

Original Article

Assessment of second-line treatments for patients with uncontrolled moderate asthma

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Abstracts: Aim: To evaluate the best second-line treatments for patients with uncontrolled moderate asthma. Methods: A single-center, random study was conducted in adult patients with uncontrolled moderate asthma to evaluate the effects of add-on treatments. After add-on treatments for 4 and 12 weeks, the concentration of exhaled nitric oxide (FeNO), average daily durnal peak expiratory flow (PEF) variability and asthma control test (ACT) score were measured. Results: 94 patients have been divided into three groups to take different add-on treatments, in tiotropium bromide group, montelukast sodium group and double-dose inhaled corticosteroid (ICS) group. After four weeks, most patients improved their symptoms and ACT scores, with lower concentration of FeNO and small PEF variability. In double-dose ICS group, almost all patients took the complete controls of asthma, compared to those in other two groups. After additional 12 weeks' therapy, patients in all three groups nearly achieved complete controls of asthma. There were two patients with pneumonia in double-dose ICS group. Patients in double-dose ICS group had higher ACT scores, lower concentrations of FeNO and smaller PEF variabilities, but a higher risk of pneumonia, compared to those in other two groups. The differences of PEF variabilities and ACT scores between tiotropium group and double-dose ICS group were not significant. Conclusion: Tiotropium in combination with ICS plus LABA showed the similar effects with double-dose ICS plus LABA, without adverse effects, which might be the best option for optimal control of asthma.

Keywords: Asthma, add-on treatments, long-acting muscarinic antagonist (LAMA), control

Introduction

Asthma affects an estimated 300 million individuals worldwide. It is a serious global health problem affecting all age groups, with increasing prevalence in China, rising treatment costs, and a rising burden for patients and the community. According to the guideline of the Global Initiative for Asthma (GINA), although the initial asthma presentations are recommended as soon as possible after the diagnosis of asthma is made, at least 50% of asthma patients still need stepping up asthma treatments even after 2 or 3 months therapy [1-5]. Medium dose inhaled corticosteroid (ICS), Leukotriene receptor antagonist (LTRA), or anti-IgE therapy are one of choices of stepping up asthma treatments.

Tiotropium bromide is an anticholinergic drug, categorized as a long-acting muscarinic antag-

onist (LAMA) or long-acting anticholinergic bronchodilator. These drugs are used primarily in the control of chronic obstructive pulmonary disease (COPD). Recently, LAMA is used for asthma patients poorly controlled with ICS and long-acting β_2 agonists (LABA) [6-10]. LAMA has the potential to improve asthma control by inducing bronchodilation, or inhibiting cholinergically-mediated bronchoconstriction, and with regular use inhibiting the airway smooth muscle hypertrophy and hyper-responsiveness characteristic of chronic asthma. It also reduces cholinergically-mediated mucus secretion and inhibits goblet cell hyperplasia and mucus gland hypertrophy, and moderates leukocyte responses in the lower airways as well as proinflammatory gene expression by airway smooth muscle and bronchial epithelium [11]. However, it is not clear which drug should be considered for add-on therapy in priority according to the guideline. The present study evaluated three

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strategies for stepping up asthma treatments, with LAMA, LTRA and double-dose ICS, in patients with uncontrolled asthma after initial 3-months therapy. To this end, we evaluated the concentration of exhaled nitric oxide (FeNO), measurement of average daily durnal peak expiratory flow (PEF) variability and asthma control test (ACT) score after add-on treatments for 4 and 12 weeks.

Material and methods

Study design

A single-center, random study was conducted in adult patients with uncontrolled asthma to evaluate the effects of add-on treatment with LAMA, LTRA and double-dose ICS. The Ethics Committee of West China Hospital, Sichuan University, approved the study, and all subjects gave written informed consent. 94 Uncontrolled asthmatic patients, all of whom were concurrently using inhaled salmeterol/fluticasone (Seretide, GlaxoSmithkline, UK, 50/250 µg twice daily) for more than 3 months at least, have been divided into three groups randomly to take the add-on treatment with tiotropium bromide (Tiotropium bromide powder for inhalation, Boehringer Ingelheim Pharma GmbH & Co. KG, GER, 18 µg once daily), montelukast sodium (Singulair, MSD, USA, 10 mg QN) and replaced salmeterol/fluticasone (Seretide, GlaxoSmithkline, UK, 50/500 µg twice daily). After add-on treatments for 4 and 12 weeks, the concentration of FeNO, average daily durnal PEF variability and ACT score were measured to evaluate the asthma control in these patients.

Subjects

Patients were diagnosed moderate asthma according to the Global Initiative for Asthma (GINA) 2014 [12]. Subject with moderate asthma had to fulfill the following criteria: daily symptoms; exacerbations that may affect activity and sleep; nocturnal symptoms more than once a week; daily use of inhaled short-acting β_2 -agonist; FEV₁ or PEF 60% to 80% predicted; and PEF or FEV₁ variability >30%. After diagnosis of asthma, patients inhaled salmeterol/fluticasone (Seretide, GlaxoSmithkline, UK, 50/250 µg twice daily) for more than 3 months at least. 94 patients with ACT score from 12 to 20, who can use inhalers correctly, have been enrolled in this study. Patients took the examinations of

concentration of FeNO, average daily durnal PEF variability and ACT score as described [13-15], then have been divided randomly into three groups and take differently add-on treatments.

Statistical analysis

All data are expressed as the mean \pm SEM. Statistical analyses were performed using SPSS 19.0 software. Statistical significance of FeNO was analyzed with Wilcoxon rank sum test. Statistical significance of average daily durnal PEF variability and ACT score were analyzed with one-way analysis of variance (ANOVA) followed by the Student-Newman-Keuls test to isolate significant difference. Chi-square test was also used. A *P* value less than 0.05 (two-tailed test) was considered statistically significant.

Results

94 patients have been divided into three groups to take different add-on treatments, in tiotropium bromide group, montelukast sodium group and double-dose ICS group. The patients' demographic characteristics are listed in **Table 1**.

The differences in age and gender among the three groups were not significant. Also the differences of PEF variability, concentration of FeNO and ACT score among three groups were not significant.

1st follow-up

94 patients in three groups have taken the different add-on treatments for 4 weeks, and then taken the examinations concentration of FeNO, average daily durnal PEF variability and ACT score to re-evaluate the patients' asthma control. After four weeks' add-on treatments, most patients improved their symptoms and ACT scores, with lower concentration of FeNO and small PEF variability. No patients discontinued the treatment because of adverse reactions. Data are listed in **Table 2**.

In double-dose ICS group, almost all patients took the complete controls of asthma after 4-weeks' additional treatments, with higher ACT scores, lower concentration of FeNO and smaller PEF variability, compared to those in other two groups. Patients in tiotropium group

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Table 1. Demographic characteristic of study subjects

	Tiotropium group (n=33)	Montelukast group (n=31)	Double-dose ICS group (n=30)
Age (year)	36.7±5.79	37.2±6.12	35.3±5.89
Gender (M/F)	18/15	16/15	16/14
PEF variability (%)	26.22±6.38	23.25±4.92	24.38±4.77
FeNO (bbp)	58.11±24.76	55.63±16.81	64.38±28.60
ACT	18.67±1.73	18.38±1.19	18.5±1.60

Data are presented as mean ± SEM. The differences in age and gender among the three groups were not significant. Also the differences of PEF variability, concentration of FeNO and ACT score among three groups were not significant.

Table 2. Data of 1st follow-up

	Tiotropium group (n=33)	Montelukast group (n=31)	Double-dose ICS group (n=30)
EF variability (%)	13.67±2.04	15.75±1.16 ^b	10.50±2.51 ^{b,c}
FeNO (bbp)	40.44±22.92	29.13±8.27 ^b	22.75±9.75 ^{b,c}
ACT	23.33±1.58	22.38±0.74 ^b	24.25±0.89 ^{b,c}

Data are presented as mean ± SEM. ^bP<0.05 compared with tiotropium group. ^cP<0.05 compared with montelukast group. In double-dose ICS group, almost all patients took the complete controls of asthma after 4-weeks' additional treatments, with higher ACT scores, lower concentration of FeNO and smaller PEF variability, compared to those in other two groups. Patients in tiotropium group had higher ACT scores and smaller PEF variability, while higher concentration of FeNO, compared to those in montelukast group.

Table 3. Data of 2nd follow-up

	Tiotropium group (n=33)	Montelukast group (n=31)	Double-dose ICS group (n=30)
PEF variability (%)	10.22±2.28	11.38±2.77 ^b	9.38±1.77 ^{a,c}
FeNO (bbp)	30.01±12.46	21.13±7.98 ^b	14.38±5.83 ^{b,c}
ACT	24.44±1.01	23.50±0.53 ^b	24.88±0.35 ^{a,c}

Data are presented as mean ± SEM. ^aP>0.05 compared with tiotropium group. ^bP<0.05 compared with tiotropium group. ^cP<0.05 compared with montelukast group. After additional 12 weeks' therapy, patients in all three groups nearly achieved complete controls of asthma. Patients in double-dose ICS group had higher ACT scores, lower concentrations of FeNO and smaller PEF variabilities, but a higher risk of pneumonia, compared to those in other two groups. The differences of PEF variabilities and ACT scores between tiotropium group and double-dose ICS group were not significant.

had higher ACT scores and smaller PEF variability, while higher concentration of FeNO, compared to those in montelukast group.

2nd follow-up

94 patients in three groups have continued the add-on treatments for 12 weeks, and then re-taken the examinations of concentrations of FeNO, average daily durnal PEF variabilities and

ACT score. After 12 weeks' add-on treatments, most patients improved their symptoms and ACT scores, with lower concentration of FeNO and small PEF variability. There were two patients with pneumonia in double-dose ICS group. No patients discontinued the treatment because of adverse reactions. Data are listed in **Table 3**.

After additional 12 weeks' therapy, patients in all three groups nearly achieved complete controls of asthma. Patients in double-dose ICS group had higher ACT scores, lower concentrations of FeNO and smaller PEF variabilities, but a higher risk of pneumonia, compared to those in other two groups. The differences of PEF variabilities and ACT scores between tiotropium group and double-dose ICS group were not significant.

Discussion

We demonstrated that almost all patients in the double-dose ICS group took the complete controls of asthma after 4-weeks' additional treatments. It means that double-dose ICS might be Tiotropium bromide might be superior to improve symptoms and lung function, but minor to eosinophils inflammation, compared to montelukast sodium. After additional 12 weeks' therapy, patients in all three groups nearly achieved complete controls of asthma. Patients in double-dose ICS group had a higher risk of pneumonia, compared to those in other two groups. Tiotropium had similar effects in PEF variability and ACT score compared to double-dose ICS.

Tiotropium might be a safe and efficient choice for asthma add-on treatment.

The GINA describes the long-term goals of asthma management as achievement of good control and minimization of future risk of exacerbation, airflow limitation, and effects [12]. For patients with moderate asthma who are symptomatic despite the both use of ICS and LABA, options are to further increase the dose of ICS

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or add further therapeutic treatments such as leukotriene modifier or antiimmunoglobulin E. However, these approaches do not benefit all patients and can be associated with additional side-effects, such as skin bruising, osteoporosis, cataracts, and anaphylactic reactions [16, 17]. Our study also showed that increased ICS could take the complete control of asthma quickly and efficiently with a higher risk of pneumonia. So it is a dilemma to find the best strategy for asthma stepping up treatment.

Tiotropium, a LAMA, is the bronchodilator of choice in symptomatic patients with chronic obstructive pulmonary disease, and has also showed potential as a controller of asthma. Findings from two replicate, 24-week, randomized active-comparator trials provide support for use of tiotropium in combination with ICS in patients with moderate symptomatic asthma [18]. In these phase 3, placebo-controlled trials of 2013 patients who were symptomatic despite use of medium-dose ICS (400-800 µg budesonide or equivalent), once-daily tiotropium, delivered via the Respimat Softmist inhaler as add-on therapy to a medium dose of ICS, reduced airflow obstruction and improved asthma control. The beneficial bronchodilator response was an increase in peak forced expiratory volume in 1 s (FEV_1) of 185 ml (95% CI 146-223) for patients receiving 5 µg tiotropium, and 223 ml (95% CI 185-262), compared with 196 ml (95% CI 158-234) for patients given salmeterol. Additionally, it was reported that significant improvements in symptom scores measured by the seven-question Asthma Control Questionnaire (ACQ-7) versus placebo. A meta-analysis that included previous studies showed that compared with a placebo or a double dose of ICS, the addition of tiotropium increased mean trough and FEV_1 by 97 ml and 103 ml (95% CI 71-122) and 103 ml (95% CI 42-163), respectively in five studies involving 1635 patients [19]. Tiotropium also reduced the risk of acute exacerbation (OR 0.73, 95% CI 0.56-0.96) and improved ACQ-7 score significantly by 0.10 (95% CI 0.04-0.16). Although clinical studies have supported the use of LAMAs in the treatment of asthma, it is not clear when LAMAs should be added to the treatment of asthma. Therefore, we performed this study for a head-to-head comparison of various second-line medications commonly used by physicians. In our study, double-dose ICS was the first add-on treatment with the complete control of asthma.

It might be the first choice for add-on treatment for patients with moderately or severely uncontrolled asthma. But long-term use of high-dose ICS had a risk of pneumonia or lung infection. Tiotropium showed the secondary effects for add-on treatments, compared to LTRA. Furthermore, it showed almost similar effects in PEF variability and ACT score after 12 weeks' treatment compared to double-dose ICS. But it had less effects on FeNO, a symbol of eosinophils inflammation in the respiratory tract of patients with asthma, compared to LTRA and double-dose ICS. Because of its rapid improvements of lung function and symptoms and less adverse effects, it might be superior to add-on treatments for asthmatic patients.

Conclusions

The data presented herein concluded that double-dose ICS, tiotropium and montelukast could improve uncontrolled asthmatic patients' lung function, symptoms and FeNO concentration. Among the 3 second-line treatments, double-dose ICS plus LABA was the most efficient to take the complete control of asthma for stepping up treatments, while having the risk of pneumonia or lung infections. Tiotropium in combination with ICS plus LABA showed the similar effects with double-dose ICS plus LABA, without adverse effects, which might be the best option for optimal control of asthma.

Disclosure of conflict of interest

None.

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