Allergy Asthma Immunol Res. 2024 Nov;16(6):652-667
https://doi.org/10.4168/aair.2024.16.6.652
pISSN 2092-7355·eISSN 2092-7363

Allergy, Asthma & Immunology Research AAIR

Original Article

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Efficacy and Safety of Montelukast+Levocetirizine Combination Therapy Compared to Montelukast Monotherapy for Allergic Rhinitis in Children

Chang-Keun Kim,[1] **Yoonha Hwang**,[2] **Dae Jin Song**,[3] **Jinho Yu**,[4] **Myung Hyun Sohn**,[5] **Yong Mean Park**,[6] **Dae Hyun Lim**,[7] **Kangmo Ahn**,[8] **Yeong-Ho Rha**[9*]

[1]Asthma and Allergy Center, Department of Pediatrics, Inje University Sanggye Paik Hospital, Seoul, Korea
[2]Department of Pediatrics, Busan St. Mary's Hospital, Busan, Korea
[3]Department of Pediatrics, Korea University Guro Hospital, Seoul, Korea
[4]Department of Pediatrics, Ulsan University Asan Medical Center, Seoul, Korea
[5]Department of Pediatrics, Yonsei University Severance Hospital, Seoul, Korea
[6]Department of Pediatrics, Konkuk University Hospital, Seoul, Korea
[7]Department of Pediatrics, Inha University Hospital, Incheon, Korea
[8]Department of Pediatrics, Sungkyunkwan University Samsung Medical Center, Seoul, Korea
[9]Department of Pediatrics, Kyung Hee University Medical Center, Seoul, Korea

ABSTRACT

Purpose: The combination therapy of leukotriene receptor antagonists and antihistamines may alleviate allergic rhinitis (AR) symptoms better than monotherapy. This study aimed to investigate the safety and efficacy of Monterizine®, a fixed-dose combination of montelukast and levocetirizine, compared to montelukast monotherapy in pediatric patients with AR.
Methods: One hundred seventy-six children aged 6 to 14 years with perennial AR symptoms were recruited. One hundred forty-seven subjects were randomized into 1 of 2 groups: the mont+levo group (fixed-dose combination of montelukast [5 mg] + levocetirizine [5 mg]) or the mont group (montelukast single agent [5 mg]). Study subjects took the treatment every evening for 4 weeks and recorded their daytime nasal symptom score (DNSS) and nighttime nasal symptom score (NNSS) in a diary every day. Adverse events (AEs) were also recorded, and patients were surveyed as to their overall satisfaction with the therapeutic product they received.
Results: When DNSS and NNSS were assessed individually, daytime nasal congestion symptom scores decreased more in the mont+levo group during the 4-week treatment period than in the mont group ($P = 0.0341$). The daytime rhinorrhea symptom scores also decreased more in the mont+levo group ($P = 0.0469$). The nighttime nasal congestion score (severity when awake) decreased more in the mont+levo group than in the mont group ($P = 0.0381$). Study subjects in the mont+levo group experienced a greater improvement in quality of life than subjects in the mont group ($P < 0.0001$).
Conclusions: The combination therapy of montelukast and levocetirizine was more effective in reducing both daytime nasal symptoms (nasal congestion and rhinorrhea) and nighttime nasal symptoms (severity of nasal congestion when awake). With fewer AEs and higher overall satisfaction, combination therapy is recommended for pediatric patients with perennial AR.

Keywords: Rhinitis, allergic; leukotriene antagonists; histamine antagonists; child; montelukast; cetirizine; drug combinations

OPEN ACCESS

Received: Sep 27, 2023
Revised: Jun 13, 2024
Accepted: Jul 23, 2024
Published online: Oct 8, 2024

Correspondence to
Yeong-Ho Rha, MD, PhD
Department of Pediatrics, Kyung Hee University Medical Center, 23 Kyungheedae-ro, Dongdaemun-gu, Seoul 02447, Korea.
Tel: +82-2-958-8306
Fax: +82-2-958-8304
Email: yhrha@khu.ac.kr

ORCID iDs
Chang-Keun Kim
https://orcid.org/0000-0003-4119-2849
Yoonha Hwang
https://orcid.org/0000-0002-6508-8168
Dae Jin Song
https://orcid.org/0000-0003-0647-3186
Jinho Yu
https://orcid.org/0000-0002-1226-8077
Myung Hyun Sohn
https://orcid.org/0000-0002-2478-487X
Yong Mean Park
https://orcid.org/0000-0002-2586-584X
Dae Hyun Lim
https://orcid.org/0000-0002-4558-3284

Kangmo Ahn
https://orcid.org/0000-0001-7751-9829
Yeong-Ho Rha
https://orcid.org/0000-0001-5593-5020

Disclosure
There are no financial or other issues that might lead to conflict of interest.

INTRODUCTION

Allergic rhinitis (AR) is a reaction to allergens in the nasal mucosa, with local vasodilatation, edema, neurogenic stimulation, and mucus secretion leading to the tell-tale signs and symptoms of nasal congestion, rhinorrhea, itchy nose, and sneezing. In the lower airways, bronchial smooth muscle contraction, edema, and mucus hypersecretion result in acute bronchial obstruction.[1] A proportion of people exhibit a late response characterized by tissue eosinophilia, nasal congestion, and mucosal hyperreactivity to both allergic and nonallergic triggers that can continue for days or weeks. It is the most common allergic condition in the world, and in Asia, 10%–40% of adults and 10%–46% of children develop the disease.[2,3] AR is closely associated with other allergic diseases, including asthma and allergic conjunctivitis. AR patients frequently have asthma or nonspecific bronchial hyperresponsiveness, while up to 80% of asthma patients also suffer from AR.[4] The disease burden in children is substantial.[5-7]

AR pathogenesis involves chronic inflammation of the nasal mucosa caused by release of several inflammatory mediators, primarily histamine and leukotrienes,[8] with higher levels of these mediators found in patients with more severe AR.[9,10] Cysteinyl leukotrienes (CysLTs) are among the most important mediators responsible for upper and lower airway diseases by contributing to airway edema, smooth muscle contraction, inflammatory cell infiltration, increased blood flow, and mucus hypersecretion. [11] Leukotriene receptor antagonists (LTRAs), like montelukast, relieve many symptoms and improve lung function by inhibiting the cysteinyl leukotriene receptor 1 (CysLT1).[12] Montelukast has demonstrated reductions in daytime and nighttime nasal symptoms in patients with rhinitis[13,14] and is widely used for asthma and AR treatment. Levocetirizine is a potent 2nd-generation histamine receptor (H1) antagonist with demonstrated efficacy for AR, including improvements in quality of life (QoL)[15] and reduced nasal congestion.[16] Combining the therapeutic effects of an antileukotriene (montelukast) and an antihistamine (levocetirizine) presents an interesting treatment option, which has had limited study previously in perennial allergic rhinitis (PAR)[17] and seasonal allergic rhinitis (SAR).[18]

This study aimed to investigate the safety and efficacy of Monterizine® (fixed-dose combination of montelukast + levocetirizine) compared to montelukast monotherapy in pediatric patients with AR.

MATERIALS AND METHODS

Study duration

Taking into consideration the typical duration for treatment of AR and observation time in previous studies, the duration of a subject's participation in the study was determined to be 4 weeks. The study was conducted from May 28, 2019, to June 15, 2022, at 9 different centers: Kyung Hee University Medical Center; Inha University Hospital; Samsung Medical Center; Sinchon Severance Hospital; Kunkuk University Hospital; Korea University Guro Hospital; Asan Medical Center; Inje University Sanggye Paik Hospital; and Busan St. Mary's Hospital. All centers are located in Korea.

Study subjects

Children aged 6–14 years with PAR were recruited for this study. Because all subjects were legal minors, informed consent was required from the subject and their legal guardians, using an assent form for children that used easy terms and descriptions they could understand.

https://doi.org/10.4168/aair.2024.16.6.652

Study design

This clinical study was designed as a multicenter, randomized, open-label, controlled study. Within 9 days of receiving written informed consent, screening was conducted at Visit 1 in accordance with the clinical study protocol. After screening, subjects wrote down their symptoms of AR in a diary every morning and evening. In the evening, they wrote down the daytime nasal symptom score (DNSS) of AR, and the nighttime nasal symptom score (NNSS) was recorded the following morning. For DNSS, subjects were instructed to assess 4 main symptoms (nasal congestion, rhinorrhea, pruritus, sneezing) of AR by themselves on a scale of 0 to 3. The scoring matrix was defined as follows: None (0 points) – "Symptoms do not appear"; Mild (1 point) – "Mild symptoms appear some of the time, but daily life is not disturbed"; Moderate (2 points) – "Moderate symptoms appear, disturbing daily life a little"; Severe (3 points) – "Very bothersome, disturbing daily life significantly". For NNSS, subjects were instructed to assess 3 symptoms (severity of a stuffy nose when awake, severity of sleep disturbance, severity of nighttime awakenings) due to AR in the nighttime by themselves on a scale of 0 to 3 (same scoring scale as for DNSS). Only subjects whose eligibility was demonstrated through screening and examinations and who maintained the diary for at least 4 days with a mean DNSS of 6 or greater were finally selected as study subjects.

Only subjects who met the inclusion/exclusion criteria at Visit 2 were stratified depending on whether they had asthma, and the investigational product was prescribed after they were randomized in a 1:1 ratio to the study group (mont+levo group) (a fixed-dose combination of montelukast and levocetirizine [Monterizine® Chewable Tab 5 mg: montelukast 5 mg and levocetirizine 5 mg]) or control group (mont group) (montelukast single agent [Montezal® Chewable Tab 5 mg]) for each stratification. Study subjects took the investigation product every evening for 4 weeks and recorded their DNSS and NNSS in the diary every day as they did during screening.

Two weeks after subject enrollment, diary keeping and AEs were checked via telephone, e-mail or social media (text message, Kakao Talk, *etc.*). At Visit 3 (4 weeks after enrollment), the followings were performed: diary review; safety tests; investigational product consumption measurement; adverse events (AEs) collation; and treatment satisfaction survey.

Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ)

PRQLQ was designed to evaluate the QoL of children with AR and consists of the following 10 questions: 1) "How much were you bothered by breathing through the mouth?"; 2) "How much were you bothered by itchy nose?"; 3) "How much were you bothered by having to rub your nose?"; 4) "How much were you bothered or irritated by having to take medicine or spray it in the nose?"; 5) "How much were you bothered by thirst after taking medicines or spraying in the nose?"; 6) "How much were you bothered by a runny nose?"; 7) "How much were you bothered by having to blow your nose?"; 8) "How much were you bothered by having to rub your eyes?"; 9) "How much were you bothered by sneezing?"; 10) "How much were you bothered by a stuffy nose?". Each question was answered by the subject in one of 5 possible ways: "Never" (0 points); "A bit" (1 point); "Somewhat" (2 points); "Quite often" (3 points); and "All of the time" (4 points).

Subject randomization

Randomization was conducted at Visit 2 (Day 0) for subjects who met the inclusion/exclusion criteria. Subjects whose asthma status had been checked through screening were stratified (with asthma or without asthma). Randomization was conducted using stratified

https://doi.org/10.4168/aair.2024.16.6.652

block randomization, with a block size determined randomly to ensure the ratio of subjects between the treatment groups to be 1:1 (montelukast:Monterizine®). The stratum with asthma was randomized in a 1:1 ratio, as was the stratum without asthma. Randomization was calculated by a statistician.

Study population selection

Inclusion criteria were as follows: 1) aged 6–14 years; 2) written consent from legal guardian; 3) symptomatic AR (at least 2 of the following 4 symptoms: rhinorrhea, nasal congestion, sneezing, pruritus) with a positive skin prick (wheal size is 3 mm or larger or wheal size is equal to or greater than that obtained from the histamine solution [1 mg/mL]) or positive serum specific immunoglobulin E [IgE] [≥ 0.35 kU/L or Class 1 or higher]; 4) at Visit 1, those whose DNSS for 4 days prior to Visit 1 were a total of 6 or higher or at Visit 2, those who had recorded DNSS in the diary for at least 4 days with a daily average DNSS of 6 or greater for up to 9 days; and 5) in the case of asthmatic patients, those who had been diagnosed with asthma by each investigating doctor.

Exclusion criteria were as follows: 1) patients with non-allergic rhinitis; 2) those with severe asthma who have been treated in an emergency room for asthma within 1 month or have been hospitalized for asthma within 3 months prior to Visit 1, or those who required treatment other than an inhaled short-acting beta-agonist bronchodilator; 3) those who had nasal polyposis or clinically significant deformity of the nose; 4) those who had upper respiratory tract infection or systemic infection, including a cold, within 2 weeks prior to Visit 1; 5) those who had a history of acute/chronic sinusitis within 1 month prior to Visit 1; 6) those who started immunotherapy increased dose of immunotherapy within 1 month prior to Visit 1; 7) those who received surgical procedure in the nasal cavity within 3 months prior to Visit 1; 8) those who had hypertrophic cardiomyopathy or other diseases that can interfere with treatment, safety evaluation, or study completion, including cancer and clinically significant disorders of the psychiatric nervous, renal, hepatic, cardiovascular, respiratory, endocrinological, or central nervous system13) those who had a history of hypersensitivity to the study drug.

Subjects who were taking the following medications that could have affected the study, or for whom their concurrent administration was expected to be inevitable, could not participate. However, patients could participate in the study based on the judgment of the investigators, if the minimum period of time had passed before the screening date: 1) 3 days for oral H1 antihistamines, albeit 10 days for long-acting medications such as loratadine, fexofenadine, or cetirizine; and 14 days for ketotifen); 2) 14 days for intranasal cromolyn or nedocromil; 3) 7 days for oral anticholinergics or 3 days for intranasal anticholinergics; 4) 3 days for intranasal and systemic decongestants; 5) 30 days for systemic corticosteroids and 14 days for ophthalmic, inhalant, and intranasal corticosteroids (INCSs); however, if patients were on a stable dose of inhaled corticosteroids for more than 4 weeks prior to screening, their concomitant use was allowed; 6) 3 days for reserpine; 7) 7 days for leukotriene antagonists including montelukast; 8) 3 days for systemic antibiotics except for azithromycin (7 days); or 9) 2 days for nonsteroidal anti-inflammatory drugs.

Laboratory tests

Blood specimens were taken at Visit 1 (screening) and Visit 3 (end of treatment). For the evaluation of safety and efficacy, the following biochemical examinations were conducted: hematology (hemoglobin [Hb], hematocrit [Hct], red blood cell [RBC] count, waist circumference [WC], platelets, neutrophils, lymphocytes, monocytes, basophils,

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eosinophils); blood chemistry (glucose, blood urea nitrogen [BUN], creatinine, uric acid, sodium, potassium, chloride, calcium, aspartate transaminase [AST], alanine aminotransferase [ALT], alkaline phosphatase, total bilirubin); urinalysis (pH, albumin, glucose, RBC, white blood cells [WBC], ketones); and pregnancy test (urine-human chorionic gonadotropin, applicable only to women whose menstruation had begun and was conducted only at screening).

For the diagnosis of allergies, a skin prick test or specific IgE test was conducted. However, any allergy test results from within the past year could also be used. A skin prick test was considered positive if the wheal obtained from allergen stimulation was 3 mm or larger or the wheal size was equal to or greater than that obtained from a histamine solution (1 mg/mL or 0.1% histamine solution). The serum specific IgE test was measured using the ImmunoCAP system (Thermo Fisher Scientific, Waltham, MA, USA) and considered positive if the result was ≥ 0.35 kU/L or Class 1 or higher.

An electrocardiogram (ECG) was conducted to check for any anomalies, and any ECG results from within 6 months prior to medication administration could also be used.

An X-ray of the sinuses or nasal endoscopy was carried out to check for symptoms of rhinitis. If results from within 2 weeks prior to screening were available, they could be utilized.

Asthma diagnosis was confirmed in accordance with the medical treatment guidelines described in the Korean Asthma Guideline 2014.[19]

Statistical analysis

This study was powered using a 2-sided test with the significance level set at 0.05. For continuous variables, the number of subjects observed, mean, standard deviation, median, minimum, and maximum values were presented. The frequency and percentage were presented for categorical data. For normally distributed data, continuous variables were tested using the 2-sample *t*-test. If data were not normally distributed, the Wilcoxon rank sum test was used. Categorical data were tested using the Pearson's χ^2 test, and in cases where there were cells with an expected frequency of less than 5, the Fisher's exact test was used.

For subjects whose values were missing at a specific time within 3 to 4 weeks after administering the investigational product, which was the time for primary efficacy evaluation, or who dropped out while the study was underway, analysis was conducted using the last observation carried forward (LOCF) method. In this method, values obtained were substituted in place of missing value(s) in the full analysis set (FAS). For analysis of safety endpoints, missing values were not substituted.

Statistical analysis set

All subjects who participated in the study and were randomized were classified into the intent-to-treat (ITT) group. The safety set, which was designed to evaluate safety, included all subjects who received at least one dose of the investigational product after randomization for this study. The statistical analysis set for efficacy evaluation was classified as FAS and per protocol set (PPS).

For efficacy evaluation, all results from both FAS and PPS were presented and these results were checked. The main analysis set was the FAS, comprising subjects who received at least

https://doi.org/10.4168/aair.2024.16.6.652

one dose of the investigational product after study enrollment and who underwent at least one primary efficacy evaluation before the study termination. The PPS included subjects who completed the study in accordance with the study protocol, without serious violations, and who were also included in the FAS. The main exclusion criteria for the PPS were as follows: confirmed violations of the inclusion/exclusion criteria since enrollment; use of prohibited concomitant medications during the administration period of the investigational product; mean compliance of less than 70%; and other violations regarded as major protocol violations.

RESULTS

Subject enrollment

Among children aged 6 to 14 years, 176 subjects with PAR symptoms were recruited (**Fig. 1**). A total of 29 subjects were excluded (28 due to screening failure and 1 for being considered a "vulnerable subject"). One hundred forty-seven subjects were randomized, and those who

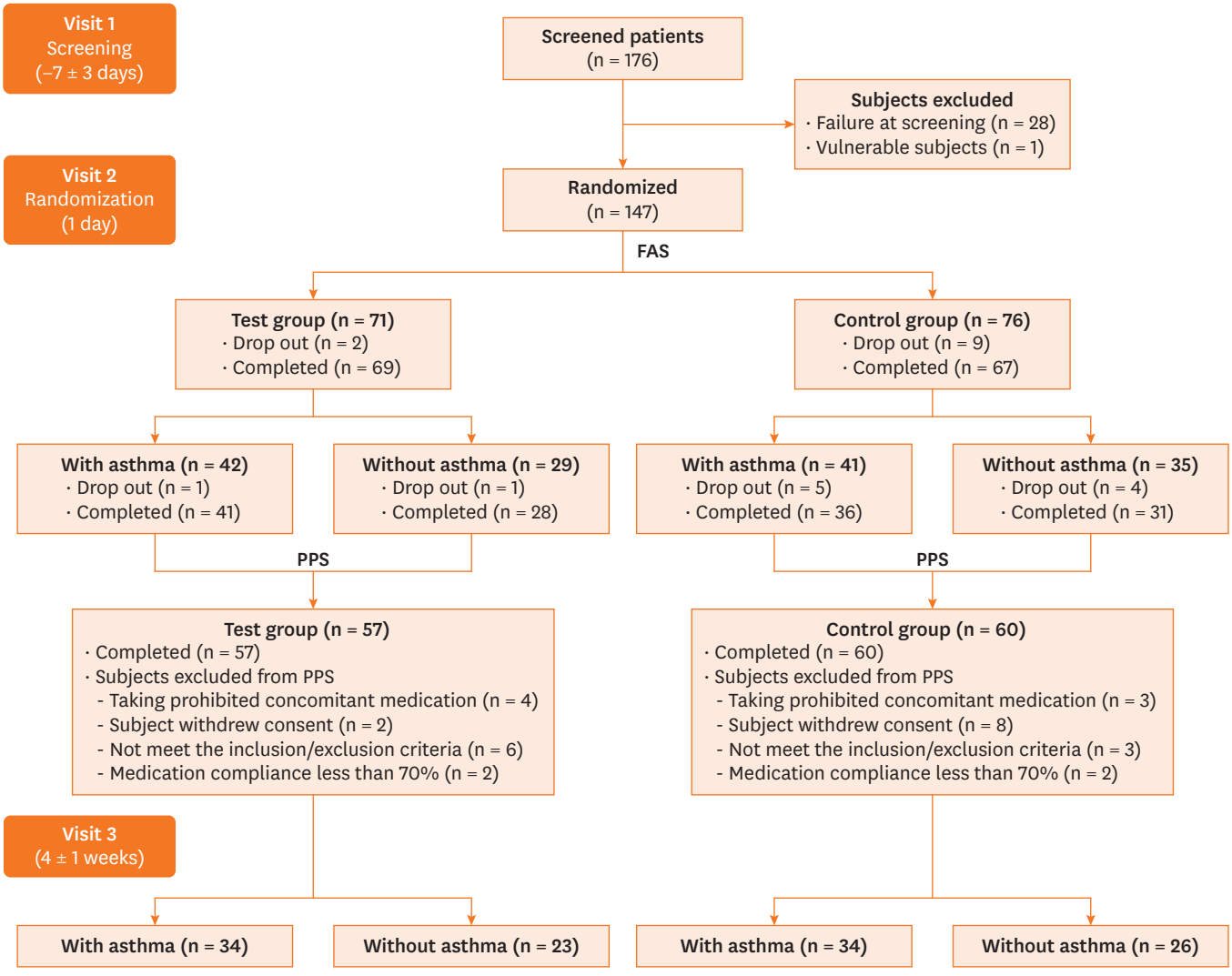

Fig. 1. Subject selection flow.
FAS, full analysis set; PPS, per protocol set.

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received the drug at least once and were evaluated for primary efficacy until the end of the study were classified as FAS (83.5% of total subjects). Thirty subjects were excluded from the PPS: 10 dropped out; 9 violated the inclusion/exclusion criteria after enrollment; 7 took prohibited concomitant medication during the administration period of the investigational product; and 4 had an average compliance of less than 70%. Seventy-one (48.3%) and 76 (51.7%) subjects were assigned to the study group (mont+levo) and the control group (Mont), respectively.

Subject demographics

The FAS consisted of 98 males (66.7%) and 49 females (33.3%), with 45 males (63.4%) and 26 females (36.6%) in the mont+levo group, and 53 males (69.7%) and 23 females (30.3%) in the mont group (**Table 1**). There was no statistical difference in the percentage of males and females between the groups ($P = 0.4139$).

Table 1. Baseline characteristics of the study patients (FAS)

Characteristic	Mont + Levo		Mont		*P* value
	(n = 71)	Missing	(n = 76)	Missing	
Age (yr)	9.44 ± 2.36		10.01 ± 2.56		0.1589
Sex					0.4139
Male	45 (63.4)		53 (69.7)		
Female	26 (36.6)		23 (30.3)		
Height (cm)	139.2 ± 15.58		144.35 ± 17.2		0.0598
Weight (kg)	38.08 ± 14.38		43.82 ± 17.13		0.0300
Asthma					0.5222
Yes	42 (59.1)		41 (53.9)		
No	29 (40.9)		35 (46.1)		
Baseline efficacy measures					
Mean DNSS	1.94 ± 0.33		1.93 ± 0.4		0.7693*
Mean NNSS	1.64 ± 0.7		1.6 ± 0.77		0.7895*
Vital signs					
Systolic blood pressure (mmHg)	107.87 ± 7.4	1	107.61 ± 8.8		0.8442
Diastolic blood pressure (mmHg)	64.59 ± 6.53	1	64.75 ± 6.26		0.8769
Pulse rate (/min)	83 ± 8.15	1	82.97 ± 10.47		0.9866
Respiratory rate (/min)	21.6 ± 7	1	21.16 ± 5.11		0.6618
Temperature (°C)	36.49 ± 0.28	1	36.45 ± 0.32		0.4703
Laboratory test					
Hematological examination					
WBC (10^9/L)	7.1 ± 1.67		7.8 ± 2.0		0.3376
RBC (10^{12}/L)	5.09 ± 3.41		4.78 ± 0.33		0.4432
Hb (g/dL)	13.16 ± 0.79		13.53 ± 0.99		0.0122
Hct (%)	39.4 ± 2.39		39.96 ± 4.99		0.3875
Platelet (10^9/L)	315.14 ± 73.66		305.68 ± 74.57		0.4312
Neutrophils (%)	34.24 ± 21.07		33.72 ± 21.06		0.8825
Lymphocytes (%)	41.37 ± 7.73		41.63 ± 9.02		0.9919
Monocytes (%)	6.66 ± 1.88		6.68 ± 2.43		0.9590
Eosinophils (%)	5.55 ± 3.8		4.6 ± 3.03		0.0958
Basophils (%)	0.71 ± 0.39		0.63 ± 0.33		0.1680
Blood chemistry test					
ALT (U/L)	15.65 ± 9.88		15.21 ± 18.15		0.2953
AST (U/L)	27.52 ± 7		26.22 ± 7.66		0.2866
GGT (IU/L)	12.89 ± 4.68	1	13.65 ± 6.17	4	0.4066
T-Bil (mg/dL)	0.47 ± 0.22		0.52 ± 0.24		0.1496
ALP (IU/L)	270.3 ± 80.05		265.32 ± 83.54		0.7130
BUN (mg/dL)	12.18 ± 2.3		11.85 ± 3.12		0.4722
Creatinine (mg/dL)	0.5 ± 0.1		0.54 ± 0.13		0.0212
Uric acid (mg/dL)	4.5 ± 1.23		4.64 ± 1.35		0.5347
LDH (IU/L)	404.2 ± 119.08	1	389.39 ± 111.57	4	0.4455
Glucose (mg/dL)	98.79 ± 12.74		100.17 ± 13.1		0.5182
Calcium (mg/dL)	9.41 ± 0.49		9.41 ± 0.42		0.9961

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Table 1. (Continued) Baseline characteristics of the study patients (FAS)

Characteristic	Mont + Levo		Mont		*P* value
	(n = 71)	Missing	(n = 76)	Missing	
Sodium (mmol/L)	137.9 ± 1.51		138.21 ± 1.74		0.2623
Potassium (mmol/L)	4.13 ± 0.27		4.17 ± 0.37		0.5021
Chloride (mmol/L)	104.02 ± 2.02		103.74 ± 2.49		0.4524
Urine test					
pH	6.09 ± 0.87		6.22 ± 1		0.3923
CrCl (mL/min)	164.82 ± 63.55		167.74 ± 62.74		0.7796
Albumin (g/dL)		61		62	-
Positive	0 (0.00)		0 (0.00)		
Negative	10 (14.08)		14 (18.42)		
Protein (g/dL)		15		13	0.1676
Positive	3 (5.36)		8 (12.70)		
Negative	53 (94.64)		55 (87.30)		
WBC (10^9/L)					0.4102
Positive	4 (5.63)		7 (9.21)		
Negative	67 (94.37)		69 (90.79)		
RBC (10^{12}/L)					0.4298
Positive	4 (5.63)		2 (2.63)		
Negative	67 (94.37)		74 (97.37)		
Glucose (mg/dL)					-
Positive	0 (0.00)		0 (0.00)		
Negative	71 (100.00)		76 (100.00)		
Ketone (mmol/L)					1.0000
Positive	0 (0.00)		1 (1.32)		
Negative	71 (100.00)		75 (98.68)		

Data shown are mean ± standard deviation or number (%).
FAS, full analysis set; DNSS, daytime nasal symptom score; NNSS, nighttime nasal symptom score; WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; Hct, hematocrit; ALT, alanine aminotransferase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase; T-Bil, total bilirubin; ALP, alkaline phosphatase; BUN, blood urea nitrogen; LDH, lactate dehydrogenase; CrCl, creatinine clearance.

Age ranged from 6 to 14 years, with a mean (± standard deviation; SD) age of 9.73 ± 2.48 years (**Table 1**). In the mont+levo group, mean age was 9.44 ± 2.36 years, while in the mont group, it was 10.01 ± 2.56 years. There was no statistically significant difference in age between the two groups ($P = 0.1589$).

DNSS

The mean (± SD) change in DNSS from Visit 2 (baseline) to Visit 3 (Week 4 of treatment) in the FAS (n = 147) was −1.27 ± 0.65 in the mont+levo group and −1.13 ± 0.63 in the mont group, with a between-group difference of −0.14 ± 0.64 ($P = 0.0905$). In the PPS (n = 117) analysis, the mont+levo group had a reduction of −1.34 ± 0.59, while the mont group experienced a reduction of −1.18 ± 0.59, which was also not statistically significant ($P = 0.1113$).

When each DNSS was analyzed independently in the FAS, comparing Visit 3 to Visit 2, the nasal congestion score in the mont+levo group decreased by −1.3 ± 0.98, and in the mont group, it decreased by −1.04 ± 0.91, with a between-group difference of −0.26 ± 0.94, which was statistically significant ($P = 0.0341$) (**Fig. 2A**). In the PPS analysis, the mont+levo group showed a reduction of −1.38 ± 0.94, while the mont group showed a reduction of −1.19 ± 0.78, with a between-group difference of −0.20 ± 0.86, which was not statistically significant ($P = 0.0882$) (data not shown). For rhinorrhea, the DNSS in the FAS decreased by −1.3 ± 0.92 in the mont+levo group and by −1.06 ± 0.82 in the mont group, respectively, with a between-group difference of −0.24 ± 0.87, which was statistically significant ($P = 0.0469$) (**Fig. 3**). In the PPS analysis, the rhinorrhea symptom score decreased by −1.4 ± 0.86 in the mont+levo group and by −1.07 ± 0.83 in the mont group with a between-group difference of −0.33 ± 0.84, which

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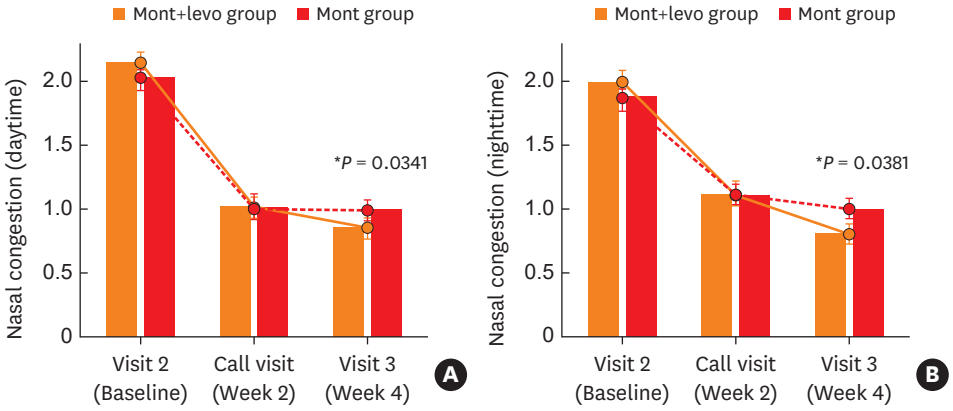

Fig. 2. Comparison of nasal symptom scores for nasal congestion between the mont+levo group and the mont group in the FAS. (A) Changes in daytime nasal congestion scores from Visit 2 (Baseline) to Visit 3 (Week 4) differed between the two groups, with a statistically significant between-group difference (P = 0.0341). (B) Changes in the severity of nighttime nasal congestion when awake from Visit 2 (Baseline) to Visit 3 (Week 4) differed between the two groups, with a statistically significant between-group difference (P = 0.0381).
FAS, full analysis set.
*P < 0.05.

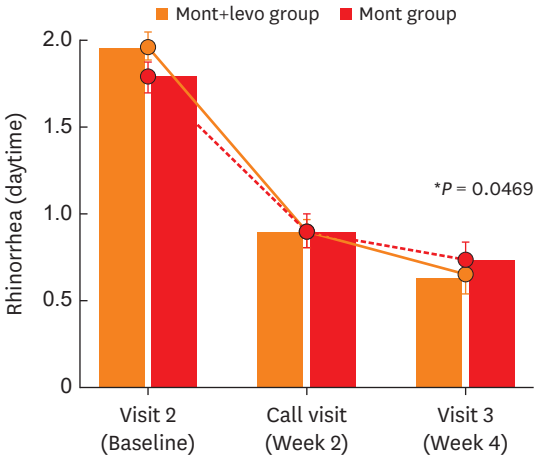

Fig. 3. Comparison of daytime nasal symptom scores for rhinorrhea between the mont+levo group and the mont group in the FAS. Changes in daytime rhinorrhea scores from Visit 2 (Baseline) to Visit 3 (Week 4) differed between the two groups, with a statistically significant between-group difference (P = 0.0469).
FAS, full analysis set.
*P < 0.05.

was statistically significant (P = 0.0396) (data not shown). Although the other two DNSSs (pruritus and sneeze) decreased between Visits 2 and 3, the differences were not statistically significant when comparing the two study groups (data not shown).

NNSS

In the FAS, the mean change from Visit 2 to Visit 3 in the mean NNSS was −1.1 ± 0.8 in the mont+levo group and −0.87 ± 0.8 in the mont group, with a between-group difference of −0.23 ± 0.80. This difference approached statistical significance (P = 0.0523). In the PPS analysis, there was a decrease in the mean NNSS from Visit 2 to Visit 3 but the difference between the two study groups was not statistically significant (P = 0.1469).

When nighttime symptom scores were analyzed individually, the severity of nasal congestion when awake changed in the FAS from Visit 2 to Visit 3 by −1.14 ± 1.05 in the mont+levo group

https://doi.org/10.4168/aair.2024.16.6.652

and −0.74 ± 1.06 in the mont group, with a between-group difference of −0.39 ± 1.06 (P = 0.0381) (**Fig. 2B**). In the PPS analysis, the severity of nasal congestion when awake changed by −1.28 ± 0.98 in the mont+levo group and −0.89 ± 0.9 in the mont group, with a between-group difference of −0.39 ± 0.94 (P = 0.0405) (data not shown). For the other two nighttime symptom scores (severity of sleep disturbance and severity of nighttime awakenings), there were reductions in both study groups, but the difference was not significant (data not shown).

PRQLQ evaluation

In the FAS (n = 146), the change in total PRQLQ score from Visit 2 to Visit 3 was −15.13 ± 8.69 in the mont+levo group and −6.09 ± 9.26 in the mont group, with a statistically significant difference between the groups (P < 0.0001) (**Fig. 4**). In the PPS (n = 117), the mean reduction in the total PRQLQ score was −15.61 ± 8.38 in the mont+levo group and −6.9 ± 9.36 in the mont group, also showing a statistically significant difference between the groups (P < 0.0001) (data not shown).

Survey on satisfaction of study subjects

At the time of study termination, subjects rated their AR symptoms compared to their symptoms at study initiation using the following 7-point Likert scale: 1) Symptoms and signs have worsened significantly (0 points); 2) Symptoms and signs have quite worsened (1 point); 3) Symptoms and signs have worsened a bit (2 points); 4) Symptoms and signs have remained unchanged (3 points); 5) Symptoms and signs have improved a bit (4 points); 6) Symptoms and signs have quite improved (5 points); 7) Symptoms and signs have improved significantly (6 points).

In the FAS (n = 138), the subjects' evaluation score was 5.43 ± 1.02 in the mont+levo group and 4.8 ± 1.02 in the mont group, confirming a statistically significant difference (P < 0.0001) (**Fig. 5A**). In the PPS (n = 117), the subjects' evaluation score was 5.44 ± 0.93 in the mont+levo group and 4.88 ± 0.94 in the mont group, also showing a statistically significant difference (P = 0.0014) (data not shown).

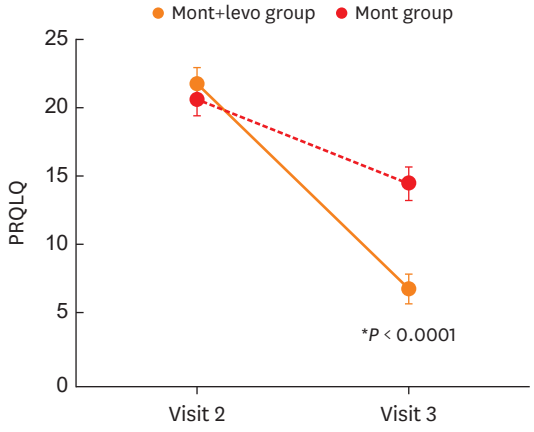

Fig. 4. Comparison of the total PRQLQ scores between the mont+levo group and the mont group in the FAS. Changes in the total PRQLQ scores from Visit 2 (Baseline) to Visit 3 (Week 4) differed between the two groups, with a statistically significant between-group difference (P < 0.0001).
PRQLQ, Pediatric Rhinoconjunctivitis Quality of Life Questionnaire.
*P < 0.05.

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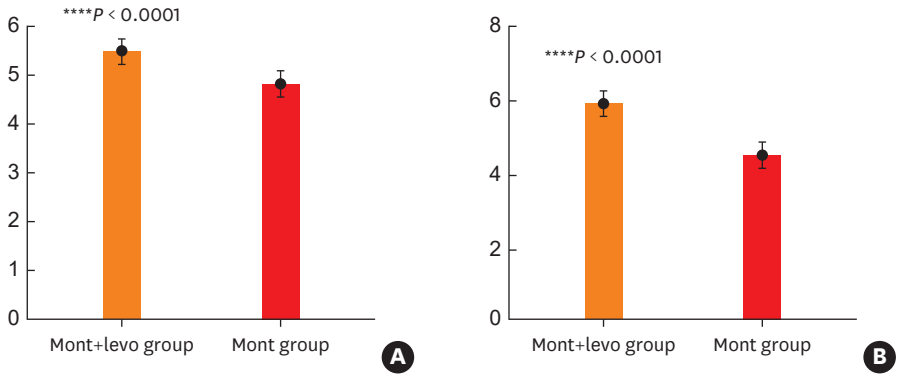

Fig. 5. Comparison of the overall treatment of effect at the end of the study using a 7-point Likert scale between the mont+levo group and the mont group in the FAS. Statistically significant differences were observed in both (A) subjects' assessment ($P < 0.0001$) and (B) investigators' assessment ($P < 0.0001$).
****$P < 0.0001$.

Investigator evaluation on overall therapeutic effects

The following is the result of the comparison of investigators' evaluation scores on overall therapeutic effects between the groups at the time of study termination, using a 7-point Likert scale. The evaluation scores in the FAS were 5.91 ± 0.87 for the mont+levo group and 4.54 ± 0.96 for the mont group, confirming a statistically significant difference ($P < 0.0001$) (**Fig. 5B**).

AEs

The incidence rate and number of AEs that occurred during the clinical study period were analyzed for each group in the FAS, with each AE classified by severity: Grade 1, "Mild"; Grade 2, "Moderate"; Grade 3, "Severe." Among the 147 subjects in the FAS, 16 experienced at least one AE: 4 (5.6%) from the mont+levo group and 12 (15.8%) from the mont group (**Table 2**). However, the difference between the two groups was not significant ($P = 0.1874$). A total of 16 AEs occurred, with 14 cases (87.5%) classified as Grade 1, 1 case (6.3%) as Grade 2, and 1 case (6.3%) as Grade 3. All 4 AEs in the mont+levo group were mild, while in the mont group, 10 were mild, 1 was moderate, and 1 was severe. In the mont group, 2 patients experienced serious AEs (2.6%): 1 (1.32%) was a headache, and the other (1.3%) was aspiration pneumonia.

Summary of safety evaluation

There were no differences between the two study groups in vital signs (systolic and diastolic blood pressure, pulse rate, body temperature, respiration rate), nor were there significant difference in the changes within each group after administration of the investigational product compared to pre-administration (**Table 3**).

Table 2. Summary of treatment-emergent AEs: safety analysis set

Variable	Safety set (n = 147)		
	Test group	Control group	*P* value
Any treatment-emergent AEs	4 (2.60)	12 (7.79)	0.1874*
Severity			
Mild	4 (2.60)	10 (6.49)	
Moderate	0 (0.00)	1 (0.65)	
Severe	0 (0.00)	1 (0.65)	
Serious AEs	0 (0.00)	2 (1.36)	-
Headache	0 (0.00)	1 (0.68)	
Pneumonia	0 (0.00)	1 (0.68)	

AE, adverse event.
**P* values are based on Fisher's exact test.

https://doi.org/10.4168/aair.2024.16.6.652

Table 3. Change in vital signs

Vital signs	Group	Change	FAS (n = 146)							
			No.	Missing	Mean	SD	Median	Min	Max	*P* value*
RESP	Study group	V3-V1	70	3	−0.21	2.05	0	−6	6	0.2683
	Control group	V3-V1	76	8	−0.16	1.93	0	−8	5	0.5327
TEMP	Study group	V3-V1	70	3	−0.02	0.25	0	−0.7	1	0.4253
	Control group	V3-V1	76	8	−0.03	0.32	0	−1.5	0.7	0.9843
SBP	Study group	V3-V1	70	3	−1.4	7.62	0	−30	11	0.2361
	Control group	V3-V1	76	8	0.1	10.05	0	−40	39	0.9822
DBP	Study group	V3-V1	70	3	0.76	8.06	0	−20	17	0.4377
	Control group	V3-V1	76	8	1.74	9.19	0	−30	24	0.0533
PULSE	Study group	V3-V1	70	3	0.28	9.57	0	−28	25	0.4069
	Control group	V3-V1	76	8	−2.35	8.85	−1	−27	18	0.4915

FAS, full analysis set; RESP, respiration rate; TEMP, temperature; SBP, systolic blood pressure; DBP, diastolic blood pressure; V3, Visit 3; V1, Visit 1 (screening); SD, standard deviation.
*Paired *t*-test/Wilcoxon signed rank test (for all *P* values).

Regarding changes in hematologic tests (WBC, RBC, Hb, Hct, platelets, neutrophils, lymphocytes, monocytes, eosinophils, and basophils), blood chemistry tests (ALT, AST, gamma-glutamyl transferase, total bilirubin [T-Bil], alkaline phosphatase, BUN, creatinine, uric acid, lactate dehydrogenase, glucose, calcium, sodium, potassium, and chloride), and urinalysis (pH), no significant differences were observed between the groups for most indices (data not shown). However, differences were noted in Hb ($P = 0.0122$) and creatinine ($P = 0.0212$) at Visit 1, and T-Bil ($P = 0.0413$) at Visit 3.

Within-group changes after administration compared to pre-administration showed no differences in most indices, except for WBC ($P = 0.0374$), monocytes ($P = 0.0022$), and eosinophils ($P = 0.0002$) in the mont+levo group, and WBC ($P = 0.0196$), RBC ($P = 0.0021$), Hb ($P = 0.0080$), Hct ($P = 0.0015$), and eosinophils ($P = 0.0423$) in the mont group.

For change in urinalysis (albumin, protein, WBC, RBC, glucose, and ketone), there were no differences between the groups, nor were there any significant changes observed within each group after administration compared to pre-administration (data not shown).

DISCUSSION

This study investigated the efficacy and safety of combination therapy (LTRA + antihistamine) in children with PAR and compared it to monotherapy with the LTRA (montelukast). Overall, both combination and monotherapy were effective in reducing nasal symptoms (daytime and nighttime); however, the combination therapy was more effective in reducing specific daytime nasal symptoms (nasal congestion and rhinorrhea) as well as the nighttime nasal symptom (severity of nasal congestion when awake) than the monotherapy. Both therapies produced significant improvements in QoL, while keeping the occurrence of AEs relatively low.

AR is one of the most common chronic allergic diseases in the world affecting 10%–30% of children.[20,21] Many AR patients have asthma or nonspecific bronchial hyperresponsiveness, so the disease burden is substantial and may even include memory deficit, fatigue, sleep deprivation, and depression.[5-7] Recommended treatments for AR include avoiding allergens, symptomatic treatment, and allergen immunotherapy.[22] According to the Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines, antihistamines are recommended for AR treatment, while INCSs are preferred over LTRAs.[23] In AR patients, both histamine and

https://doi.org/10.4168/aair.2024.16.6.652

CysLTs are elevated in nasal secretions. Histamine triggers early-phase reactions like sneezing, itching, and rhinorrhea, while CysLTs mediate early and late-phase reactions that cause nasal congestion. LTRA treatment has shown improvements in daytime and nighttime nasal symptoms, QoL, and eosinophil levels–the major effector cell for many allergic diseases like AR and asthma.[24] In our present study, the LTRA (montelukast) reduced daytime and nighttime symptoms and improved QoL. It has been suggested that LTRAs provide more benefit than antihistamines for AR patients with asthma.[25] Antihistamines are recommended treatment for AR and improve symptoms such as rhinorrhea, sneezing, nasal itching, and eye symptoms.[26] INCSs are recommended over oral antihistamines (OAHs) due to their greater efficacy, although many patients prefer oral antihistamines leading to better drug adherence.[23]

The combination therapy for AR has been studied previously. Ciebiada *et al.*[27] found that the combination therapy with montelukast and levocetirizine was effective in reducing nasal eosinophilia and the severity of nasal symptoms. In a separate study,[28] they also found that the combination provided additional QoL benefits over monotherapy with either montelukast or levocetirizine. Another study by the same group[29] demonstrated that combination therapy with montelukast and levocetirizine was more effective in reducing nasal symptoms and eosinophilic cationic protein (ECP) levels compared to monotherapy. ECP is a eosinophil granule protein used as a biomarker for eosinophil activity in allergic diseases.[30] A more recent study on adult patients with asthma and AR found that Monterizine® (a combination of montelukast + levocetirizine) reduced total nasal symptom scores as well as individual nasal symptoms like nasal congestion, sneezing, rhinorrhea, nasal itching.[31] These findings align with the results of our study, which also demonstrated improvements in both total and individual nasal symptom scores, along with QoL. They concluded that Monterizine® is an effective and safe drug for improving PAR symptoms, even with long-term use.

A previous phase III study by the same group[31] found similar results when comparing montelukast monotherapy with montelukast+levocetirizine combination therapy. The combination therapy led to significantly greater reductions in mean daytime and nighttime nasal symptom scores, mean composite symptom scores, and overall AR assessments by both subjects and physicians than montelukast monotherapy. Our results differ slightly from this study. When we analyzed daytime symptom scores as a whole, no statistically significant difference was observed between combination therapy and monotherapy. However, when each daytime symptom was analyzed individually, a significant difference was found in 2 of the 4 symptoms measured (nasal congestion and rhinorrhea). A similar pattern occurred for nighttime symptoms. When evaluated individually, only nighttime nasal congestion showed a significantly greater reduction with combination therapy compared to montelukast monotherapy. Nasal congestion is often regarded as the most troublesome symptom of AR. First-generation and older second-generation antihistamines have limited efficacy in relieving nasal congestion. However, levocetirizine[16] and other newer second-generation antihistamines (*e.g.*, desloratadine and fexofenadine) have demonstrated significant reductions in both objective (*i.e.*, maintenance of nasal airflow) and subjective (symptom scores) measures of nasal congestion compared to placebo. A review of 26 clinical trials concluded that levocetirizine is an appropriate option for treating nasal congestion in AR patients.[32]

The most recent revisions to AR treatment guidelines in Korea, conducted by the Korean Academy of Asthma, Allergy and Clinical Immunology (KAAACI), were published in 2023.[33] These guidelines provided 4 recommendations: one was the use of an OAH in combination with an INCS for patients with AR, and another recommendation was administration of

https://doi.org/10.4168/aair.2024.16.6.652

an LTRA for patients with both AR and asthma. Asthma and AR often coexist in the same patient. The connection between upper and lower respiratory tract allergic diseases, known as the "United Airways Hypothesis,"[34] suggests these 2 conditions are manifestations of the same or closely related inflammatory processes. Administration of a LTRA (montelukast) to patients in our combination therapy group was appropriate, as up to 60% of them had both asthma and AR.

Currently, there are no guidelines for OAH + LTRA combination therapy. However, as previously noted, there is growing evidence supporting the benefits of this combination. LTRAs have been used successfully in the treatment of patients with both AR and asthma. INCSs are not effective within 2 hours, whereas a fast-acting OAH, like levocetirizine, rapidly exerts its therapeutic effect.[33] This likely explains why our combination therapy group, receiving levocetirizine, showed greater improvements in QoL than the group receiving montelukast monotherapy.

With significantly greater improvements in daytime and nighttime symptoms, as well as QoL, the combination of montelukast (LTRA) and levocetirizine (antihistamine) has demonstrated safety and efficacy for children with PAR. Although further studies are needed, this combination therapy should be considered for this demographic, especially if there are concerns over the use of INCSs in young children.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Zak Callaway for help with writing and editing the manuscript. This study was funded by Hanmi Pharmaceutical Co.,Ltd.

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