children experiencing severe and mild symptomatic asthma.

Significant improvements were noted in peak FEV_{1(0-3 h)} and trough FVC changes. Moreover, the mean weekly rescue treatment usage, PEF and symptom-free days showed improvements in both groups with statistically significant differences. These results are in agreement with those of the randomized

trials in children (6,9,16). Children who received tiotropium add-on to ICS with ≥1 controller treatment showed comparable tolerability profiles.

The efficacy and safety parameters of ICS + tiotropium in contrast to ICS + LABA are available in other studies (14,18). In a randomized trial (14) on adult patients with moderate asthma, tiotropium showed comparable efficacy and tolerability to LABA (salmeterol). To the best of our knowledge, however, few studies have investigated the efficacy of ICS + LABA vs. ICS + anticholinergic drugs in children (9,15). Tiotropium add-on to ICS with ≥1 controller treatment appears to be efficacious and safe in severe and mild asthmatic children.

Poor adherence to treatment is one of the common issues in children that leads to poor asthma control (19,20). Administering asthma treatments once rather than twice per

day improves adherence (21). Once-daily tiotropium may be advantageous during step-wise approach of asthma therapy in children (age, 6-11 years) with severe and mild asthma (4), especially when LABA is ineffective or not suitable (22). Tiotropium add-on to ICS with ≥ 1 controller treatment has good adherence and efficacy in children with severe and mild asthma.

A limitation of the present study is the accuracy of treatment usage/adherence and recall bias. The present study was a multi-center observational study with a small sample size and the results are not generalizable. The short study period limited analysis of seasonal/severe exacerbation, asthma outcome and deterioration. Additionally, short duration and small sample size may overestimate effects of therapy (type-I error). Nonetheless, the present data support evidence from a randomized trial (6) in children and adolescents and demonstrate the safety and efficacy of tiotropium against severe and mild asthma in a real-world setting.

In conclusion, tiotropium (5 μ g) administered once/day as an add-on treatment to ICS with ≥ 1 controller treatment in children (age, 6-11 years) with severe or mild symptomatic asthma was found to be efficacious and safe. This treatment may have good adherence, improve lung function and improve asthma control in 6-11-year-old children with severe or mild asthma.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

AA and BWMEMYSF were project administrators, contributed equally to the acquisition of resources, as well as to the methodology design, conceptualization, literature review, visualization and validation of the study. PX contributed to the investigation, data curation, formal analysis and literature review, and drafted and edited the manuscript for intellectual content. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy. All authors have read and approved the final manuscript. AA, BWMEMYSF and PX confirm the authenticity of all the raw data.

Ethics approval and consent to participate

This was a prospective cohort study. The ethics committee of the Xinjiang Medical University approved the study (approval no. XMU1454; 11 February 2016) and the Helsinki Declaration (2008) guidelines were followed. Patient confidentiality was strictly maintained. Written informed consent was obtained from the parents/guardians of each patient.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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