

# Efficacy of Add-on Montelukast in Nonasthmatic Eosinophilic Bronchitis: The Additive Effect on Airway Inflammation, Cough and Life Quality

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## Abstract

**Background:** The efficacy of montelukast (MONT), a cysteinyl leukotriene receptor antagonist, in nonasthmatic eosinophilic bronchitis (NAEB), especially its influence on cough associated life quality is still indefinite. We evaluated the efficacy of MONT combined with budesonide (BUD) as compared to BUD monotherapy in improving life quality, suppressing airway eosinophilia and cough remission in NAEB.

**Methods:** A prospective, open-labeled, multicenter, randomized controlled trial was conducted. Patients with NAEB (aged 18-75 years) were randomized to inhaled BUD (200 µg, bid) or BUD plus oral MONT (10 µg, qn) for 4 weeks. Leicester cough questionnaire (LCQ) life quality scores, cough visual analog scale (CVAS) scores, eosinophil differential ratio (Eos), and eosinophil cationic protein (ECP) in induced sputum were monitored and compared.

**Results:** The control and MONT groups contained 33 and 32 patients, respectively, with similar baseline characteristics. Significant with-in group improvement in CVAS, LCQ scores, Eos, and ECP was observed in both groups during treatment. After 2-week treatment, add-on treatment of MONT was significantly more effective than BUD monotherapy for CVAS decrease and LCQ scores improvement (both  $P < 0.05$ ). Similar results were seen at 4-week assessment (both  $P < 0.05$ ). 4-week add-on therapy of MONT also resulted in a higher percentage of patients with normal sputum Eos ( $< 2.5\%$ ) and greater decrease of ECP (both  $P < 0.05$ ).

**Conclusions:** MONT combined with BUD was demonstrated cooperative effects in improvement of life quality, suppression of eosinophilic inflammation, and cough remission in patients with NAEB.

**Key words:** Budesonide; Cough; Quality of Life; Montelukast; Bronchitis

## INTRODUCTION

Nonasthmatic eosinophilic bronchitis (NAEB), which was first identified by Gibson *et al.* in 1989,<sup>[1]</sup> is one of the most frequent causes of chronic cough (7.2%–33.0%) in global adult non-smokers.<sup>[2-5]</sup> Recently, a prospective multicenter survey on causes of chronic cough in China showed the proportion of NAEB to be 17.2% of chronic cough patients.<sup>[6]</sup> It manifests as a corticosteroid-responsive chronic cough with airway eosinophilia which is similar to that seen in asthma. However, in contrast to asthma, there is no evidence of airway hyperresponsiveness (AHR) and variable airflow obstruction in NAEB.<sup>[7-9]</sup> The pathogenesis of NAEB is still not clearly understood. Clinical treatment of NAEB is aimed at controlling airway inflammation and relieving

cough. Inhaled corticosteroid (ICS) is suggested as a first-line therapy for NAEB.<sup>[7,10-12]</sup> Inhibition of cough is proved within 4 weeks of initiating therapy with ICS (800 µg/d) in the vast majority of cases,<sup>[3,13,14]</sup> although some patients may require oral corticosteroids or add-on antileukotrienes and antihistamines.<sup>[15-17]</sup>

Cysteinyl leukotrienes (cys-LTs) are important in the pathogenesis of allergic inflammation.<sup>[18-20]</sup> Up-regulation of cys-LTs is reported in the asthma, allergic rhinitis (AR), and NAEB.<sup>[20-24]</sup> In addition, proinflammatory pathway of cys-LTs is independent of those suppressed by corticosteroids.<sup>[18,20]</sup>

Montelukast (MONT) is a cys-LT type 1 receptor antagonist (LTRA), with the ability to inhibit eosinophilic inflammatory reaction of airway, reduce cys-LTs-induced expression of macrophage adhesion molecule-1 and migration of eosinophils,<sup>[25]</sup> inhibit LTD4 triggered proliferation and activation and also suppress, to different degrees, release of

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multiple inflammatory reaction mediators and cell factors such as interleukin-5 (IL-5), IL-13, vascular cell adhesion molecules, interferons, and LTD4.<sup>[26]</sup> Improvement of cough and prevention of exercise-induced bronchoconstriction was demonstrated with MONT in asthma.<sup>[27-30]</sup> Inclusion of MONT in NAEB treatment should be helpful to conferring addictive anti-inflammatory effects to ICS.

Little report on the efficacy of MONT for treating NAEB is at hand, unfortunately. A trial, performed by Cai *et al.*,<sup>[31]</sup> comparing the efficacy and tolerability of add-on therapy with MONT and double-dose ICS (800 µg/d) in NAEB had a conclusion of non-inferiority of add-on MONT in suppressing airway eosinophilia and decreasing cough severity. However, this finding was based on a single-center design and its relative small sample size ( $n = 26$ ). Cough visual analog scale (CVAS),<sup>[32,33]</sup> which was used in that trial, had not been psychometrically tested. Cough-specific health-related quality-of-life instruments (cough quality-of-life questionnaire and Leicester cough questionnaire [LCQ]) which have undergone extensive psychometric testing should be a better alternative choice.<sup>[34-37]</sup> In addition, it was impossible to decide whether 400 µg/d budesonide (BUD) monotherapy is effective enough to suppress airway eosinophilia and cough symptom in those patients, as lack of a control group of single-dose ICS (400 µg/d).

Accordingly, providing further clues in NAEB management, we aimed to undertake a prospective, open-labeled, multicenter, randomized controlled trial to evaluate the efficacy of MONT combined with single-dose BUD (400 µg/d) in the improvements of cough-specific health-related quality-of-life (LCQ scores), CVAS and airway eosinophilic inflammation (eosinophils [Eos] and eosinophil cationic protein [ECP] in induced sputum) in steroid-naïve NAEB patients, compared with single-dose BUD (400 µg/d). In addition, the inclusion of MONT plus double-dose BUD (800 µg/d) as a treatment group and double-dose BUD (800 µg/d) as a control group will be taken into consideration in future.

## METHODS

### Subjects

Determination of the sample size required was carried out on the basis of a retrospective analysis of outpatient cases, for which a reduction in CVAS assessment of 20 mm or greater was considered effective: The effectiveness of 2-week combined treatment with MONT and BUD was approximately 70%, while that of BUD alone was approximately 36%. Z-pooled normal approximation was employed to estimate the sample size required: For a level of significance ( $\alpha$ ) of 0.05 (two-sided test), a test power ( $1-\beta$ ) of 0.8,  $P_t = 0.70$ ,  $P_c = 0.36$ , and under the condition that  $N_t:N_c = 1$ , the sample size required was calculated to be 33 in the test group and 33 in the control group.

A multicenter, prospective, randomized, open-labeled, parallel-controlled study was performed in three hospitals in

Shanghai (Shanghai First People's Hospital, Shanghai Tongji Hospital, Shanghai Putuo People's Hospital). The study was approved by the Ethics Committee of these hospitals. Before starting any procedure, written informed consent was obtained from each patient after full explanation.

Patients who was 18–75 years and suffered from chronic cough persisting for longer than 8 weeks, and were newly diagnosed with steroid-naïve NAEB according to the Cough Diagnosis and Treatment Guidelines (2009) of the Society of Respiratory Diseases of the Chinese Medical Association<sup>[38]</sup> and the 2006 American College of Chest Physicians (ACCP) cough guidelines<sup>[12]</sup> were invited to for pre-study screening from May 2009 to December 2011 consecutively. Patients with occupational allergens or sensitizers' exposure, co-morbidity with AR and/or gastroesophageal reflux disease, and current smokers were excluded.

Briefly, following investigations were undertaken during the 2 weeks before randomization: Clinical history, physical examination, peripheral white blood cell differential counts, spirometry, methacholine provocation test and induced sputum eosinophil counts. All females of childbearing potential will be required to have a negative urine pregnancy test prior to any further study procedures.

The diagnosis criteria of NAEB were as follows: (1) Isolated chronic nonproductive cough lasting more than 8 weeks; (2) normal spirometry without AHR; (3)  $Eos \geq 2.5\%$  in induced sputum; (4) response to oral or inhaled glucocorticosteroids.<sup>[12,38]</sup>

A distinction must be made between NAEB, cough variant cough (CVA) and atopic cough (AC), which present with chronic cough and characterized by airway eosinophilia. The presence of sputum eosinophilia is a diagnostic criterion for NAEB, while it is only consistent with, but not diagnostic of CVA and AC. AHR is a cardinal feature of asthma, which is absent in NAEB and AC. Measurement of AHR is essential for the etiologic diagnosis of eosinophilic airway disorders associated with chronic cough. AC does not involve bronchoalveolar eosinophilia, has no evidence of airway remodeling, unlike CVA and NAEB.<sup>[12,38]</sup>

The exclusion criteria were as follows: (1) Presence of other acute or chronic pulmonary diseases; (2) previous upper respiratory tract infection within 8 weeks of enrollment in the study; (3) current smokers, or abstinence from smoking for <6 months; (4) medication with glucocorticoids and/or LTRA within 4 weeks of enrollment in the study; (5) use of LTRA or glucocorticoid drugs, other than MONT and BUD, during the treatment period; (6) use of antitussive drugs, bronchodilator, anti-histamine drugs or theophylline-based drugs during the treatment period.

Patients recruited successfully were randomized into the MONT/BUD group and BUD monotherapy group. Patients in the MONT/BUD group accepted oral MONT (Singulair®, Merck and Co., Hangzhou, China; 10 mg/tablet) 10 mg q.n plus inhaled BUD (Pulmicort Turbuhaler®, AstraZeneca,

Lund, Sweden; 100 µg/puff) 200 µg twice daily for 4 weeks. And patients in BUD group accepted inhaled BUD 200 µg twice daily for 4 weeks.

After inclusion, patients were assessed at three separate visits: Visit 1, before starting therapy; visit 2, 2 weeks after the start of therapy; visit 3, 4 weeks after the start of therapy [Figure 1]. At each visit, physical examination, clinical response assessments, and adherence to therapy were recorded.

### Assessment of efficacy

The co-primary endpoints were the CVAS and the LCQ scores during treatment. Secondary endpoints were in induced sputum Eos level and ECP.

### Cough visual analog scale assessment

At baseline, after 4-week and 8-week treatment, all subjects recorded severity of their cough by CVAS assessment, a 100 mm horizontal visual analog scale with 0 being no cough and 100 equaling to the worst cough ever. The efficacy of MONT in NAEB was evaluated on the basis of the decrease of CVAS scores, by between-timepoints and between-groups analyses.

### Leicester cough questionnaire assessment

Cough-related quality- of- life was measured using the LCQ, a self-administered 19-item questionnaire which is scored

on a 7-point Likert-type scale for each item. A higher score indicates better quality-of-life.<sup>[34]</sup> All subjects completed the LCQ assessments at baseline, after 4-week and 8-week treatment. The efficacy of MONT in NAEB was evaluated on the basis of the improvement of LCQ scores, by between-timepoints and between-groups analyses.

### Sputum induction and processing

Sputum induction was performed by inhalation of nebulized 4.5% hypertonic saline for 5 minutes via an ultrasonic nebulizer.<sup>[39]</sup> Cells were dispersed with dithiothreitol and filtered through nylon gauzes. The cell smear was stained with hematoxylin and eosin for differential count. The technician who was blinded to the grouping of the subjects counted at least 400 non-squamous cells for every specimen. Differential leukocyte counts were expressed as percentage of total inflammatory cells. The upper limit of the normal range for sputum eosinophils was 2.5%.<sup>[38,40]</sup>

Eosinophil cationic protein levels in the supernatant of sputum were measured by UniCAP fluoroenzyme immunoassay (Pharmacia Upjohn AB, Uppsala, Sweden), with a detection limit 0.5 µg/L.<sup>[41]</sup>

### Statistical analysis

Data normally distributed were expressed as mean ± standard deviation. Data with non-normally distribution were expressed as median and range. ECP was log-transformed. Continuous variables were compared between two groups using Mann–Whitney test. Categorical data were compared between two groups with contingency table analysis using Fisher’s exact test. Kruskal–Wallis test followed by Dunn’s multiple comparison test was used for between-timepoints analyses of CVAS, LCQ, sputum Eos and ECP. All statistical tests were two-sided, and significance was accepted at the 95% level ( $P < 0.05$ ). Statistical analyses were performed with GraphPad Prism for Mac (version 5; GraphPad Software Inc., San Diego, CA, USA).

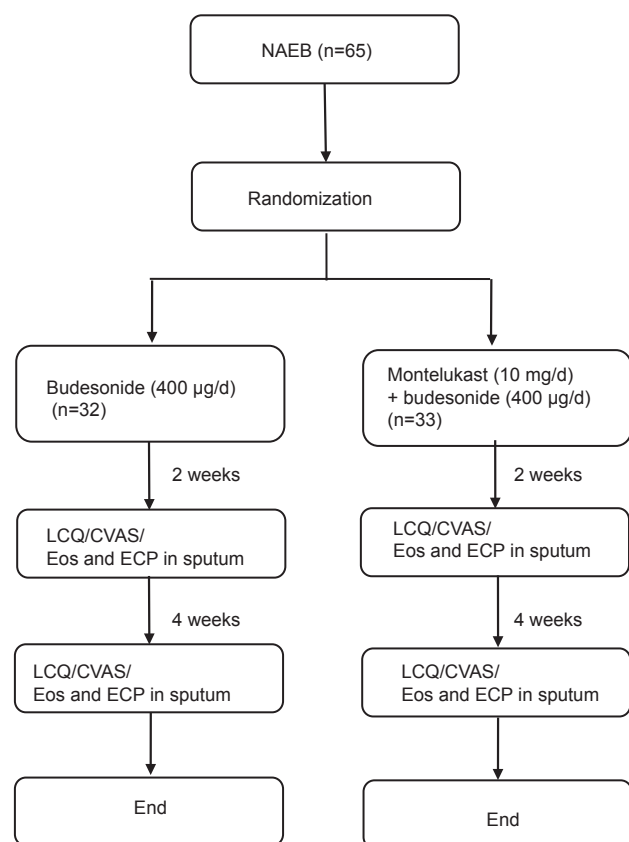
## RESULTS

### Patient characteristics

A total of patients were enrolled in this study, totally; 32 in the BUD group and 33 in the MONT/BUD group. Baseline characteristics of subjects analyzed ( $n = 65$ ) are presented in Table 1. The two groups were comparable in distributions of gender, age, smoking history, cough duration, CVAS scores, LCQ scores, eosinophils in blood and sputum, sputum ECP (log transformed), and spirometric measurements ( $P > 0.05$  for all variables). All patients tested negative for AHR.

### Cough visual analog scale assessment

As demonstrated in Figure 2, compared with those baseline values, CVAS scores at 2-week in both treatment groups were decreased substantially (for MONT/BUD group,  $47.88 \pm 19.49$  vs.  $21.82 \pm 13.10$ ,  $P < 0.001$ ; for BUD group,  $44.38 \pm 21.99$  vs.  $27.19 \pm 16.11$ ,  $P < 0.05$ ). Additional reduction was proved in analyzing CVAS scores at 4-week (for MONT/BUD group,  $8.49 \pm 11.76$ ; for BUD



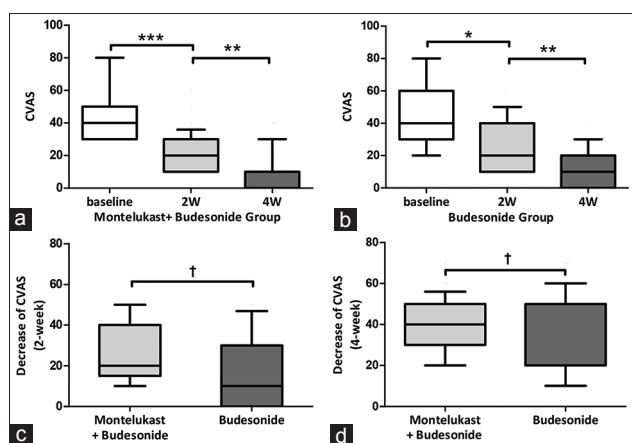
**Figure 1:** Flowchart summarizing the study protocol. Nonasthmatic eosinophilic bronchitis; leicester cough questionnaire; cough visual analogue scale; Eos: Eosinophil differential count in induced sputum; eosinophil cationic protein.

group,  $13.13 \pm 12.03$ , both  $P < 0.01$ , compared with CVAS of 2-week). In addition, after 2-week treatment, the decrease of CVAS was significantly different between MONT/BUD group and BUD group ( $26.06 \pm 13.91$  vs.  $17.19 \pm 17.64$ ;  $P = 0.0210$ ), which demonstrated add-on treatment of MONT was significantly more effective than BUD monotherapy

**Table 1: Comparison of patient demographics and other baseline characteristics**

Items	Budesonide/ montelukast ( <i>n</i> = 33)	Budesonide ( <i>n</i> = 32)	<i>P</i> *
Age, mean±SD, years	43.76 ± 9.65	48.34 ± 12.40	0.0548
Gender, female %	45.45	43.75	1.0000
Smoking history, %	27.27	28.13	1.0000
Cough duration, median (range), months	4 (2 - 309)	9 (2 - 165)	0.9788
Eos in blood, median (range), %	1.8 (0.3 - 8.9)	2.6 (0.3 - 7.6)	0.1066
FEV <sub>1</sub> %PRED, mean ± SD	93.66 ± 11.49	93.15 ± 9.84	0.8438
FEV <sub>1</sub> /FVC, mean±SD	85.69 ± 5.10	85.63 ± 4.59	0.9477
AHR	Negative	Negative	1.0000
CVAS, mean ± SD, mm	47.88 ± 19.49	44.38 ± 21.99	0.2505
LCQ scores, mean ± SD	67.70 ± 16.96	71.19 ± 19.55	0.2424
Eos in sputum, median (range), %	6.6 (3.9 - 58.1)	7.4 (3.5 - 33.4)	0.9895
ECP in supernatant of sputum, mean ± SD, log (µg/L)	2.32 ± 0.45	2.28 ± 0.46	0.7728

\*Comparison between the montelukast/budesonide and budesonide groups. There were no significant differences between the two groups for any of the variables. Continuous variables were compared using Mann-Whitney test, and categorical variables were compared with Fish's exact test. SD: Standard deviation, Eos: Eosinophil differential count in induced sputum; FEV<sub>1</sub>: Forced expiratory volume in 1 second, PRED: Predicted value; FVC: Forced vital capacity; AHR: Airway hyperresponsiveness; CVAS: Cough visual analogue scale; LCQ: Leicester cough questionnaire; ECP: Eosinophil cationic protein.



**Figure 2: Cough visual analog scale (CVAS).** Changes of CVAS during 4 weeks treatment in montelukast (MONT) budesonide (BUD) group (Panel A) and BUD group (Panel B); Effects of 2-weeks (Panel C) and 4-weeks (Panel D) add-on montelukast treatment on decrease of CVAS. Data are expressed as median (10–90% range). \* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ , compared using Kruskal-Wallis test followed by Dunn's multiple comparison test. † $P < 0.05$ , compared using Mann-Whitney test.

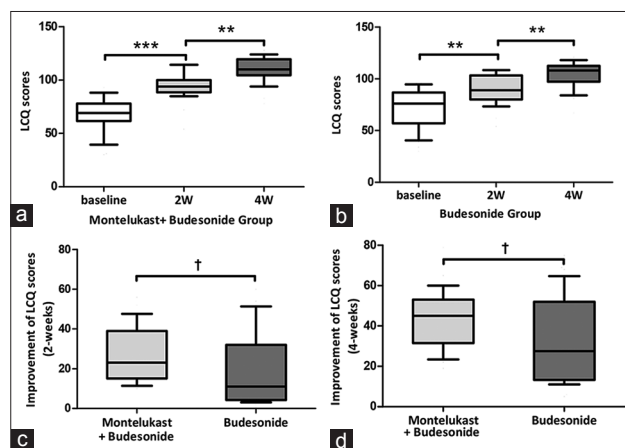
for cough symptom alleviation. Similar results were seen at 4-week ( $39.39 \pm 13.45$  vs.  $31.25 \pm 19.30$ ;  $P = 0.0415$ ).

### Leicester cough questionnaire assessment

As demonstrated in Figure 3, compared with those baseline values, LCQ scores in both groups were increased substantially after 2-week treatment (for MONT/BUD group,  $67.70 \pm 16.96$  vs.  $95.06 \pm 12.87$ ,  $P < 0.001$ ; for BUD group,  $71.19 \pm 19.55$  vs.  $90.25 \pm 14.84$ ,  $P < 0.01$ ). Additional improvement was proved in analyzing LCQ scores at 4-week (for MONT/BUD group,  $110.3 \pm 11.96$ ; for BUD group,  $104.25 \pm 12.99$ , both  $P < 0.01$ , compared with LCQ scores of 2-week). After 2-week treatment, LCQ scores improved more obviously in MONT/BUD group, compared with BUD group ( $27.36 \pm 13.56$  vs.  $19.06 \pm 17.75$ ;  $P = 0.0066$ ). Similar results were seen at 4-week ( $42.64 \pm 14.02$  vs.  $33.06 \pm 20.25$ ;  $P = 0.0293$ ).

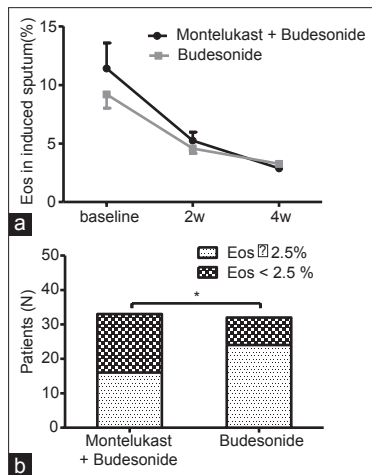
### Sputum eosinophils

For patients in BUD group or MONT/BUD group, compared with baseline values ( $9.20 \pm 6.65$  vs.  $11.42 \pm 12.44$ ), both treatments significantly reduced sputum eosinophils in the first 2 weeks ( $4.58 \pm 2.35$  vs.  $5.25 \pm 4.17$ ; both  $P < 0.001$ , compared with baseline values) [Figure 4, Panel A]. There was no obviously additional reduction of sputum eosinophils between 2-week and 4 week in BUD group ( $3.27 \pm 1.47$  at 4-week,  $P > 0.05$ , compared with 2-week values). In contrast, add-on therapy of MONT was proved additional inhibition of eosinophilic inflammation in the last 2 weeks of treatment ( $2.89 \pm 1.47$  at 4-week,  $P < 0.05$ , compared with 2-week values). After 4 weeks treatment, percentage of patients with normal sputum eosinophils (<2.5%) in MONT/BUD group was higher than BUD group (51.52% vs. 25.00%,  $P = 0.0414$ ) [Figure 4, Panel B], which also demonstrated the cooperative effects of MONT.



**Figure 3: Leicester cough questionnaire (LCQ) life quality scores.** Changes of LCQ scores during 4 weeks treatment in montelukast (MONT)/budesonide (BUD) group (Panel A) and BUD group (Panel B); Effects of 2-weeks (Panel C) and 4-weeks (Panel D) add-on montelukast treatment on improvement of LCQ scores. Data are expressed as median (10–90% range). \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ , compared using Kruskal-Wallis test followed by Dunn's multiple comparison test. † $P < 0.05$ , compared using Mann-Whitney test.





**Figure 4:** Eosinophil differential count (Eos) in induced sputum. (Panel A) Changes of Eos in induced sputum during 4 weeks treatment; and (Panel B) effects of 4-weeks add-on montelukast (MONT) treatment on Eos. Data are expressed as mean  $\pm$  standard error. \* $P < 0.05$ , compared using Fish's exact test. Eos, eosinophil differential count in induced sputum; Mont., MONT; Bude, budesonide.

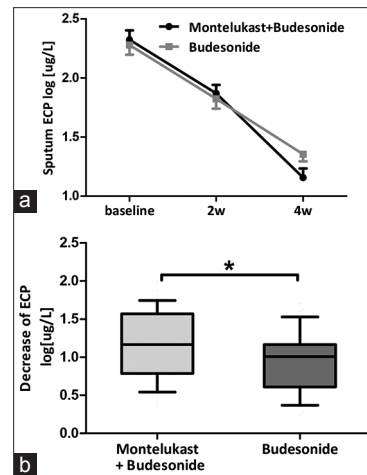
### Sputum eosinophil cationic protein

The reductions of eosinophils and ECP were in parallel with the treatment course. For patients in BUD group or MONT/BUD group, compared with baseline values ( $2.28 \pm 0.46$  vs.  $2.32 \pm 0.45$ , log [ $\mu\text{g/L}$ ]), both treatments significantly reduced sputum ECP in the first 2 weeks ( $1.82 \pm 0.48$  vs.  $1.87 \pm 0.42$ ; both  $P < 0.001$ , compared with baseline values) [Figure 5, Panel A]. Additional improvement was proved in analyzing sputum ECP for both groups at 4-week (for BUD group,  $1.35 \pm 0.34$ ,  $P < 0.05$ ; for MONT/BUD group,  $1.16 \pm 0.44$ ,  $P < 0.01$ ; both compared with ECP of 2-week). After 4 weeks treatment, add-on therapy of MONT was found to result in greater decrease of ECP compared with BUD group ( $1.17 \pm 0.46$  vs.  $0.92 \pm 0.39$ ,  $P = 0.0454$ ) [Figure 5, Panel B].

### DISCUSSION

To our knowledge, we report the first multicenter randomized controlled trial of add-on MONT for the treatment of NAEB. The present study, performed on a relative large number of corticosteroid-naïve NAEB patients, demonstrates the superiority of MONT combined with single-dose BUD (400  $\mu\text{g/d}$ ) over BUD (400  $\mu\text{g/d}$ ) monotherapy in improvements of cough-specific health-related quality-of-life, cough symptom remission, and inhibition of airway eosinophilic inflammation. This observation provides different clues about a possible adjunctive anti-inflammatory role of LTRAs in NAEB.

Nonasthmatic eosinophilic bronchitis has been globally proposed as one of the most common causes of chronic cough in guidelines by Chinese Medical Association, ACCP, and European Respiratory Society.<sup>[10-12]</sup> For patients with chronic cough and essentially normal chest radiograph findings, it has been shown in repeated studies that NAEB is frequent



**Figure 5:** Eosinophil cationic protein (ECP) in supernatant of induced sputum. (Panel A) Changes of ECP during 4 weeks treatment; and (Panel B) effects of 4-weeks add-on montelukast treatment on decrease of ECP (%). Data are expressed as mean  $\pm$  standard error (Panel A) or median (10–90% range) (Panel B). \* $P < 0.05$ , compared using Mann-Whitney test ECP.

enough to warrant early consideration, especially in those patients without sneezing and wheezing.<sup>[3,5-7]</sup> In our study, NAEB patients typically present with chronic cough (median: 6 months; range: 2–309 months), abundance eosinophils in induced sputum (95% confidence interval: 7.85–12.80%), normal airway responsiveness before treatment, which is similar with the results from other NAEB trials.<sup>[3,5-7,31]</sup>

In our patients, add-on MONT suppressed the airway eosinophilia and improved CVAS and LCQ scores significantly at 2-week and 4-week. After 4 weeks of add-on MONT, percentage of patients with normal sputum eosinophils (<2.5%) was lower than single dose BUD monotherapy. The exact mechanisms of MONT in NAEB are not clear. cys-LT are potent proinflammatory mediators<sup>[42]</sup> as well as bronchoconstrictors<sup>[43]</sup> in asthma, and the antitussive effect of MONT might be attributable to its anti-inflammatory ability rather than bronchodilation, which was proved previously.<sup>[44,45]</sup> The decrease of sputum eosinophils and attenuation of cough VAS were similar with the results from our study after 4 weeks treatment of MONT.<sup>[44]</sup> Spirometry, airway responsiveness, and respiratory resistance and reactance were unchanged.<sup>[45]</sup> A decrease of capsaicin cough sensitivity C5 after MONT treatment was also demonstrated.<sup>[44]</sup> That was the cue that LTRAs may involve different mechanisms from that of corticosteroid, since ICSs do not suppress cough sensitivity.<sup>[46]</sup> If so, MONT is potentially useful in the treatment not only of asthma, but also of nonasthmatic chronic cough with airway eosinophilia and/or cough hypersensitivity, especially in poor users of inhaled medications. One possible reason is the link between cys-LTs and a tussive neuropeptide substance P. Cys-LTs amplify action potential-dependent release of tachykinins such as substance P from airway afferent nerve fibers and LTRAs inhibit such release.<sup>[47]</sup> Increased concentrations of substance P are proved in plasma or nasal secretions from

patients with persistent cough.<sup>[48,49]</sup> LTRAs such as MONT might involve antitussive effects in cough through the effect on substance P. More evidence and clinical experience about the relationship between the substance P and cough sensitivity in NAEB are needed in the future.

Eosinophil cationic protein, produced by eosinophils' large secondary granules, has been developed as a marker for eosinophilic disease.<sup>[50,51]</sup> Elevated ECP levels are observed in T helper lymphocyte type 2 atopic diseases such as asthma and AR.<sup>[51]</sup> However, the correlation between ECP and cough symptom of NAEB is still unclear. In our study, we found the reductions of ECP levels, CVAS and LCQ scores were in parallel with the treatment course. After 4 weeks treatment, the decrease of ECP levels was obvious in both groups. But, the intensity in decrease was greater with add-on MONT.

Overall, 400 µg/d BUD monotherapy cannot be adequate to suppress eosinophilic inflammation in our patients with steroid-naïve NAEB. A greater antitussive effect, consequent improvement of cough-associated quality-of-life and the addictive anti-inflammatory effect offered by MONT was similar to the observations in most studies investigating add-on therapy with MONT in NAEB and asthma.<sup>[25,27,31]</sup> This might support the potential therapeutic value of antileukotrienes for treatment of NAEB, especially for patients unresponsive to ICS which require higher dose ICS or oral corticosteroid therapy.

This study has a few limitations. The sample was small and future larger studies with placebo-controlled design and a longer duration are required to confirm the beneficial effect of MONT for the management of NAEB. Objective methods for cough remission assessment, such as tussigenic challenges can be used to describe the effect of therapy on cough sensitivity. Substance P analysis will be illuminating for the research of the link between cys-LTs and cough sensitivity in NAEB patients. Analyses of cys-LTs concentration will be helpful to clarify the mechanism of its anti-inflammation action. Furthermore, inclusion of MONT plus double-dose BUD (800 µg/d) as treatment group and double-dose BUD (800 µg/d) as control group will also be taken into consideration in future.

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