A multicenter, prospective, observational study on montelukast monotherapy or montelukast-based combinations treating cough variant asthma

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Background: Evidence of treatment against cough variant asthma (CVA) is insufficient for the clinical practice in China. We aimed at evaluating the real-world effectiveness of montelukast (MONT) alone or in combination with low-dose inhaled corticosteroids (ICS) and low-dose ICS plus long-acting beta-2-agonists (LABA) for Chinese CVA patients in a multicentre, prospective, cohort study.

Methods: Adult patients diagnosed with CVA defined as chronic cough >8 weeks with a positive bronchial provocation test and normal chest X-ray findings were enrolled at respiratory clinics. Study treatment followed routine clinical practice. The investigators initiated MONT by 10 mg/day alone or in combination with a low-dose ICS +/− LABA and followed up treatment outcomes for 4 weeks. The primary outcome measure was the change in cough score (CS) from baseline.

Results: The study enrolled 247 patients (MONT =146, MONT + ICS =38, MONT + ICS/LABA =63). In the primary analysis, the mean change (95% CI) in CS at the end of the study was −1.2 (−1.6, −0.9), −0.9 (−1.5, −0.4), and −1.3 (−1.7, −0.8) in the three groups, respectively. MONT monotherapy had a satisfactory rate of weekly asthma control at the end of the study (83.5%, 95% CI: 75.1%, 89.4%) in the per-protocol analysis. Rates of weekly asthma control were similar in two MONT-based combination regimens (83.9%, 81.4%). Short-acting beta-2-agonist (SABA) user (≥2 times per week) was 16.8% in the MONT group.

Conclusions: The real-world effectiveness of MONT alone or in combination with ICS or ICS and LABA was acceptable for CVA short-term control.

Introduction

Cough variant asthma (CVA) is atypical with cough as the predominant symptom and normal pulmonary function associated with airway hyperresponsiveness (1). CVA shares several pathophysiological features with classical asthma (CA) (2-5). The prevalence of CVA is 5–6% in children but unclear in adults (6,7). CVA represents one of the most common causes of chronic cough, accounting for 24–35% of patients in western countries (8,9), 42% in Japan (10) and 32.6% in China (11).

The disease nature of CVA varies. Some patients may progress to CA, whereas others may resolve cough without long-term treatment (6). Inhaled corticosteroids (ICS) is the standard treatment to initiate among CVA patients (4,5,12-14). Cysteinyl leukotriene receptor (CysLTR) antagonists (LTRA) such as montelukast (MONT) or zafirlukast are effective alternative to ICS for CVA (15,16). The Global Initiative for Asthma (GINA) recommended a stepwise algorithm for the long-term asthma control commencing with as-needed low-dose ICS-formoterol or low-dose ICS taken with SABA (controller medication) for symptoms control against mild asthma (17). A step-up by using daily low-dose ICS or LTRA and adding long-acting beta-2-agonists (LABA) or LTRA to ICS, or ICS dose up-titration, is considered if there were uncontrolled symptoms or exacerbations within 2–3 months or any clinical emergency due to exacerbations.

Some evidence showed that CVA causes more psychological and social burdens (12,18) and maybe more challenging to manage than mild CA (19). Small studies examined LTRA as monotherapy treating CVA for 2–4 weeks. Cough and life quality indexes improved significantly with anti-inflammatory effects (15,16,20,21). Treating CVA as severe asthma has also been proposed and investigated (18,22). Nevertheless, this investigation aimed at addressing CVA-associated psychological burdens. China's 2009 guideline supported LTRA use for CVA but did not specify its treatment algorithm (23). Local clinical practice prescribes less ICS and favours non-steroid medicines for asthma control (24), similarly to other Asian countries (25).

Therefore, we aimed to evaluate the effectiveness of MONT monotherapy or in combination with low-dose ICS +/– LABA for short-term CVA control for Chinese patients in the real-world clinical setting. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-1898).

Methods

Study design and setting

This was a multicentre, prospective, observational cohort study (MK-0476-916) in China to evaluate the effectiveness of MONT as monotherapy or in combination with low-dose ICS or low-dose ICS and LABA for CVA in the real-world clinical setting. The enrollment commenced in December 2015 and ended in March 2018 at respiratory clinics from 16 tertiary hospitals. The study followed the routine clinical practice of CVA short-term control. The investigator specialised in respiratory medicine assessed and decided if the patient was appropriate for MONT alone or MONT-based combination therapy and followed up the patient for 4 weeks after the treatment initiation. Merck Sharp & Dohme (MSD) China designed and sponsored the study and analysed the data. The study was approved by the independent ethics committee of all study sites (approval no. 2015-109) and conducted following the guidelines of the International Conference on Harmonization and Good Pharmacoepidemiology Practice (GPP), the Declaration of Helsinki (as revised in 2013) and local regulatory guidance.

Participants

Patients were eligible if they were Chinese aged 18 years or above, had confirmed CVA defined as chronic cough >8 weeks with a positive bronchial challenge test and normal chest X-ray findings and normal spirometry, and indicated for MONT treatment as the investigator's discretions. Patients were excluded if they had impaired pulmonary function as measured by spirometry [forced expiratory volume in 1 second (FEV1)/(forced vital capacity (FVC) <70%], had been smoking >10 pack-years, had other diseases causing

chronic cough [e.g., bronchitis, lung cancer, left ventricular dysfunction, psychologic or angiotensin-converting enzyme (ACE) inhibitor-induced cough], had received any therapy for CVA within 28 days before the study inclusion (e.g., ICS, LABA, theophylline, or a LTRA other than MONT), or were pregnant or breastfeeding. All patients provided written informed consent before study screening.

Study procedure and assessments

The investigator screened patients based on findings from medical history and laboratory and radiological assessments at the initial study visit (baseline). The investigator decided the treatment option against the patient's cough symptoms and comorbidities, including allergic rhinitis. As in normal clinical practice, the investigator and the patient were both aware of the treatment scheme allocated. The patient used a paper-formed diary to record the severity of cough, SABA use (in every 12 hours), and change or discontinuation of study medications for 4 weeks. The investigator reviewed diary information and assessed the patient every 1 or 2 weeks for treatment effectiveness. Also, the patient was instructed to complete the self-administered Leicester Cough Questionnaire (LCQ) at the site every 2 weeks. Fractional exhaled nitric oxide (FeNO) and sputum eosinophil counts were done at the initial visit and the end of the study for patients who were willing to accept. The patient may discontinue by consent withdrawal or based on the investigator's decision and was not allowed to re-enroll.

Cough score (CS) and LCQ

CS is a verified tool recommended by Chinese Guideline (23) for diagnosis and treatment of cough to measure cough-specific symptoms. This scoring system reflects cough frequency and influence on life quality by a simple and quantifiable index (grades 0–3) for daytime, nighttime and daily total (Table S1). The local clinical practice considers 25% of CS reduction as clinically significant.

LCQ is a 19-item self-administered quality of life measure of chronic cough which is responsive to change (26). Before the study execution, LCQ was translated into Chinese language and validated for its accuracy for CVA patients.

Exposure and outcome measures

MONT was initiated at 10 mg daily as monotherapy or in combination with low-dose ICS (included beclomethasone 100–200 mg, budesonide 200–400 mg or another ICS as appropriate) or low-dose ICS and LABA (i.e., fixed-dose formulations of budesonide/formoterol). The investigator may adjust the regimen to achieve asthma control. The extent of exposure by counting daily doses was not documented.

Treatment outcome was primarily measured as changes in CS at the end of each week from baseline and the proportion of patients who had a reduction in CS >25% at the end of each week from baseline. Weekly asthma control, as a real-world effectiveness outcome, was defined, if the patient met all following criteria at each week: (I) no more than 2 days of daytime cough (CS >1); (II) no any night sleep disturbance by cough (CS >1); (III) no changes in observed treatment regimen; and (IV) no significant SABA use (≥2 times) (17). Secondary analyses were performed to assess cough-free days and nights (CS =0), the patient's LCQ, and SABA user (if weekly SABA ≥2 times).

Statistical analysis

Sample size consideration

The sample size was calculated by achieving the precision of estimation [two-sided 95% confidence interval (CI)] by 5% of the mean change in CS at the end of the study from baseline by MONT alone or two MONT-based combinations. Literature has suggested such mean (SD) changes are 1.5 (0.4), 2.5 (0.4), respectively (27,28). Therefore, a sample size of 112 achieved a two-sided precision of 0.075 of the point estimate for the monotherapy group; a sample size of 42 achieved a two-sided precision of 0.125 of the point estimate for each of the two combination groups. Assuming 20% of patients who had premature discontinuation, a total sample size of 240 patients (MONT monotherapy: 140, MONT + ICS: 50, and MONT + ICS/LABA: 50, respectively) were planned for the study.

Analysis population

The efficacy analysis population included patients who had at least one dose of MONT and any post-baseline study observations. Two analysis subsets were defined to include and analyze patients who had CS since the baseline visit. The CS evaluable population included patients who received at least one dose of MONT and documented CSs >2 days in the first week of the study. The CS per protocol population included patients who received at least one dose of MONT, had no change in treatment regimen

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and recorded CSs >2 days in each week during the study. Outcome measures including CS and weekly asthma control were analyzed in the CS evaluable and the CS per protocol populations.

Analysis of endpoints

Changes in CS from baseline were calculated as CS at the end of each week minus that at the baseline. Mean (SD) and corresponding 95% CIs were given under t-distribution of the sample. The mean change in CS from baseline was considered statistically significant if its 95% CI does not contain 0. Total CS reduction (>25%) and weekly asthma control were presented as the number and percentage. Corresponding 95% CI for the proportion was estimated based on exact (Clopper-Pearson) method. For the primary analysis of CS changes, a between-group statistical comparison was not made, which avoided producing potential incorrect statistical conclusion favouring one particular treatment group. A *post-hoc* Chi-square test was made to compare asthma control between MONT alone versus MONT-based combination (pooled by two combination groups). Baseline CS was defined as the CS collected on the date of the initial visit. CS at the end of each week was defined as the last non-missing value in the week. If CS collected were ≤2 days in each week, the highest CS in the previous 7 days were carried forward to impute the missing data throughout the week. For patients who had change in treatment regimen, the highest CS in the previous 7 days were carried forward to all subsequent CS data points throughout the study. These patients were analysed in the original treatment exposure.

Secondary analyses are descriptive. The study created a multivariate logistic regression model to explore the association between asthma control at the end of the study and clinical characteristics. The model displays all selected variables with an adjusted odds ratio (OR) with corresponding 95% CI and P value by a Wald test. Statistical analyses were performed using SAS 9.4 and SAS JMP 13.0 (SAS Institute, Cary, NC, USA). P value of 0.05 was considered as statistically significant whenever applicable.

Results

Patients disposition and demographics characteristics

There were 247 patients enrolled (MONT =146, MONT + ICS =38, MONT+ ICS/LABA =63) and 197 patients

(79.8%) included in the study, among which 211 (85.4%) were in the CS evaluable population and 177 (71.7%) were in the CS per protocol population (*Figure 1*). The enrollment ended in March 2018 as there was no potential to enroll more patients in the MONT + ICS group. Among 146 patients in the MONT group, 120 completed the study procedures, and 26 discontinued prematurely (13 withdrew consent, 11 had lost-to-follow-up, and 2 were removed from the study by the investigator, respectively). The reasons for premature discontinuation in the MONT + ICS and MONT + ICS/LABA groups were similar to those in the MONT group. A total of 131 patients were assessed having efficacy-related data in the MONT group, but 103 patients were finally included in the CS per protocol population for analysis. Among 28 patients who did not meet the definition to enter the CS per protocol population, 14 had their treatment switched to combination therapies, 6 did not give complete CS diary; 4 had consent withdrawal during the treatment, 3 had LCQ data only, and 1 were removed by the investigator from the study. There were 33 and 54 patients who were assessed having efficacy-related data in the MONT + ICS and MONT + ICS/LABA groups, respectively; 31 and 43 were finally included in the CS per protocol population in these two groups.

Table 1 shows the patient's baseline characteristics. Patients were middle-aged adults (mean age 42.0–44.9 years) and most CVA patients were newly diagnosed (>85%). The proportion of patients with allergic rhinitis was higher in the MONT + ICS group [42.1% (16/38)]. Baseline CS presented as total, daytime, and nighttime did not differ significantly among the three treatment groups.

CS and asthma control

The mean change (95% CI) in total CS at the end of the study from baseline was –1.2 (–1.6, –0.9) in the MONT group, –0.9 (–1.5, –0.4), and –1.3 (–1.7, –0.8) in the MONT + ICS and MONT + ICS/LABA groups in the CS per protocol population. CS reductions were statistically significant among all groups (95% CIs do not include 0, *Figure 2*). The analysis in the CS evaluable population showed similar results. The frequency distribution of patients' total CS over time supported the trend in CS reduction over time (Figure S1).

In the CS per protocol population, the proportion of patients who had a CS reduction >25% from baseline at the end of the study [78.6% (81/103), 95% CI: 69.5%, 86.1%] was numerically higher than that at week 2 [67.0% (69/103),
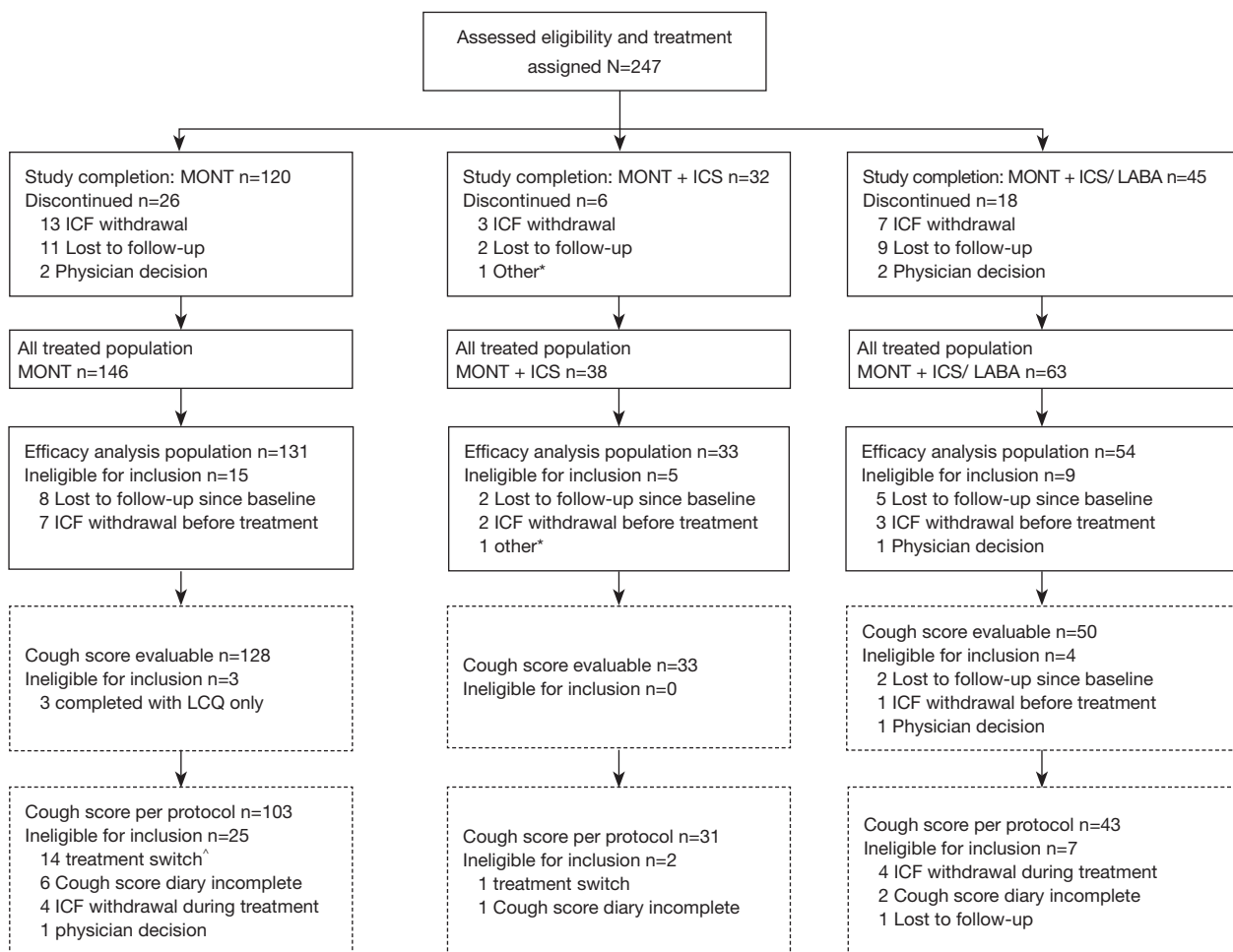
Figure 1 Study flow for enrolment and patient disposition. Patients may have been excluded from the analyses for more than one reason, but were counted in one outstanding reason leading to the exclusion. Patients were included in the study if diagnosed with cough variant asthma (cough >8 weeks with positive bronchial provocation test and normal chest X-ray) and had an indication for MONT treatment. Proportions of individual analysis populations in all treated patients (n=247): efficacy analysis population (218/247, 88.3%), cough score evaluable (211/247, 85.4%), and cough score per protocol (177/247, 71.7%). Efficacy analysis population included patients receiving at least one dose of MONT from whom any post-treatment efficacy data (cough score or LCQ) were available. *, 1 subject reported pregnancy and then discontinued treatment with no cough score or LCQ data; ^, treatment was switched from observed MONT monotherapy to ICS alone or ICS plus MONT. MONT, montelukast; ICF, informed consent form; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LCQ, Leicester cough questionnaire.

95% CI: 57.0%, 75.9%] in the MONT group (*Figure 3*); proportions of patients who had a CS reduction >25% from baseline were numerically comparable between the two combination groups at weeks 2 and 4 (*Figure 3*).

Table 2 presents weekly asthma control. In the CS per protocol population, the MONT group showed a moderate CVA control at weeks 1 and 2 [51.5% (53/103), 95% CI: 41.9%, 60.9%; 66.0% (68/103), 95% CI: 56.4%, 74.4%] and a markedly high rate of asthma control at the end of study [83.5% (86/103), 95% CI: 75.1%, 89.4%]. In

the CS evaluable population, analyses suggested a similar trend in the MONT group. The MONT + ICS group had rates of asthma control between 72.7% (24/33, 95% CI: 55.8%, 84.9%) and 83.9% (26/31, 95% CI: 67.4%, 92.9%) during the study in the two analysis populations, where rates in the MONT + ICS/LABA group were numerically lower. There was no significant difference in the rate of weekly asthma control between the MONT group and MONT-based combination in the two analysis populations.

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Table 1 Demographic and baseline characteristics

Characteristics	Monotherapy	Combination therapy		
	MONT (N=146)	MONT + ICS (N=38)	MONT + ICS/LABA (N=63)	Combination-pooled (N=101)
Age (years)	42.0 (13.4)	40.8 (13.1)	44.9 (13.9)	42 (13.6)
≤65	137 (93.8)	37 (97.4)	59 (93.7)	96 (95.0)
>65	8 (5.5)	1 (2.6)	4 (6.3)	5 (5.0)
Gender				
Female	98 (67.1)	23 (60.5)	36 (57.1)	59 (58.4)
Male	48 (32.9)	15 (39.5)	27 (42.9)	42 (41.6)
CVA diagnosis				
New	143 (97.9)	33 (86.8)	61 (96.8)	94 (93.1)
Recurrent	3 (2.1)	5 (13.2)	1 (1.6)	6 (5.9)
History of allergic rhinitis	42 (28.8)	16 (42.1)	12 (19.0)	28 (27.7)
AR with no treatment	38 (26.0)	16 (42.1)	12 (19.0)	28 (27.7)
AR with ongoing treatment	4 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)
Concurrent medical history	15 (10.3)	6 (15.8)	8 (12.7)	14 (13.9)
Respiratory disorders	1 (0.7)	1 (2.6)	2 (3.2)	3 (3.0)
Infections	3 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	1 (0.7)	1 (2.6)	1 (1.6)	2 (2.0)
Baseline cough score	2.3 (1.5)	1.9 (0.9)	2.5 (1.4)	2.3 (1.2)
Cough score—day	1.3 (0.8)	1.1 (0.5)	1.3 (0.7)	1.3 (0.7)
Cough score—night	1.0 (0.9)	0.8 (0.7)	1.1 (0.9)	1.0 (0.8)

Data are presented as mean (SD) or n (%). 1 subject did not report date of birth at the time of study inclusion, and another 1 subject was not accessed for CVA disease history in the MONT + ICS/LABA group due to insufficient information. MONT, montelukast; ICS, inhaled corticosteroid; LABA, long-acting beta 2 agonist; CVA, cough variant asthma.

Secondary analyses

As shown in *Table 3*, weekly cough-free days (3.4–3.6) and nights (4.5–4.8) remained consistent from week 2 in the MONT + ICS group and was the highest; whereas the MONT and MONT + ICS/LABA groups had numerically comparable cough-free days and nights. At week 4, cough-free days and nights were more than those at week 1 within the three treatment groups, respectively. As the 95% CIs for cough-free days and nights were overlapped between any two treatment groups at week 4, there was no statistical difference among three treatment groups for any between-group statistical comparison.

At week 1, the proportion of patients who had SABA ≥2 times a week was 16.8% (22/131, 95% CI: 10.8%, 24.3%), 5.6% (3/54, 95% CI: 1.2%, 15.4%) in the MONT and the MONT + ICS/LABA groups, respectively. SABA use decreased overtime during the 4-week observation. At week 4, the proportion of patients who had SABA ≥2 a week was 6.9% (9/131, 95% CI: 3.2%, 12.6%), 1.9% (1/54, 95% CI: 0.0%, 9.9%) in the MONT and the MONT + ICS/LABA groups, respectively. No patient used SABA ≥2 times in the MONT + ICS group during the study.

Also, there was an increase in LCQ scores over time in three treatment groups during the study. At week 4, the proportion of patients who had a reduction >1.3 in LCQ was 1.9% (2/106, 95% CI: 0.2%, 6.6%), 0.0% (0/32, 95% CI: 0.0%, 10.9%), and 6.7% (3/45, 95% CI: 1.4%, 18.3%), in the MONT, the MONT + ICS, and the MONT + ICS/LABA groups, respectively.
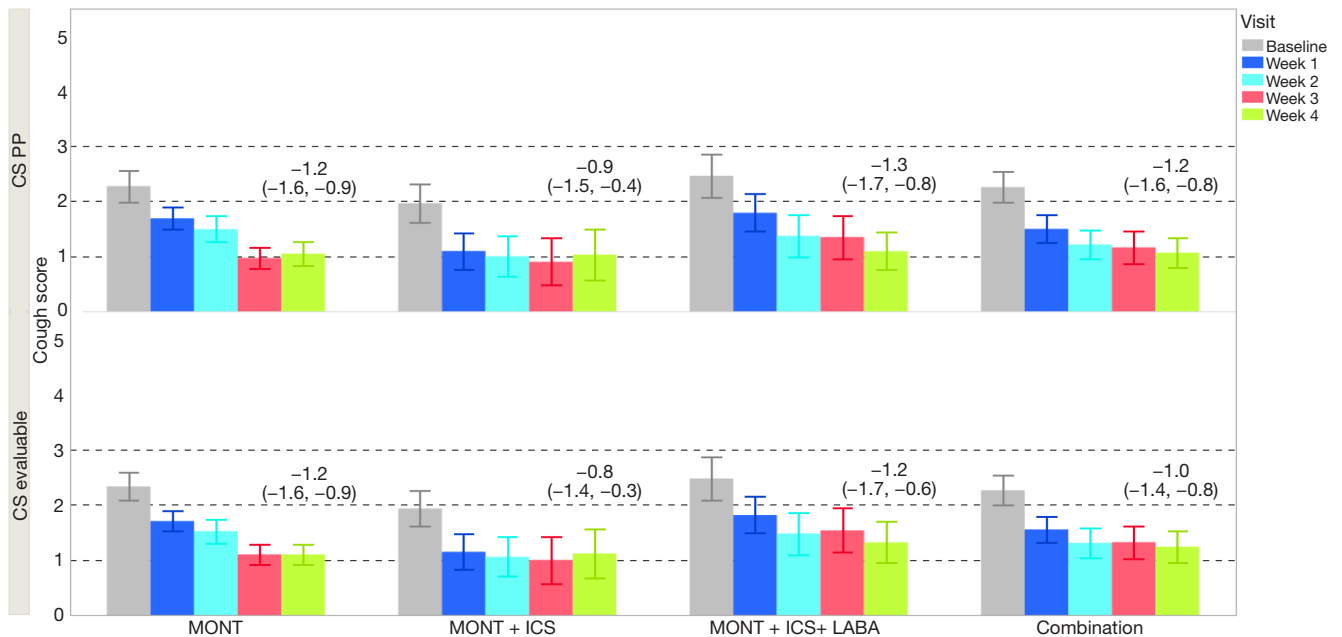
Figure 2 Changes of total cough scores over time (cough score evaluable/PP populations). Data are presented as mean (95% CI); cough score PP N=177; cough score evaluable N=211; total cough score by mean (95% CI) decreased from baseline to week 2, and baseline to week 4 (all 95% CIs confidence limits do not contain 0). MONT, montelukast; ICS, inhaled corticosteroid; LABA, long-acting beta 2 agonist; CS, cough score; PP, per protocol.
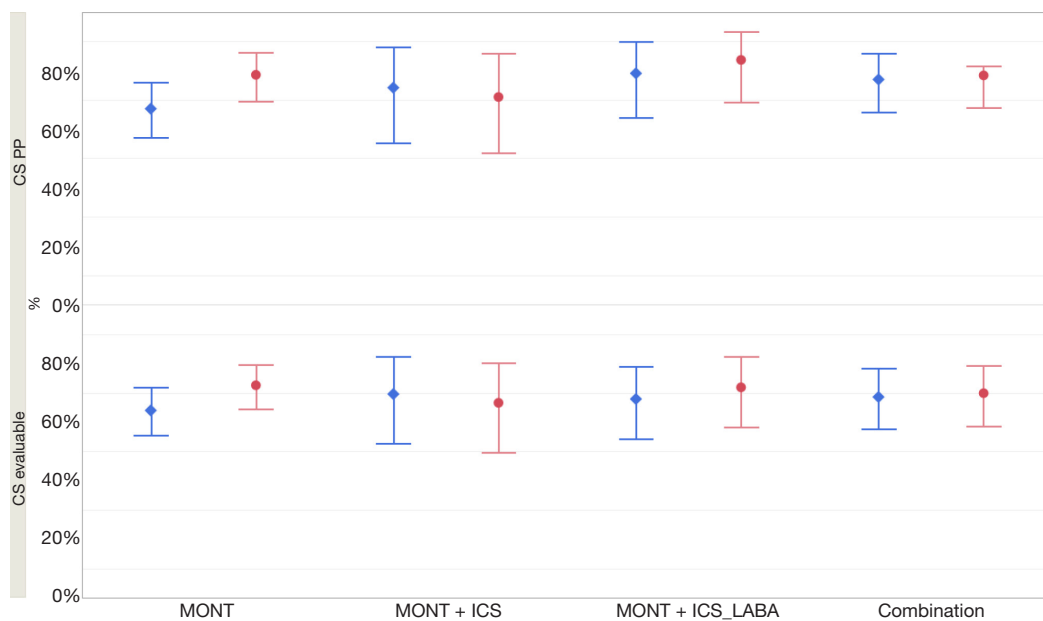

Figure 3 Proportions of patients who had a reduction of total cough score >25% over baseline (cough score evaluable/PP populations). Data are presented as percentage (point estimate) and 95% CI; cough score PP N=177; cough score evaluable N=211. MONT, montelukast; ICS, inhaled corticosteroid; LABA, long-acting beta 2 agonist; CS, cough score; PP, per protocol.

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Table 2 Proportions of patients who had asthma control over 4 weeks (cough score evaluable/PP populations)

Analysis population	Monotherapy		Combination therapy					
	MONT, n/N (%)	95% CI	MONT + ICS, n/N (%)	95% CI	MONT + ICS/LABA, n/N (%)	95% CI	Combination-pooled, n/N (%)	95% CI^
Cough score PP (N=177)								
Week 1	53/103 (51.5)	41.9, 60.9	23/31 (74.2)	56.8, 86.3	25/43 (58.1)	43.3, 71.6	48/74 (64.9)	53.5, 74.8
Week 2	68/103 (66.0)	56.4, 74.4	29/31 (93.5)	79.3, 98.2	29/43 (67.4)	52.5, 79.5	58/74 (78.4)	67.7, 86.2
Week 3	86/103 (83.5)	75.1, 89.4	26/31 (83.9)	67.4, 92.9	33/43 (76.7)	62.3, 86.8	59/74 (79.7)	69.2, 87.3
Week 4	86/103 (83.5)	75.1, 89.4	26/31 (83.9)	67.4, 92.9	35/43 (81.4)	67.4, 90.3	61/74 (82.4)	72.2, 89.4
Cough score evaluable (N=211)								
Week 1	63/128 (49.2)	53.1, 69.7	24/33 (72.7)	72.7, 95.2	28/50 (56.0)	52.2, 77.6	52/83 (62.7)	64.4, 82.8
Week 2	79/128 (61.7)	66.0, 81.0	29/33 (87.9)	62.3, 89.3	33/50 (66.0)	60.4, 84.1	62/83 (74.7)	65.7, 83.8
Week 3	95/128 (74.2)	66.0, 81.0	26/33 (78.8)	62.3, 89.3	37/50 (74.0)	64.8, 87.2	63/83 (75.9)	68.3, 85.8
Week 4	95/128 (74.2)	41.9, 60.9	26/33 (78.8)	56.8, 86.3	39/50 (78.0)	43.3, 71.6	65/83 (78.3)	53.5, 74.8

Patients who had the treatment change at a particular week (from MONT to MONT + ICS or MONT + ICS/LABA) were deemed as failed asthma control for the assigned treatment at the week and forwards. N = number of patients assigned in the treatment regimen; n = number of patients who had asthma control per week. ^, P = NS for all statistical comparisons between the MONT group and the pooled MONT-based combination group at each week in the two analysis populations. MONT, montelukast; ICS, inhaled corticosteroid; LABA, long-acting beta 2 agonist; PP, per protocol; CI, confidence interval.

Predictors for asthma control

Multivariate analysis on predictors for asthma control at the end of the study was performed in the CS evaluable population (*Table 4*). Adjusted for variables, treatment option (MONT *vs.* MONT-based combinations) was not a significant predictor for CVA control at the end of the study (OR: 0.97, 95% CI: 0.47, 1.98, P=0.94). Allergic rhinitis was inversely associated with asthma control at the end of the study (OR: 0.52, 95% CI: 0.25, 1.08, P=0.07). Early asthma control (at week 1) resulted in a 4.60-fold likelihood in achieving asthma control at the end of the study (OR: 4.60, 95% CI: 2.30, 9.64, P<0.0001).

Discussion

Despite global evidence on asthma control (29,30), clinical investigations on CVA are few and limited to small sample size (15,16,20,21,31-36). This study, however, had a relatively larger sample size to evaluate the short-term control of CVA by MONT-based regimens as initial treatment in the real-world practice. The study warranted CVA diagnosis by clinical, spirometric and radiological findings based on guideline-recommended criteria and differentiate comorbidities from CVA diagnosis. Study findings suggested that MONT alone or in combination with low-dose ICS or low-dose ICS plus LABA significantly reduced CS and had an improvement in asthma control and considerable cough-free days at the end of 4-week study observation.

Uncontrolled CVA interferes with sleep, physical, and social activities across all age groups. CVA was shown to cause higher depression levels compared with CA (18) and progress to CA (6,19). Cough control to destress patients and delink classic asthma is thus necessary. Studies have indicated that 1–2 weeks of therapy by bronchodilator, ICS (6) or MONT (15,16,20,21) improved cough symptoms. In this study, CS reduced remarkably since week 2 and most patients had CS reduction>25% at the end of the study in all treatment groups. Most short-term studies measured and compared cough on scale or scores (15,16,20,21). However, our study defined weekly asthma control using an approach to reflect a real-world clinical setting. MONT monotherapy exhibited an improvement in asthma control after three weeks of treatment. When adding confounding (treatment switch, SABA use, or missing CS) to weekly asthma control, rates of asthma control did not decrease dramatically. One interesting finding is that the triple therapy had a similar rate of weekly asthma control compared with MONT

Table 3 Secondary analysis results

Outcome measures	Monotherapy		Combination therapy					
	MONT	95% CI#	MONT + ICS	95% CI	MONT + ICS/LABA	95% CI	Combination-pooled	95% CI
Cough free (day/night) (N=177)^	9.1 (8.7)/13 (9.2)	(7.4, 10.8)/(11.2, 14.8)	12.0 (8.9)/17 (8.5)	(8.9, 15.1)/(14.0, 20.0)	8.1 (8.8)/11.0 (8.7)	(7.9, 8.3)/(8.4, 13.6)	9.8 (9.0)/13 (9.1)	(7.7, 11.9)/(10.9, 15.1)
Week 1	1.1 (1.9)/2.0 (2.3)	(0.7, 1.5)/(1.6, 2.4)	1.4 (1.9)/2.7 (2.4)	(0.7, 2.1)/(1.9, 3.5)	0.9 (1.7)/2.7 (2.4)	(0.4, 1.4)/(2.0, 3.4)	1.1 (1.8)/1.8 (2.2)	(0.7, 1.5)/(1.3, 2.3)
Week 2	2.0 (2.6)/3.1 (2.9)	(1.5, 2.5)/(2.5, 3.7)	3.4 (2.8)/4.8 (2.7)	(2.4, 4.4)/(3.9, 5.8)	1.8 (2.5)/2.6 (2.7)	(1.1, 2.5)/(1.8, 3.4)	2.5 (2.7)/3.5 (2.9)	(1.9, 3.1)/(2.8, 4.2)
Week 3	2.9 (2.9)/3.9 (3.0)	(2.3, 3.5)/(3.3, 4.5)	3.7 (2.8)/4.9 (2.7)	(2.7, 4.7)/(4.0, 5.9)	2.5 (3.0)/3.1 (3.1)	(1.6, 3.4)/(2.2, 4.0)	3.0 (2.9)/3.9 (3.0)	(2.3, 3.7)/(3.2, 4.6)
Week 4	3.1 (2.9)/4.2 (2.8)	(2.5, 3.7)/(3.7, 4.7)	3.6 (2.9)/4.5 (2.8)	(2.6, 4.6)/(3.5, 5.5)	2.8 (2.9)/3.9 (2.8)	(1.9, 3.7)/(3.1, 4.7)	3.2 (2.9)/4.1 (2.8)	(2.5, 3.9)/(3.5, 4.7)
SABA use ≥2 times/week*								
Week 1	22/131 (16.8)	10.8, 24.3	0/33 (0.0)	0.0, 10.6	3/54 (5.6)	1.2, 15.4	3/87 (3.4)	1.2, 9.7
Week 2	14/131 (10.7)	6.0, 17.3	0/33 (0.0)	0.0, 10.6	1/54 (1.9)	0.0, 9.9	1/87 (1.1)	0.2, 6.2
Week 3	10/131 (7.6)	3.7, 13.6	0/33 (0.0)	0.0, 10.6	2/54 (3.7)	0.5, 12.7	2/87 (2.3)	0.6, 8.0
Week 4	9/131 (6.9)	3.2, 12.6	0/33 (0.0)	0.0, 10.6	1/54 (1.9)	0.0, 9.9	1/87 (1.1)	0.2, 6.2
LCQ change (N=183)¶								
Week 2-reduction >1.3	4/106 (3.8)	1.0, 9.4	1/32 (3.1)	0.1, 16.2	4/45 (8.9)	2.5, 21.2	5/77 (6.5)	2.8, 14.3
Week 4-reduction >1.3	2/106 (1.9)	0.2, 6.6	0/32 (0.0)	0.0, 10.9	3/45 (6.7)	1.4, 18.3	3/77 (3.9)	1.3, 10.9
Baseline	13.2 (3.3)	12.6, 13.8	13.1 (3.2)	11.9, 14.2	12.7 (2.8)	11.9, 13.6	12.9 (3.0)	12.2, 13.6
Week 2	16.4 (3.0)	15.8, 17.0	17.2 (3.0)	16.1, 18.3	16.3 (3.1)	15.4, 17.2	16.7 (3.1)	16.0, 17.4
Week 4	17.8 (3.0)	17.2, 18.4	18.3 (2.8)	17.3, 19.3	17.6 (2.7)	16.8, 18.4	17.9 (2.8)	17.3, 18.5

N = number of patients assigned and treated in the treatment regimen; n = number of patients who had the analyzed event. ^, a cough free day (night) was defined as a day (night) when the patient had cough score =0; weeks 1 and 4 among all the treatment groups; a statistically significant difference in cough free nights between weeks 1 and 4 in the MONT group; *, the proportion of patients who had SABA twice or more per week was analyzed in the efficacy analysis population N=218; 1 patient had recorded 0 times of SABA; #, all 95% CIs for the rate was estimated based on exact (Clopper-Pearson) method; all 95% CIs for the mean was estimated under the t-distribution assumption; ¶, statistical significant differences in the LCQ change between weeks 1 and 4 among all treatment groups. MONT, montelukast; ICS, inhaled corticosteroid; LABA, long-acting beta 2 agonist; SABA, short-acting beta-2-agonist; LCQ, Leicester Cough Questionnaire; CI, confidence interval.

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Table 4 Multivariate analysis on predictors for asthma cough control at the end of the study observation (cough score evaluable)

Variable	Total (N=211)	N (%) of subjects (with asthma control at week 4)	Odds ratio[#] (adjusted)	95% CI[^]	P value[*]
Age (years)					
≤40	112	89 (79.5)	1.69	0.85, 3.43	0.14
>40	99	71 (71.7)	Ref.	–	
Gender					
Female	135	100 (74.1)	0.76	0.36, 1.55	0.45
Male	76	60 (78.9)	Ref.	–	
Allergic rhinitis					
Yes	66	46 (69.7)	0.52	0.25, 1.08	0.07
No	145	114 (78.6)	Ref.	–	
CVA diagnosis					
New	202	154 (76.2)	1.47	0.26, 7.10	0.64
Recurrent	9	6 (66.7)	Ref.	–	
Early asthma control[¶]					
Yes	115	101 (87.8)	4.60	2.30, 9.64	<0.0001
No	96	59 (61.5)	Ref.	–	
Treatment[§]					
MONT	128	95 (74.2)	0.97	0.47, 1.98	0.94
MONT-based combination	83	65 (78.3)	Ref.	–	

Data are presented as n (%), odds ratio, and corresponding 95% CIs. [#^], tests and confidence intervals on odds ratio are likelihood ratio-based; [*], P values were calculated by Wald test; [¶], early asthma control was defined as the patient who had asthma cough control at week 1; [§], MONT based combinations are MONT + ICS or MONT + ICS/LABA. MONT, montelukast; ICS, inhaled corticosteroid; LABA, long-acting beta 2 agonist; CVA, cough variant asthma; CI, confidence interval.

monotherapy. This finding differed from one Canadian study where add-on MONT to ICS/LABA was more effective among asthma patients with allergic rhinitis (37). In addition, MONT-based combinations did not show significantly better asthma control. One Japanese study proposed CVA treatment as severe CA to achieve symptom control (18) and thus, may favour combination therapies. In this study, however, the proportion of patients who had allergic rhinitis was higher in the MONT + ICS group, which may affect the effectiveness of the combination therapy. Also, current evidence indicates that the additive effect of LTRA is very limited to the effects of ICS combination treatment on CVA patients. Our findings merit further investigations.

As CS significantly decreased, approximately 3 or 4 cough-free days and nights have been noted after 2 weeks of treatment in all treatment groups. One study in the 1990s found that CVA patients were free of cough after a median follow-up of 28 months (12). Our results showed a promising trend to eliminate cough in the short term. LCQ analysis suggested an overall improvement in scores from three domains, which confirmed that addressing cough episodes destresses patients. MONT monotherapy had a higher proportion of SABA ≥2 times each week during the study. Patients may choose to self-administer more ICS or ICS/LABA as relief medications for cough and related stress as needed. The study did not collect complete treatment compliance. It is not clear if occasional dose titrations of ICS or ICS/LABA replaced SABA use for better symptom control. Finally, multivariate logistic regression suggested achieving early asthma control (week 1) was a strong predictor for asthma control at the end of the study. Clinical relevance of allergic rhinitis to CVA has been established by increasing eosinophilic lower airway inflammation (38).

Our results indicated that patients with allergic rhinitis were less likely to achieve asthma control at the end of the study, but this association is not statistically significant. A MONT-based combination did not result in a better chance of having asthma control at the end of the study.

This study has limitations. Firstly, this study did not randomise and compare treatments. Adding a placebo group to compare treatments is challenging in real-world clinical practice. The magnitude of treatment effectiveness as measured by CS cannot exclude the placebo effect. In addition, the investigator had a selection bias on the treatment regimen, and the patient had an assessment bias on the study's questionnaire. These biases may influence the study results. Secondly, the study was initially designed to assess the quantitative measures, including the CS and LCQ within four weeks. Long-term CVA control was not measured. Also, due to a difficulty in assessing drug accountability in a real-world setting, the extent of treatment compliance associated with the outcomes was not studied. Last, the generalizability of study results needs caution because treatment effectiveness may vary due to different symptom severity and outcome measures in real-world practice.

Conclusions

In conclusion, the effectiveness of MONT alone or in combination with ICS or ICS and LABA was acceptable for CVA short-term control in clinical practice.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the independent ethics committee of all study sites (approval no. 2015-109) and conducted following the guidelines of the International Conference on Harmonization and Good Pharmacoepidemiology Practice (GPP), the Declaration of Helsinki (as revised in 2013) and local regulatory guidance. All patients provided written informed consent before study screening.

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