Original Research

A Randomized, Multicenter, Double-blind, Phase III Study to Evaluate the Efficacy on Allergic Rhinitis and Safety of a Combination Therapy of Montelukast and Levocetirizine in Patients With Asthma and Allergic Rhinitis

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ABSTRACT

Purpose: The aim of this study was to evaluate the efficacy and safety of a fixed-dose combination of montelukast and levocetirizine in patients with perennial allergic rhinitis with mild to moderate asthma compared with the efficacy and safety of montelukast alone.

Methods: This study was a 4-week, randomized, multicenter, double-blind, Phase III trial. After a 1-week placebo run-in period, the subjects were randomized to receive montelukast (10 mg/day, n = 112) or montelukast (10 mg/day)/levocetirizine (5 mg/day) (n = 116) treatment for 4 weeks. The primary efficacy end point was mean daytime nasal symptom score. Other efficacy end points included mean nighttime nasal symptom score, mean composite symptom score, overall assessment of allergic rhinitis by both subjects and physicians, forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1/FVC, asthma control test score, and the frequency of rescue medication used during the treatment period.

Findings: Of 333 patients screened for this study, 228 eligible patients were randomized to treatment. The mean (SD) age of patients was 43.32 (15.02) years, and two thirds of subjects were female (66.67%). The demographic characteristics were similar between the treatment groups. Compared with the montelukast group, the montelukast/levocetirizine group reported significant reductions in mean daytime nasal symptom score (least squares mean [SE] of combination vs montelukast, −0.98 [0.06] vs −0.81 [0.06]; P = 0.045). For all other allergic rhinitis efficacy end points, the montelukast/levocetirizine group showed greater improvement than the montelukast group. Similar results were observed in overall assessment scores and in FEV_1, FVC, FEV_1/FVC, and asthma control test score changes from baseline for the 2 treatment groups. Montelukast/levocetirizine was well tolerated, and the safety profile was similar to that observed in the montelukast group.

Implications: The fixed-dose combination of montelukast and levocetirizine was effective and safe in treating perennial allergic rhinitis in patients with asthma compared with montelukast alone. ClinicalTrials.gov identifier: NCT02552667. (*Clin Ther*. 2018;40:1096−1107) © 2018 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license. (http://creativecommons.org/licenses/by-nc-nd/4.0/)

Key words: allergic rhinitis, asthma, clinical trial, fixed-dose combination, levocetirizine, montelukast.

INTRODUCTION

Rhinitis is an inflammation of the mucous lining of the nose, accompanied by symptoms that include rhinorrhea, sneezing, itching, nasal obstruction, and postnasal drip. Allergic rhinitis, an immunoglobulin E−mediated allergic inflammatory response caused by exposure to allergens, accounts for more than one half of all rhinitis cases and is observed in 10% to 50% of the world population. Specifically, in Asia, the

incidence of allergic rhinitis is 10% to 40% in adults and 10% to 46% in children.[1]

Asthma is a chronic inflammatory disorder of the lower airway. Approximately 300 million people worldwide are estimated to have asthma, and its prevalence ranges from 1% to 18%, depending on the country surveyed.[2] Allergic rhinitis and asthma have long been regarded as separate clinical manifestations of upper and lower respiratory tract diseases, respectively. However, recent advances in research have shown that allergic respiratory diseases are not restricted to specific areas, such as the nasal cavity or bronchi, but are present throughout the respiratory system; they appear as a wide range of clinical disorders, including rhinitis and asthma, which are closely related to each other epidemiologically, clinically, and pathophysiologically.[3−8]

The features of airway hypersensitivity, as well as early- and late-phase allergic reactions, can be present in both the nose and lungs simultaneously. In patients with rhinitis without asthma, methacholine inhalation induces lower respiratory tract responses similar to those observed in patients with asthma. Several clinical and experimental studies have reported that anatomic and physiological similarities exist between the nose and the lung, and that a decrease in nasal function can exert a negative influence on lung function.[9−12] The development of 1 disease may precede the other, and the 2 diseases are induced by the same triggers. Thus, they frequently manifest symptoms simultaneously.[13] This concept is referred to as "united airway disease," "one airway one disease," or "allergic rhinobronchitis."[3−8] On the basis of this concept, international treatment guidelines, including Allergic Rhinitis and its Impact on Asthma, recommend that clinicians check for the presence of asthma in patients with allergic rhinitis, and vice versa, so that an integrated therapeutic approach for the 2 diseases can be appropriately applied.[8]

Many mediators, cytokines, and growth factors produced by various cells are involved in the chronic inflammation seen in rhinitis and asthma. They contribute to airway hyperreactivity and repetitive symptoms, including wheezing, dyspnea, chest tightness, and coughing. Among these, cysteinyl leukotrienes are one of the important mediators responsible for upper (rhinitis) and lower (asthma) airway diseases.[14] These mediators contribute to the manifestations of asthma, including airway edema, smooth muscle contraction, and inflammatory cell infiltration. In addition,

cysteinyl leukotrienes induce increased blood flow and mucus oversecretion, which elicits nasal obstruction in allergic rhinitis. Montelukast effectively relieves asthma symptoms and improves lung function via the inhibition of cysteinyl leukotriene receptor 1.[15] It also reduces daytime and nighttime nasal (ie, late-phase) symptoms of patients with rhinitis.[16−19]

Histamine is a major mediator of allergic rhinitis via stimulation of H_1 receptors in the upper airway. Levocetirizine is a nonsedating, oral antihistamine that is widely used in alleviating early-phase symptoms of allergic rhinitis, including sneezing, nasal itchiness, and rhinorrhea. However, the effect of antihistamine on nasal obstruction is minimal.[20,21]

Theoretically, the therapeutic effectiveness of treating nasal symptoms may be enhanced by a combination of levocetirizine and montelukast, thus affecting inhibition of both early- and late-phase reactions in allergic rhinitis. The aim of the present study was to compare the efficacy and safety of a fixed-dose combination (FDC) of montelukast (10 mg/day) and levocetirizine (5 mg/day) versus those of montelukast (5 mg/day) monotherapy in subjects with perennial allergic rhinitis and mild to moderate asthma.

PATIENTS AND METHODS
Study Patients

Patients with mild to moderate asthma and allergic rhinitis, aged >15 years, were recruited to the study if they met 1 of the following criteria: (1) they were newly diagnosed with asthma after reversibility testing (≥12% increase in forced expiratory volume in 1 second [FEV_1] after inhaling a short-acting beta-agonist) or bronchial challenge testing (methacholine or mannitol hyperresponsiveness); (2) they were taking montelukast (10 mg/day) as monotherapy for asthma treatment for at least 4 weeks before screening (step II according to the Global Initiative for Asthma guideline); or (3) they required step-up with add-on montelukast therapy (10 mg/day) from inhaled corticosteroids (ICS) (step III according to the Global Initiative for Asthma guideline) to treat partially controlled asthma with stable doses of ICS for >4 weeks before screening. All subjects had at least 2 of the following symptoms: rhinorrhea, nasal obstruction, sneezing, and itching. They also had positive skin prick test or specific immunoglobulin E test results for at least 1 of 10 perennial allergens: house dust, *Dermatophagoides farinae*, *Dermatophagoides*

pteronyssinus, cat dander, dog dander, *Alternaria*, *Aspergillus*, *Cladosporium*, *Penicillium*, and cockroach mix.

Exclusion criteria included nonallergic rhinitis (eg, vasomotor, infectious, drug related), lung diseases (eg, pulmonary tuberculosis, chronic obstructive pulmonary disease), and upper respiratory tract infection within 3 weeks and nasal surgery within 3 months before visit 1. Patients on a stable dose of ICS were eligible based on the inclusion criteria. Other medications for allergic rhinitis, conjunctivitis, and asthma were not allowed during the placebo run-in and treatment periods, including: H_1 antihistamines; intranasal cromolyn; nedocromil; anticholinergics; decongestants; oral, parenteral, ophthalmic, inhaled, and intranasal corticosteroids; beta-agonists; and antileukotrienes.

Study Design

This analysis was a multicenter, double-blind, randomized Phase III study conducted at 22 centers in the Republic of Korea from October 2014 to July 2015. Written informed consent was obtained from all subjects before the study participation. The protocol was approved by the institutional review boards of each institution, and the study was registered at www.clinicaltrials.gov (NCT02552667). The study adhered to the tenets of the Declaration of Helsinki.

This study was conducted over 5 weeks (a 1-week placebo run-in period and a 4-week treatment period). The subjects who voluntarily participated in this clinical trial were screened based on set inclusion/exclusion criteria at the first visit (visit 1). After screening, a placebo was administered to those patients eligible for study participation once daily during the 1-week run-in period. At visit 2, daytime nasal symptom scores recorded in a daily diary during the run-in period were assessed, and the subjects who met the criteria described in the assessment section were randomly assigned to either the montelukast (10 mg/day) group (n = 112) or the montelukast (10 mg/day)/levocetirizine (5 mg/day) group (n = 116) with 1:1 allocation. Randomization was stratified on the basis of ICS use during the run-in period. The subjects took the study drug once every evening throughout the treatment period and visited the study centers at 2-week intervals (visits 3 and 4) for safety and efficacy assessments.

During the study, the treatment groups were double-blinded by using matched placebos of the study drugs. The FDCs of montelukast and levocetirizine and its placebo capsule were both beige-colored and were supplied by Hanmi Pharmaceutical Co (Seoul, Republic of Korea). The placebo capsule contained cellulose and lactose and had the identical size, shape, and weight as the FDC capsule. Montelukast was provided as beige-colored, film-coated tablet, which was produced by MSD Korea (Seoul, Republic of Korea). Its placebo was composed of mannitol, cellulose, and starch and was produced in the same shape by Hanmi Pharmaceutical Co.

Assessment Methods
Allergic Rhinitis Symptom Score

The participants completed diary card entries for the entire 5-week study duration. Throughout the 1-week run-in and 4-week treatment periods, rhinitis symptoms were evaluated based on the daily diary card entries for both daytime (assessed in the evening) and nighttime (assessed in the morning) symptoms, using a 4-point scale (see the Supplemental Table in the online version at doi:10.1016/j.clinthera.2018.04.021). Daytime nasal symptoms included rhinorrhea, nasal obstruction, sneezing, and itching, each scored from 0 to 3 (0 = none; 1 = mild; 2 = moderate; and 3 = severe). Nighttime nasal symptoms included nasal obstruction awakening (0 = none; 1 = mild; 2 = moderate; 3 = severe), difficulty getting to sleep (0 = not at all; 1 = little; 2 = moderate; 3 = severe), and nighttime awakening (0 = not at all; 1 = once; 2 = more than once; 3 = awake all night).

Subjects were enrolled at visit 2 when their recorded daytime nasal symptom scores for at least 4 days during the 1-week placebo run-in period and the average of their total daytime nasal symptom scores were ≥6 of the maximum total score of 12.

Overall Assessment of Allergic Rhinitis

At visit 4, overall allergic rhinitis symptoms were evaluated separately by the subjects and the physicians and were compared with those of visit 2. The following scoring system was used: 0 = very much improved, 1 = much improved, 2 = slightly improved, 3 = no change, 4 = slightly worse, 5 = much worse, and 6 = very much worse.

Spirometry

FEV_1, forced vital capacity (FVC), and FEV_1/FVC percentages were measured at visits 2 and 4. The use of

rescue medication was prohibited for at least 6 hours before spirometric measurement.

Asthma Control Test

Subjects completed the asthma control test (ACT) questionnaire at visits 2 and 4.

Rescue Medication

A rescue medication (120 μg/puff of salbutamol sulfate*) was administered as needed. The subjects were asked to record in their daily diaries the number of times that they used rescue medication.

Efficacy End Points

The primary efficacy end point was the change in mean daytime nasal symptom score (MDNSS) from baseline to the treatment period (visits 3−4). The daytime nasal symptom score was the mean of 4 individual symptom scores for rhinorrhea, nasal obstruction, sneezing, and itching. The MDNSS was measured by averaging all daily daytime nasal symptom scores during the placebo run-in period for baseline and during each 2-week treatment period (visits 2−3 and 3−4).

The secondary allergic rhinitis efficacy end points were mean nighttime nasal symptom score (MNNSS), mean composite symptom score (MCSS), and overall assessment scores recorded by both the subjects and the physicians. The MNNSS was measured by averaging all daily nighttime nasal symptom scores for nasal obstruction awakening, difficulty getting to sleep, and nighttime awakening, and MCSS was calculated by averaging the MDNSS and the MNNSS.

The other secondary efficacy end points were the changes in FEV_1, FVC, FEV_1/FVC percentages, and ACT scores from visit 2 to visit 4, as well as the total and mean daily frequency of rescue medication use per subject.

Safety Assessment

Safety assessments included treatment-emergent adverse events (TEAEs), physical and laboratory examinations, vital signs, and 12-lead ECGs. TEAEs were evaluated by assessing the incidence and severity at every visit, and their relationship to the study drug was evaluated according to the physician's judgment.

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* Trademark: Ventolin® Evohaler (GlaxoSmithKline, Research Triangle Park, North Carolina).

Laboratory tests, including hematology, biochemistry, urinalysis, and 12-lead ECGs, were conducted at randomization and the end of the study.

Statistical Analysis

Efficacy end points were analyzed by using the intention-to-treat approach. Efficacy data analyses were performed on all randomized subjects who had received at least 1 dose of the double-blind study drug and had had at least 1 measurement recorded both at baseline and during the treatment period for the primary efficacy end point (full analysis set). Safety analyses were performed on the safety analysis set, which included all randomized patients who had taken at least 1 dose of the investigational product.

Diary-based efficacy end points were analyzed as their mean changes from baseline, but any missing values on the diary were not imputed for statistical analysis. An ANCOVA model was applied to determine the efficacy end points (excluding overall assessment and frequency of rescue medication use), with baseline data as a covariate. Two-sample independent t tests were used to analyze the overall assessment scores of allergic rhinitis made by the subjects and the physicians, as well as the frequency of rescue medication used between the treatment groups. The incidence of adverse events was compared by using either Pearson's χ^2 test or Fisher's exact test. All tests were 2-sided at the 5% significance level. SAS version 9.4 (SAS Institute, Inc, Cary, North Carolina) was used for all statistical analyses.

The difference in change from baseline in MDNSS between the treatment groups was determined as −0.23, with an SD of 0.6, a power of 80%, and a significance level of 5%. This approach yielded a sample size of 107 subjects per group. Considering a dropout rate of 5%, a sample size of 226 (113 per treatment group) was calculated.

RESULTS
Patient Disposition and Baseline Characteristics

Of the 333 subjects screened, 228 were randomized to treatment, and 209 completed the study. A total of 19 subjects dropped out; the most common reason for dropout was withdrawal of consent (6 subjects) (Figure 1). The number of subjects included in the full analysis set was 210, and their baseline characteristics

Figure 1. Subject disposition. L = levocetirizine 5 mg; M = montelukast 10 mg.
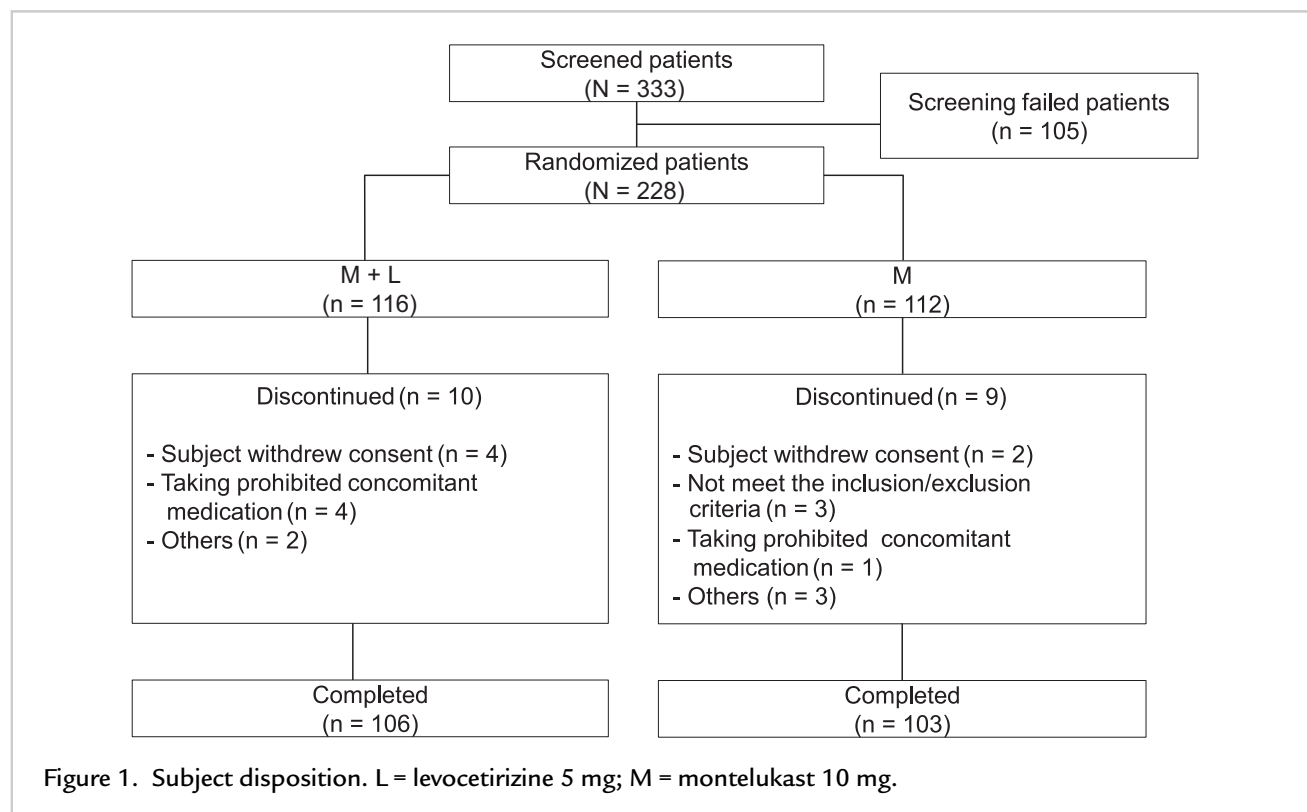
are summarized in Table I. The mean age of all subjects was 43.32 (15.02) years, and two thirds of them were female (66.67%). The mean duration of asthma was 72.30 (86.77) months, and most of the subjects had mild asthma (84.29%). There were no statistically significant differences in baseline characteristics, except that the frequency of rescue medication used during the placebo run-in period was significantly higher in the montelukast/levocetirizine group than in the montelukast group.

Efficacy Evaluation

Allergic Rhinitis

The change from baseline in allergic rhinitis symptom scores for the 2 treatment groups is shown in Figure 2 and Table II. The montelukast/levocetirizine group achieved statistically significant improvement in change from baseline in MDNSS (least squares mean [SE]) during the 2-week treatment period (visits 3−4) compared with that of the montelukast group (−0.98 [0.06] vs −0.81 [0.06]; P = 0.0450).

The montelukast/levocetirizine group exhibited a statistically significant improvement in sneezing compared with the montelukast alone group, although

rhinorrhea, itching, and nasal obstruction were marginally improved (P = 0.060 to 0.387). The combination group scores also revealed greater improvement in MDNSS, excluding nasal obstruction, compared with that of the montelukast group (P = 0.0194). However, there were no statistically significant differences between the treatment groups in terms of MNNSS and MCSS.

The subjects' overall assessment score (mean [SD]) was 1.83 (1.05) for the montelukast/levocetirizine group and 1.99 (1.06) for the montelukast group; the physicians' overall assessment score was 1.80 (1.07) for the combination group and 1.89 (0.96) for the montelukast group. There were no significant differences between the treatment groups (P = 0.2740 and P = 0.5017, respectively).

Asthma

The change in FEV_1 from baseline to the end of the study (least squares mean [SE]) was −0.00 (0.23) L for the montelukast/levocetirizine group, which was similar to the result of 0.01 (0.16) L for the montelukast group (P = 0.6848).

Table I. Baseline characteristics of the study patients (full analysis set). Data are given as mean (SD) unless otherwise indicated.

Characteristic	M + L (n = 107)	M (n = 103)	Total (N = 210)	P
Age, y	42.55 (14.35)	44.13 (15.71)	43.32 (15.02)	0.4488[*]
Sex				
Male	35 (32.71%)	35 (33.98%)	70 (33.33%)	0.8452[†]
Female	72 (67.29%)	68 (66.02%)	140 (66.67%)	
Height, cm	163.26 (8.52)	162.09 (8.22)	162.68 (8.37)	0.3120[*]
Weight, kg	63.47 (13.03)	63.90 (12.84)	63.68 (12.91)	0.8142[*]
Asthma status				
Duration of asthma, mo	77.35 (94.94)	67.05 (77.50)	72.30 (86.77)	0.3892[*]
Asthma severity				
Mild	88 (82.24%)	89 (86.41%)	177 (84.29%)	0.4071[†]
Moderate	19 (17.76%)	14 (13.59%)	33(15.71%)	
Inhaled corticosteroid use	47 (43.93%)	49 (47.57%)	96 (45.71%)	0.5958[†]
Montelukast administration	44 (41.12%)	43 (41.75%)	87 (41.43%)	0.9266[†]
Newly diagnosed asthma	16 (14.95%)	11 (10.68%)	27 (12.86%)	0.3550[†]
Baseline efficacy measures related to rhinitis[‡]				
MDNSS	1.89 (0.34)	1.89 (0.32)	1.89 (0.33)	0.9095[§]
MDNSS excluding nasal obstruction	1.86 (0.38)	1.84 (0.39)	1.85 (0.38)	0.7018[§]
MNNSS	1.33 (0.59)	1.34 (0.64)	1.34 (0.61)	0.8232[*]
MCSS	1.61 (0.38)	1.62 (0.39)	1.61 (0.38)	0.8972[*]
Baseline efficacy measures related to asthma				
FEV_1	2.62 (0.74)	2.57 (0.73)	2.60 (0.74)	0.5361[§]
FVC	3.36 (0.85)	3.37 (0.86)	3.36 (0.85)	0.9339[§]
FEV_1/FVC, %	78.28 (10.90)	76.46 (10.03)	77.4 (10.5)	0.1776[§]
ACT total score	17.88 (4.39)	18.73 (4.00)	18.30 (4.21)	0.1568[§]
Daily rescue medication use	0.72 (1.03)	0.38 (0.61)	0.55 (0.86)	0.0237[§]

ACT = asthma control test; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; L = levocetirizine 5 mg; M = montelukast 10 mg; MCSS = mean composite symptom score; MDNSS = mean daytime nasal symptom score; MNNSS = mean nighttime nasal symptom score.
[*] P values are based on 2-sample independent t test.
[†] P values are based on Pearson's χ^2 test.
[‡] Mean score during the placebo run-in period; all symptoms were scored on a scale from 0 to 3.
[§] P values are based on Wilcoxon's rank sum test.

The change in FVC, FEV_1/FVC, and ACT scores from baseline was also similar between the 2 treatment groups (Table III). Both the total and mean daily frequencies of rescue medication use during the treatment period were significantly higher for the montelukast/levocetirizine group than for the montelukast group (total use [mean (SD)], 15.62 [27.15] vs 8.51 [21.06], $P = 0.035$; mean daily usage [mean (SD)], 0.53 [0.93] vs 0.29 [0.74], $P = 0.039$).

Safety Evaluation

The safety analysis set included 224 patients. During the study period, 19 subjects (16.67%) in the montelukast/levocetirizine group and 18 subjects (16.36%) in the montelukast group experienced TEAEs (Table IV). Common adverse events (≥1% incidence) in the montelukast/levocetirizine group were reported as "upper respiratory tract infection" in 4 subjects (3.51%), "nasopharyngitis" in 3 subjects (2.63%), "gastrointestinal
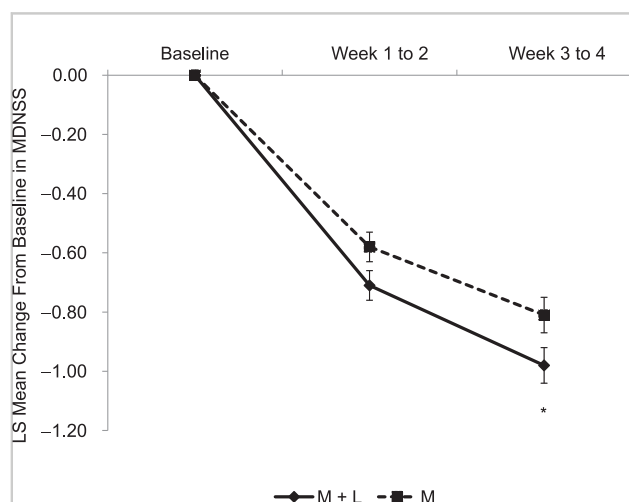
Figure 2. Change from baseline in mean daytime nasal symptom score (MDNSS). L = levocetirizine 5 mg; LS = least squares; M = montelukast 10 mg. *P < 0.05 M + L versus M at the indicated time point based on ANCOVA, with baseline data as covariate.

disorder" in 2 subjects (1.75%), and "tonsillitis" in 2 subjects (1.75%). In the montelukast group, "upper respiratory tract infection" in 4 subjects (3.64%), "pruritus" in 2 subjects (1.82%), and "tonsillitis" in 1 subject (0.91%) were reported. Adverse drug reactions were reported by 2 subjects (1.75%) in the montelukast/levocetirizine group and by 2 subjects (1.82%) in the montelukast group. For serious adverse events, 1 subject in the montelukast/levocetirizine group reported "gastric cancer," and 1 subject in the montelukast group reported "cholelithiasis." Neither of these was considered to be related to the study drugs. No significant differences were found in TEAEs, adverse drug reactions, or serious adverse events between the treatment groups. There were no laboratory adverse events, and no clinically meaningful changes in vital signs, ECGs, or physical examination results reported in this study, and these profiles were comparable between the 2 treatment groups.

DISCUSSION

The primary purpose of the present study was to show the efficacy of an FDC of montelukast and levocetirizine on allergic rhinitis in patients with asthma. The montelukast/

Table II. Change from baseline in allergic rhinitis symptom score during the treatment period (weeks 3−4)[*]: full analysis set.

Symptom Score[†]	M + L (n = 107)	M (n = 103)	Difference (95% CI)	P
MDNSS	−0.98 (0.06)	−0.81 (0.06)	−0.17 (−0.33 to −0.00)	0.0450
Rhinorrhea	−0.91 (0.06)	−0.77 (0.07)	−0.14 (−0.32 to 0.04)	0.1349
Nasal obstruction	−0.91 (0.07)	−0.83 (0.07)	−0.09 (−0.28 to 0.11)	0.3871
Sneezing	−1.08 (0.06)	−0.81 (0.07)	−0.26 (−0.45 to −0.08)	0.0050
Pruritus	−1.02 (0.07)	−0.84 (0.07)	−0.18 (−0.37 to 0.01)	0.0610
MDNSS excluding nasal obstruction	−1.00 (0.06)	−0.81 (0.06)	−0.19 (−0.36 to −0.03)	0.0194
MNNSS	−0.61 (0.05)	−0.53 (0.05)	−0.08 (−0.23 to 0.07)	0.2924
Nasal obstruction on wakening	−0.64 (0.06)	−0.57 (0.07)	−0.07 (−0.25 to 0.11)	0.4363
Difficulty getting to sleep	−0.61 (0.06)	−0.51 (0.06)	−0.10 (−0.26 to 0.06)	0.2085
Nighttime awakening	−0.56 (0.06)	−0.49 (0.06)	−0.07 (−0.23 to 0.10)	0.4257
MCSS	−0.79 (0.05)	−0.67 (0.05)	−0.12 (−0.27 to 0.02)	0.0995

L = levocetirizine 5 mg; M = montelukast 10 mg; MCSS = mean composite symptom score; MDNSS = mean daytime nasal symptom score; MNNSS = mean nighttime nasal symptom score.
* Reported as least squares mean (SE). Least squares mean, SE, 95% CIs, and P values are based on ANCOVA with baseline data as covariate.
† Mean score during blinded treatment period − Mean score during the placebo run-in period; all symptoms were scored on a scale from 0 to 3.

Table III. Change from baseline in lung function parameters and asthma control test (ACT) total score[*]: full analysis set.

Variable	M + L (n = 105[†])	M (n = 103)	Difference (95% CI)	P
FEV$_1$, L	0.00 (0.02)	0.01 (0.02)	−0.01 (−0.06 to 0.04)	0.6848
FVC, L	0.00 (0.02)	0.02 (0.02)	−0.01 (−0.07 to 0.05)	0.6632
FEV$_1$/FVC, %	−0.04 (0.37)	0.00 (0.38)	−0.04 (−1.09 to 1.02)	0.9459
ACT total score	2.08 (0.25)[‡]	2.42 (0.26)	−0.33 (−1.05 to 0.38)	0.3604

FEV$_1$ = forced expiratory volume in 1 second; FVC = forced vital capacity; L = levocetirizine 5 mg; M = montelukast 10 mg.
* Reported as least squares mean (SE). Least squares mean, SE, 95% CIs, and P values are based on ANCOVA, with baseline as covariate.
† The data analysis set included all randomized subjects who had received at least 1 dose of the double-blind study drug and had both baseline and postbaseline measurements for the lung function parameters.
‡ The data analysis set of ACT total score involved 106 subjects in the M + L group.

Table IV. Summary of treatment-emergent adverse events (TEAEs)[*]: safety analysis set.

Variable	M + L (n = 114)	M (n = 110)	P
Any TEAEs	19 (16.67)	18 (16.36)	0.9513[†]
Severity			0.3761[‡]
Mild	16 (14.04)	12 (10.91)	
Moderate	2 (1.75)	5 (4.55)	
Severe	1 (0.88)	1 (0.91)	
Adverse drug reactions	2 (1.75)	2 (1.82)	1.0000[‡]
Serious adverse events	1 (0.88)	1 (0.91)	1.0000[‡]
Gastric cancer	1 (0.88)	0 (0.00)	
Cholelithiasis	0 (0.00)	1 (0.91)	
Common TEAEs			
Upper respiratory tract infection	4 (3.51)	4 (3.64)	1.0000[‡]
Nasopharyngitis	3 (2.63)	0 (0.00)	0.2469[‡]
Tonsillitis	2 (1.75)	1 (0.91)	1.0000[‡]
Gastrointestinal disorder	2 (1.75)	0 (0.00)	0.4979[‡]
Pruritus	0 (0.00)	2 (1.82)	0.2400[‡]

L = levocetirizine 5 mg; M = montelukast 10 mg.
* Reported as number (percentage). Adverse events occurring in safety analysis set in any treatment group.
† P values are based on Pearson's χ^2 test.
‡ P values are based on Fisher's exact test.

levocetirizine group exhibited a statistically significant improvement in change from baseline in the primary end point, MDNSS, compared with that of the montelukast group. In addition, the montelukast/levocetirizine group exhibited numerical improvement in all allergic rhinitis efficacy end points, including each symptom score of MDNSS, compared with those of the montelukast alone group, and in sneezing score and MDNSS, excluding nasal obstruction, which showed a statistically significant difference between the groups (Table II).

Similar results have been presented in previous clinical studies that evaluated the efficacy of a montelukast and antihistamine combination in treating patients with allergic rhinitis.[22−26] Meltzer et al[23] reported that the co-administration of montelukast and loratadine significantly improved the daytime nasal symptoms score ($P <$ 0.001) compared with that after placebo administration and each agent alone, with a safety profile comparable to that of the placebo or each agent alone. They concluded that the combination of montelukast and loratadine provides clinical benefits against prevalent respiratory diseases, because asthma and allergic rhinitis comorbidities are common.[23] In addition, Ciebiada et al reported that a combination of montelukast and either desloratadine or levocetirizine is more effective than monotherapy for persistent allergic rhinitis.[25]

Allergic rhinitis and asthma have long been regarded and treated as separate disorders.[3] Recent advances in research, however, have shown that links between the 2 diseases exist, resulting in frequent coexistence of the diseases in the same patients.[4]

Asthma is reportedly prevalent in 10% to 40% of patients with allergic rhinitis, which is higher than the prevalence rate in healthy populations, and that 80% of patients with asthma have allergic rhinitis.[1,8,26,27] In another study, the incidence of asthma was reported to be >10-fold higher in patients with allergic rhinitis than in those without it.[28] Moreover, the severity of rhinitis has been associated with the severity of coexisting asthma.[29] Specifically, rhinitis not only worsens asthma prognosis but also lowers a patient's quality of life by limiting daily activities and reducing efficiency at work.[27,30] Rhinitis in asthma can also contribute to more frequent asthma exacerbations and relapses, as well as hospitalization and emergency department visits.[31−34]

These associations can be explained through the anatomic, physiological, and immunologic mechanisms of the upper and lower airways. These airways share anatomic similarities, including continuity of the basement membranes, pseudostratified ciliated columnar epithelia, mucus transport, serous glands, nasal epithelial cells, sympathetic and parasympathetic nerve distribution, and responses to the circadian rhythm. In addition, the same stimuli, including nonspecific irritants such as cold air and cigarette smoke, as well as allergens, induce inflammatory responses in both airways. They also share the same inflammatory mediators released from mast cells, eosinophils, basophils, and Th2 lymphocytes.

Nasal eosinophilic inflammation is present in asthma patients with or without nasal symptoms.[10−12]

All of this information indicates that rhinitis and asthma are manifestations of either the same or similar inflammatory processes that develop in the common respiratory tract tissue. It is therefore important that rhinitis and asthma not be evaluated as separate disorders, and both need to be treated when they coexist.

In the present study, the end points related to asthma were evaluated as secondary end points because the 4-week treatment period was too short for asthma evaluation. The changes in lung function parameters (FEV_1, FVC, and FEV_1/FVC) and ACT scores from baseline were similar between the montelukast/levocetirizine group and the montelukast group. However, both the total and mean daily frequencies of rescue medication use during the treatment period were higher in the montelukast/levocetirizine group than in the montelukast group. It is assumed that these differences between the groups were attributed to the baseline characteristics rather than treatment effects. During the run-in period, the mean daily frequency of rescue medication use was statistically significantly higher in the montelukast/levocetirizine group than in the montelukast group. This difference in the baseline might have affected the outcome. In the correlation analysis between the frequencies of rescue medication use during the run-in period and during the treatment period, there was a positive correlation between the frequency of rescue medication use during the run-in and treatment periods ($R = 0.764$). This finding means that the subjects who had a tendency to use rescue medication frequently during the run-in period were more likely to continue using rescue medicine in the treatment period.

A potential limitation of the present study is the short duration of assessment of asthma symptom (4 weeks). Generally, the recommended duration of asthma assessment in clinical trials for controller medication is at least 6 months.[34] In future studies, we will consider a longer assessment period so that the effects of combination therapy on asthma can be examined in greater depth.

CONCLUSIONS

This study shows that although both montelukast and levocetirizine are widely used therapeutic agents, administered alone or in combination, greater improvement in allergic rhinitis symptoms occurred with the FDC of montelukast and levocetirizine than

with montelukast alone. Moreover, the combination therapy was well tolerated and demonstrated an acceptable safety profile, similar to that observed with montelukast. We therefore fully expect that the FDC of montelukast and levocetirizine will provide significantly improved rhinitis outcomes in patients with allergic rhinitis and asthma.

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CONFLICTS OF INTEREST

SUPPLEMENTARY MATERIALS

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.clinthera.2018.04.021.

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SUPPLEMENTARY MATERIAL

Supplemental Table.   Ratings for the nasal symptoms.

	Daytime nasal symptoms				Nighttime nasal symptoms		
Score	Rhinorrhea	Nasal obstruction	Sneezing	Itching	Nasal obstruction awakening	Difficulty getting to sleep	Nighttime awakening
0	None (symptoms not noticeable)				None	Not at all	Not at all
1	Mild (mild intermittent symptoms that do not interfere with daily activities)				Mild	Little	Once
2	Moderate (moderate symptoms that interfere slightly with daily activities)				Moderate	Moderate	More than once
3	Severe (very severe symptoms that interfere greatly with daily activities)				Severe	Severe	Awake all night

Each symptom was scored using a 4-point scale (0 to 3). Daytime nasal symptoms were assessed in the evening and nighttime nasal symptoms were assessed in the morning every day.