RESEARCH ARTICLE

Comparison of the Efficacy of Rupatadine with Levocetirizine in Patients with Persistent Allergic Rhinitis

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Abstract

Allergic rhinitis is a global health problem of increasing prevalence. Its bothersome symptoms can disturb sleeping patterns and impact on daily activities. A prospective, randomized, single-blind, active controlled study was performed to compare the clinical efficacy, particularly on the nasal obstruction of rupatadine 10 mg (RUP) with levocetirizine 5 mg in the treatment of persistent allergic rhinitis (PER) for 4 weeks. The clinical assessments included the total nasal symptom score (TNSS), total ocular symptom score (TOSS), nasal peak inspiratory flow (PNIF), nasal cytology as well as the percentage of the responders who exhibiting the TNSS declined by 50% or more. After 4 weeks of treatment, TNSS and TOSS of both groups were significantly improved with no difference between groups. Percentages of the responders were 50% and 57.3% in LEV and RUP group, respectively. Only the PNIF of LEV group significantly improved from baseline value. There was no significant change in inflammatory cells when compared with the baseline data of nasal cytology. The mean changes in PNIF and nasal inflammatory cells did not differ between both treatment groups. Although RUP group seemed to use the rescue treatment less than LEV group but no significant difference was found. The most common adverse events were somnolence and drowsiness with similar frequency in both groups. In conclusion, RUP 10 mg provides effective control of allergic symptoms, including nasal obstruction comparable to LEV 5 mg in PER patients.

Keywords: Levocetirizine, rupatadine, persistent allergic rhinitis

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การเปรียบเทียบประสิทธิผลระหว่างยารูพาทาดีนและยาเลโวเซทิริซีนในผู้ป่วยโรคจมูกอักเสบจากภูมิแพ้ที่มีอาการต่อเนื่อง

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บทคัดย่อ

จมูกอักเสบจากภูมิแพ้เป็นปัญหาสุขภาพทั่วโลกที่มีอัตราความชุกของโรคเพิ่มสูงขึ้น อาการของโรครบกวนการนอนหลับและส่งผลกระทบต่อการดำเนินชีวิตประจำวัน การศึกษานี้ทำแบบไปข้างหน้า สุ่ม ปกปิดทางเดียว มีกลุ่มควบคุมเพื่อเปรียบเทียบประสิทธิผลในการรักษาโดยเฉพาะอย่างยิ่งต่ออาการคัดจมูกของยารูพาทาดีน ขนาด 10 มิลลิกรัม กับยาเลโวเซทิริซีน ขนาด 5 มิลลิกรัม ติดต่อกัน 4 สัปดาห์ในผู้ป่วยโรคจมูกอักเสบจากภูมิแพ้ที่มีอาการต่อเนื่อง การประเมินทางคลินิกประกอบด้วยคะแนนรวมอาการทางจมูก คะแนนรวมอาการทางตา การตรวจนับเซลล์อักเสบจากเยื่อบุจมูก การวัดค่า peak nasal inspiratory flow (PNIF) และจำนวนผู้ที่ตอบสนองต่อการรักษาซึ่งเป็นผู้ที่มีคะแนนรวมอาการทางจมูกลดลงอย่างน้อยร้อยละ 50 หลังการรักษาติดต่อกัน 4 สัปดาห์ อาสาสมัครทั้งสองกลุ่มมีคะแนนรวมอาการทางจมูกและตาดีขึ้นอย่างมีนัยสำคัญ แต่ไม่พบความแตกต่างระหว่างกลุ่ม สัดส่วนของผู้ที่ตอบสนองต่อการรักษามีค่าร้อยละ 50 และ 57.3 ในกลุ่มเลโวเซทิริซีนและกลุ่มรูพาทาดีนตามลำดับ เฉพาะกลุ่มเลโวเซทิริซีนเท่านั้นที่มีค่า PNIF ดีขึ้นกว่าก่อนการรักษาอย่างมีนัยสำคัญ การตรวจนับเซลล์อักเสบจากเยื่อบุจมูกพบว่าไม่มีการเปลี่ยนแปลงจำนวนเซลล์อักเสบอย่างมีนัยสำคัญหลังการรักษา เมื่อเปรียบเทียบค่าเฉลี่ยของ PNIF และเซลล์อักเสบจากเยื่อบุจมูกที่เปลี่ยนแปลงหลังรักษาของทั้งสองกลุ่มไม่มีความแตกต่างกัน กลุ่มรูพาทาดีนใช้ยาช่วยบรรเทาอาการน้อยกว่ากลุ่มเลโวเซทิริซีนแต่ไม่พบความแตกต่างอย่างมีนัยสำคัญ เหตุการณ์ไม่พึงประสงค์ที่พบบ่อยได้แก่ ง่วงนอนและเซื่องซึม โดยมีอัตราการเกิดในทั้งสองกลุ่มใกล้เคียงกัน กล่าวโดยสรุป ยารูพาทาดีน ขนาด 10 มิลลิกรัม มีประสิทธิผลเทียบเท่ากับยาเลโวเซทิริซีน ขนาด 5 มิลลิกรัม ในการควบคุมอาการภูมิแพ้รวมถึงอาการคัดจมูกในผู้ป่วยจมูกอักเสบจากภูมิแพ้ที่มีอาการต่อเนื่อง

คำสำคัญ: เลโวเซทิริซีน, รูพาทาดีน, จมูกอักเสบจากภูมิแพ้ที่มีอาการต่อเนื่อง

Introduction

Allergic rhinitis (AR) is a chronic inflammatory condition of nasal mucosa after exposure to allergens such as house dust, dust mite, mold, and pollen. AR has significant impacts on cognitive function, work productivity, school performance, sleep, and quality of life (QOL).[1-3] Antihistamines have been used in the treatment of AR for more than 50 years. They are universally well known for controlling sneezing, nasal itching, and rhinorrhea.[1,4] However, the first-generation H_1-antihistamines have significant anticholinergic and sedative effects leading to impair performance of daily tasks. The relatively nonsedating second-generation H_1-antihistamines (e.g., levocetirizine [LEV] and rupatadine [RUP]) are now more commonly used[4,5] and are recommended for the treatment of all types and all stages of severity of AR.[1] Some of them also have anti-inflammatory activity in addition to histamine blocking effect.[6] LEV, the R-enantiomer of cetirizine, has rapid onset of action, minimal hepatic metabolism, minimal side effects together with increased duration of action.[7] The efficacy of LEV in relieving the symptoms of AR is well established.[8] RUP, an *N*-alkyl pyridine derivative, inhibits H_1- and platelet-activating factor (PAF) receptors. It has shown efficacy in reducing nasal and ocular symptoms in patients with AR.[9] Both LEV and RUP have anti-inflammatory property and could reduce nasal obstruction which affects sleep and QOL.[7,9] Thus, the objectives of this study was to compare the efficacy of RUP, a new H_1-antihistamine and PAF antagonist, with LEV in patients with persistent allergic rhinitis (PER) evaluated by subjective measures of symptom scores and by objective measures of nasal cytology and nasal peak inspiratory flow (PNIF).

Materials and Methods

Study design

This study was a prospective, randomized, single-blind, active controlled study. The patients considered eligible for the study were randomized into 2 groups to receive either LEV 5 mg (LEV group) or RUP 10 mg (RUP group). Both drugs were administered orally 30 minutes before breakfast for 4 weeks. This study was performed in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of the Faculty of Medicine, Chiang Mai University. All patients were informed and gave written consent before being included in the study.

Subjects

The sample size calculation was based on the assumptions that the percentage of the responders, i.e., the patient who exhibiting the total nasal symptom scores (TNSS) declined by 50% or more, in each group would be the main efficacy criterion, and that the respond rate was estimated to be 74% in each group.[10] The non-inferiority margin or superiority margin (δ) was estimated to be 20. Using the following formula for a non-inferiority trial or superiority trial for binary data, the required sample size to achieve an 80% power ($\beta = 0.2$) at $\alpha = 0.05$ for detecting such a difference was 60 patients. With a projected drop-out rate of 10%, sixty six patients per treatment group were needed.

Consider:

$$n_2 = \frac{(z_{1-\alpha}+z_{1-\beta})^2}{(\epsilon-\delta)^2}\left[\frac{p_1(1-p_1)}{k} + p_2(1-p_2)\right]$$
$$\epsilon = p_1 - p_2$$
$$k = \frac{n_1}{n_2}$$
$$n_1 = kn_2$$

Inclusion and exclusion criteria

Patients aged between 18 to 60 years of both sexes with a diagnosis of PER according to Allergic Rhinitis and its Impact on Asthma (ARIA) guideline[1] who had allergic symptoms for at least 12 months with a TNSS ≥ 6 were included into the study. Patients were excluded if they had hypersensitivity or intolerance to RUP, LEV, pseudoephedrine or ingredients of the drugs, rhinitis medicamentosa, acute or chronic upper respiratory infections within 30 days before the study, structural abnormalities of the nose such as nasal septum deviation more than 50% and nasal polyp, kidney or liver disease, sinusitis, asthma, uncontrolled hypertension, diabetes mellitus, or severe chronic illness, treatment with nasal surgery, antibiotics, systemic or intranasal corticosteroids in the previous 4 weeks, immunotherapy (previous year), oral antihistamines within 2 weeks prior to enrollment, drug abuse, smoking, pregnancy or lactating.

Assessments

During a 1-week run-in period and 4-week-study period, patients had to stop using any medication for allergic treatment and were instructed to daily record 24-hour-reflective symptoms in a diary card. Severity scores for 4 individual nasal symptoms: rhinorrhea, sneezing, nasal itching, and nasal obstruction, and 3 individual ocular symptoms: eye itching, tearing, and eye redness were recorded according to the 4-point scales with 0 = absent, 1 = mild (symptom was present but not troublesome), 2 = moderate (symptom was frequently troublesome but did not interfere with either normal daily activity or night-time sleep), 3 = severe (symptom was sufficiently troublesome to have interfered with normal daily activity or night-time sleep). TNSS were the sum of each individual nasal symptom score and total ocular symptom scores (TOSS) were the sum of each ocular symptom score. Patients were provided pseudoephedrine 60 mg tablet and normal saline solution (NSS) for nasal irrigation as rescue treatments for intolerable nasal obstruction and rhinorrhea, respectively. The rescue treatments were not allowed 24 hours before each visit.

The nasal patency was measured by PNIF (In-Check Nasal®, Clement Clark International, United Kingdom) at each visit (week 0, 2 and 4). Patients were instructed how to sniff correctly for PNIF measurement and tested for 3 times. The mean PNIF of each subject was calculated and used for analysis. The nasal cytology was done at week 0 and 4 by scraping the middle-third of inferior turbinate mucosa with disposable plastic scoop (Rhinoprobe®, Allertech Corp., Thailand) to obtain nasal specimen. The nasal specimen was then spread on the microscopic slide and stained with modified Wright-Giemsa stain.[11] The nasal cytogram was viewed at high power (oil immersion, ×1000), 200 cells count categorized as eosinophils, basophilic cells, neutrophils, macrophages, lymphocytes

and epithelium cells. The percentages of individual inflammatory cells per total 200 cells were analyzed.[12]

In order to acquire a safety assessment, physical examination including anterior rhinoscopy and non-directive questioning for adverse events were performed every visit. Patients were asked to report every adverse event (AE) to the investigator.

Statistical analyses

One way ANOVA with repeated measurement was used to determine the differences in the means of TNSS, TOSS, number of inflammatory cells in nasal scraping, PNIF, and number of rescue medications used between baseline and subsequent assessment points in each treatment group.

In the analysis among the two treatment groups, the mean changes of TNSS, TOSS, number of inflammatory cells in nasal specimen, PNIF, and number of rescue medications used were compared by Student's *t*-test. The chi-square test was used to determine whether the two groups differed in the number of responders and adverse events.

Analysis of both efficacy and safety was based on modified intention to treat (mITT), including all patients who were randomized, received at least one dose of the study drug, and participated at least 2 visits. mITT was performed by using the individual last observation carried forward change from baseline.

All statistical analyses were 2-tailed, with a significance level set at $p < 0.05$. Statistical analyses were performed using SPSS version 22.0.

Results

Patient characteristics

A total of 188 patients were enrolled into the study, 56 of whom were excluded (Figure 1). The remaining 132 patients were randomized into LEV and RUP groups; 66 per group. In the LEV group, 1 patient withdrew from the study before receiving any medication and 1 patient lost to follow-up at week 2. In the RUP group, 2 patients dropout before any drug intake and 4 patients withdrew from the study before week 2 due to chicken pox ($n = 1$) and lost to follow up ($n = 3$) while 1 patient had severe nasal obstruction thus PNIF could not be measured in this patient. Therefore, the mITT populations were 64 and 59 patients in the LEV and RUP groups, respectively.

Demographic and clinical characteristics at the end of one week run-in period are shown in Table 1. The groups did not differ significantly in baseline data. Among nasal symptoms, nasal obstruction was the most severe, followed by rhinorrhea. Eye itching was the most severe ocular symptom in both treatment groups.

Efficacy of treatments

In a within-group comparison, the mean values of TNSS, TOSS, and individual symptom scores at each time point decreased significantly from their respective baseline values. Table 2 shows the mITT analysis for nasal and ocular symptom scores at baseline, and at week 2 and 4 of treatment. After 4 weeks of treatment, the TNSS and TOSS declined by 49.74% and 56.72%, respectively in the LEV group while those of the RUP group declined by 51.65% and 61.08%, respectively.

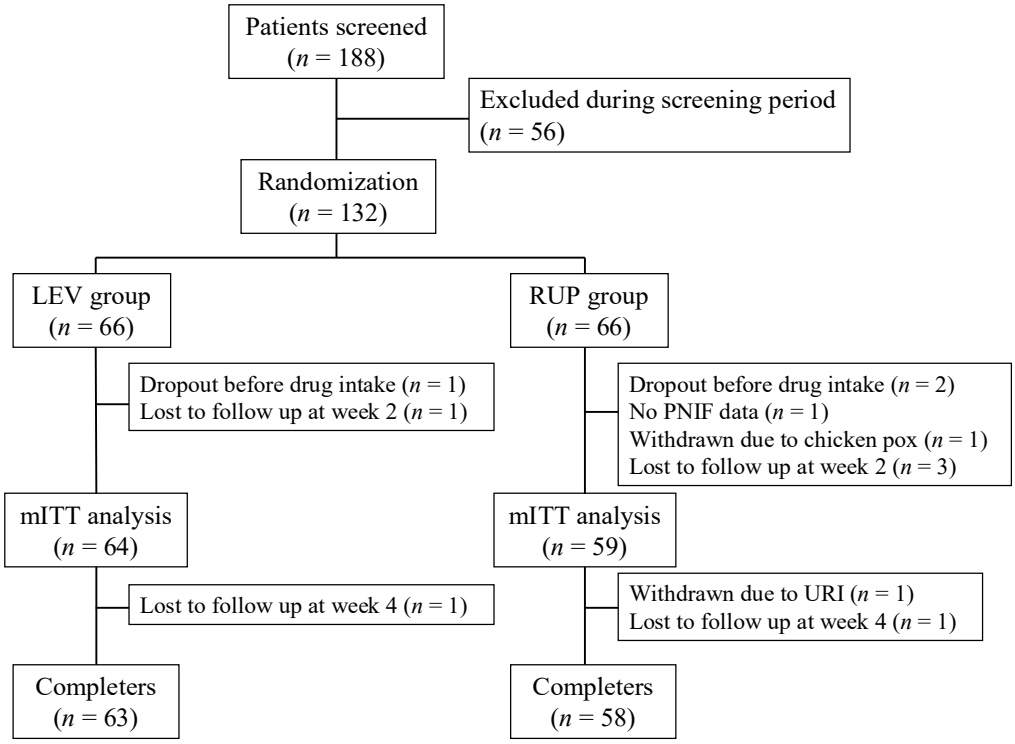

Figure 1. Flow chart of patients participating in the study. URI: upper respiratory tract infection.

Table 1. Demographic and clinical characteristics at baseline (week 0).

Characteristic	Treatment group		*p* value
	LEV	RUP	
n (M:F)	64 (23:41)	59 (18:41)	0.52
Age (y)	34.28 ± 12.20	30.59 ± 10.60	0.19
Duration of AR (y)	6.28 ± 5.38	4.92 ± 3.42	0.64
TNSS[a]	7.62 ± 1.47	7.26 ± 1.34	0.21
Rhinorrhea scores	2.00 ± 0.63	1.89 ± 0.50	0.19
Sneezing scores	1.74 ± 0.59	1.75 ± 0.58	0.95
Nasal itching scores	1.78 ± 0.51	1.62 ± 0.63	0.16
Nasal obstruction scores	2.10 ± 0.58	2.00 ± 0.68	0.39
TOSS[b]	2.68 ± 2.29	2.03 ± 1.79	0.17
Tearing scores	0.86 ± 0.85	0.61 ± 0.68	0.09
Eye itching scores	1.26 ± 0.94	1.05 ± 0.80	0.28
Redness scores	0.56 ± 0.76	0.37 ± 0.58	0.31
PNIF (L/min)	83.44 ± 34.16	87.88 ± 32.58	0.38
Mean of the percentage of the inflammatory cells per total cells			
Eosinophils	1.34 ± 2.74	1.74 ± 3.10	0.49
Basophilic cells	0.86 ± 1.42	0.86 ± 1.54	0.30
Neutrophils	6.00 ± 11.60	3.36 ± 6.63	0.51

Data represent mean ± SEM. [a]Sum of rhinorrhea, sneezing, nasal itching, and nasal obstruction scores. [b]Sum of tearing, eye itching, and eye redness scores.

Table 2. Means of TNSS and TOSS.

	Treatment group	Week 0	Week 2	Week 4
TNSS[a]	LEV	7.62 ± 0.18	4.96 ± 0.30*	3.86 ± 0.28*
	RUP	7.26 ± 0.17	4.03 ± 0.27*	3.51 ± 0.29*
Rhinorrhea	LEV	2.00 ± 0.08	1.27 ± 0.10*	1.03 ± 0.09*
	RUP	1.89 ± 0.06	0.98 ± 0.09*	0.84 ± 0.09*
Sneezing	LEV	1.74 ± 0.07	1.09 ± 0.09*	0.86 ± 0.08*
	RUP	1.75 ± 0.08	0.84 ± 0.08*	0.77 ± 0.07*
Nasal itching	LEV	1.78 ± 0.06	1.08 ± 0.09*	0.74 ± 0.07*
	RUP	1.62 ± 0.08	0.80 ± 0.08*	0.71 ± 0.09*
Nasal obstruction	LEV	2.10 ± 0.07	1.52 ± 0.09*	1.24 ± 0.09*
	RUP	2.00 ± 0.09	1.41 ± 0.11*	1.20 ± 0.11*
TOSS[b]	LEV	2.68 ± 0.29	1.53 ± 0.22*	1.16 ± 0.17*
	RUP	2.03 ± 0.23	0.99 ± 0.16*	0.79 ± 0.14*
Tearing	LEV	0.86 ± 0.11	0.55 ± 0.09*	0.43 ± 0.07*
	RUP	0.61 ± 0.09	0.34 ± 0.06*	0.26 ± 0.06*
Eye itching	LEV	1.26 ± 0.12	0.76 ± 0.10*	0.54 ± 0.08*
	RUP	1.05 ± 0.10	0.49 ± 0.08*	0.40 ± 0.07*
Eye redness	LEV	0.56 ± 0.10	0.22 ± 0.06*	0.18 ± 0.04*
	RUP	0.37 ± 0.08	0.17 ± 0.05*	0.13 ± 0.04*

Data represent mean ± SEM. [a]Sum of rhinorrhea, sneezing, nasal itching, and nasal obstruction scores. [b]Sum of tearing, eye itching, and eye redness scores. *$p \leq 0.001$ compared to their respective baseline values (week 0).

The mean changes in TNSS, TOSS, and individual symptom scores did not significantly differ between the two groups throughout the study period except the sneezing scores in RUP group decreased more than that of LEV group at week 2 ($p = 0.03$). The mean changes of TNSS and individual symptom scores at week 2 and week 4 are shown in Figure 2. Number of responders (defining as the patients who had TNSS decreased ≥ 50% from their own baseline values) were 32 (50%) and 34 (57.63%) patients in LEV and RUP groups, respectively. There was no significant difference between the groups.

The PNIF data are shown in Table 3. In LEV group, PNIF at week 4 increased significantly when compared with the baseline data. In RUP group, PNIF at week 2 and 4 increased from their baseline values but without significant difference. Mean changes of PNIF at week 2 and week 4 were not significantly different between the two groups. After 4 weeks of treatment, there was no significant change in the percentage of inflammatory cells (eosinophils, basophilic cells, and neutrophils) when compared with the baseline data and no significant difference between the two treatment groups was found.

The use of rescue therapy in both groups was decreased at week 4 when compared to those of week 2 (Table 4). At the end of treatment, 67.19% and 79.66% of the patients in LEV and in RUP groups did not use pseudoephedrine. Number of pseudoephedrine tablets used per person in RUP group were less than those of LEV group. However, there was no statistically significant difference in number of subjects and frequency of NSS and pseudoephedrine usages between LEV and RUP groups (Table 4).

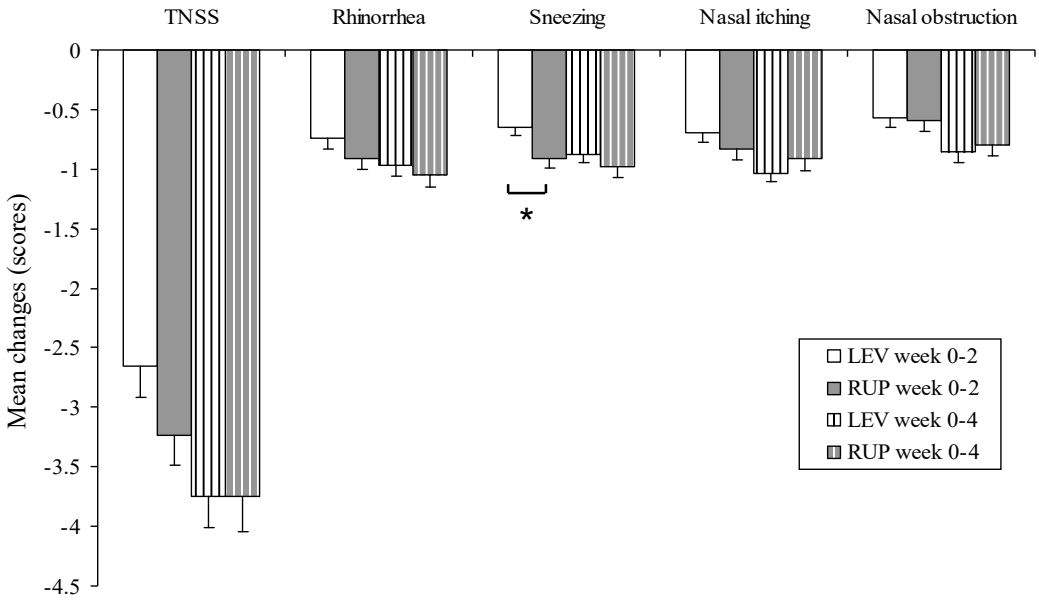

Figure 2. Mean changes from baseline of TNSS and individual symptom scores at week 2 and 4. Data are expressed as mean ± SEM. *Significantly different between groups at p value < 0.05.

Table 3. Mean of PNIF (L/min).

	Week 0	Week 2	Mean change	Week 4	Mean change
LEV	83.44 ± 4.27	91.25 ± 5.12	7.81 ± 3.39	96.95 ± 5.70*	13.52 ± 3.81
RUP	87.88 ± 4.24	89.66 ± 4.22	1.78 ± 3.60	92.03 ± 4.28	4.15 ± 3.32

Data represent mean ± SEM. *$p \leq 0.01$ compared to their respective baseline values (week 0).

Table 4. Number of subject and frequency of using rescue treatment.

Treatment period/Rescue treatment	Treatment group		p value
	LEV	RUP	
NSS			
Week 2			
• Number of subjects	26 (40.63%)	28 (47.46%)	0.50
• Times of use (times/person/2 wk)	2.58 ± 0.56	2.80 ± 0.67	0.80
Week 4			
• Number of subjects	24 (37.50%)	14 (23.73%)	0.14
• Times of use (times/person/2 wk)	2.33 ± 0.51	1.81 ± 0.61	0.51
Pseudoephedrine HCl			
Week 2			
• Number of subjects	21 (32.81%)	13 (22.03%)	0.17
• Number of tablets (tablets/person/2 wk)	1.44 ± 0.32	0.76 ± 0.25	0.10
Week 4			
• Number of subjects	21 (32.81%)	12 (20.34%)	0.16
• Number of tablets (tablets/person/2 wk)	0.98 ± 0.20	0.49 ± 0.18	0.06

Data represent mean ± SEM.

Safety of treatments

Summary of AEs occurrence during the study are shown in Table 5. No AEs were encountered in 23.44% of patients in LEV group and in 18.33% in RUP group. The overall AEs in both groups were similar. The most common AEs were somnolence (56.25% in LEV and 62.71% in RUP) and dry throat (57.81% in LEV and 49.15% in RUP). Most AEs were mild to moderate in severity. There were no serious AEs occurred in this study. Therefore, both drugs were well tolerated by the studied patients.

Table 5. AEs occurrence in the study.[a]

AEs	Treatment group		*p* value
	LEV n (%)	RUP n (%)	
No AEs	15 (23.44)	11 (18.33)	0.80
Central nervous system			
Somnolence	36 (56.25)	37 (62.71)	0.54
Drowsiness	22 (34.38)	22 (37.29)	0.79
Dizziness	9 (14.06)	4 (6.78)	0.18
Fatigue	9 (14.06)	5 (8.47)	0.32
Headache	5 (7.81)	5 (8.47)	0.92
Asthenia	3 (4.69)	1 (1.69)	0.34
Confusion	1 (1.56)	2 (3.39)	0.52
Gastrointestinal system			
Dry throat	37 (57.81)	29 (49.15)	0.29
Diarrhea	2 (3.13)	0	0.17
Nausea	0	1 (1.69)	0.30
Eye			
Dry eye	15 (23.44)	13 (22.03)	0.81
Blurred vision	3 (4.69)	1 (1.69)	0.34
Cardiovascular system			
Tachycardia	5 (7.81)	1 (1.69)	0.11
Kidney and urinary bladder			
Dysurea	1 (1.56)	0	0.33

[a] More than one AEs in some patients. Statistical analysis: chi-square test.

Discussion

We have demonstrated that the once-daily administration of either RUP 10 mg or LEV 5 mg for 4 weeks significantly improved nasal and ocular allergic symptoms in PER patients, with no difference between these two treatment groups.

According to the ARIA classification system which is based on duration and severity of symptoms and their impact on QOL, PER is defined by symptoms that last more than 4 days per week and more than 4 consecutive weeks.[1] In PER, local inflammation is closely linked to nasal obstruction. Vasodilation induced by allergic inflammation causes engorgement of sinusoidal capacitance vessels follow

by mucosal swelling.[13] Therefore, some second-generation H_1-antihistamines with anti-inflammatory effect could be more effective to reduce nasal obstruction than their first generation counterparts. In this study, LEV and RUP statistically significantly decreased TNSS and individual nasal symptom scores, including nasal obstruction. TNSS is the accepted primary efficacy outcome for clinical study of AR.[14] The clinically significant difference in TNSS can be estimated through determination of a minimal clinically important difference (MCID), which is defined as the minimal amount of a treatment effect that is important to the patient.[15] Barnes *et al*.[16] recommend using MCID of 0.55 scores for TNSSs. In addition, the Agency for Healthcare Research and Quality (AHRQ) in the USA recommends using an MCID equal to 30% of the maximum TNSS (3.6 scores on a 12-score scale).[15] In the present study, the mean changes in TNSS from baseline values at week 4 were 3.75 ± 0.26 and 3.75 ± 0.29 scores in LEV and RUP groups, respectively. These changes were greater than the MCID values recommended by Barnes *et al*. and AHRQ. Therefore, the reduction of nasal symptoms in both treatment groups was of clinical significance. These findings were similar to previous studies.[9, 17-20] The 4-week-treatment period was enough to summarize the efficacy of these drugs as shown in previous studies that second-generation H_1-antihistamines exhibit the efficacy in PER patients as early as 1 week after treatment.[1, 17-18]

PNIF which was used as an objective measurement for nasal obstruction was increased in both treatment groups (96.95 ± 5.70 L/min in LEV group and 92.03 ± 4.28 L/min in RUP group). However, only LEV treatment significantly improved PNIF at week 4 from baseline value. The cut-off point of determining the improvement of nasal obstruction for PNIF is 90 L/min.[21] Thus, LEV and RUP could increase PNIF to normal level. In addition, the mean change from baseline value in LEV group was 13.52 ± 3.81 L/min which exceeded the 5 L/min as indicated by the MCID for PNIF.[16]

The more beneficial positive effects of LEV on symptom scores, especially the nasal obstruction over the older H_1 receptor blockers are likely due to its additional anti-inflammatory activities.[7] Ciprandi *et al*.[22] found that LEV significantly reduces nasal obstruction, increases nasal airflow, reduces the percentage of reversibility in decongestant test together with decreased nasal eosinophils and IL-4 in patients with perennial allergic rhinitis. In patients with PER, Bocsan *et al*.[18] found that LEV significantly reduces plasma levels of IL-1β, IL-6, IL-8, and TNF-α after 4 weeks of treatment. In a meta-analysis, LEV exhibits a wide range of anti-inflammatory activities in several *in vitro* and *in vivo* studies and could reduce nasal obstruction as early as the first 2 h and the efficacy could be sustained over 6 weeks under artificial and natural allergen exposure conditions.[23]

RUP also exhibits anti-inflammatory activity as it can block PAF receptors. PAF is a newly generated phospholipid-derived mediator. Its effects include platelet aggregation, mast cell degranulation, eosinophil chemotaxis and activation, and activation of neutrophils and macrophages. In AR, PAF increases vascular permeability which contributes to nasal obstruction and rhinorrhea. It also exacerbates nasal inflammation by attracting and activating granulocytes within the nasal endothelium.[9] RUP shows competitive PAF-antagonistic activity *in vitro*. It also exhibits anti-PAF effect in animal studies. For example, it can inhibit PAF-

induced bronchospasm in guinea pigs and PAF-induced wheal formation in dogs. In addition, it has other anti-inflammatory activities such as inhibiting mast cell degranulation and reducing inflammatory cell recruitment. Several clinical studies in PER found that RUP 10 mg improves all nasal symptom scores including nasal obstruction as well as QOL better than those of placebo.[9]

The patients in this study were allowed to use rescue treatment when their symptoms were intolerable. Therefore, the beneficial results on reducing nasal symptoms by RUP and LEV observed in this study might be partly due to the effects of rescue treatment. However, only one-third of patients used rescue treatment which was minimal and no statistically significant difference between both treatment groups. At week 2, patients in RUP group used NSS comparable to LEV group but used pseudoephedrine less than LEV group. Even though RUP significantly reduced sneezing scores more than that of LEV which is consistent with previous study[24] that RUP reduces TNSS and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores to a greater extent than LEV in seasonal allergic rhinitis patients. Patients in RUP group seem to use NSS and pseudoephedrine less than that of LEV group, especially the number of pseudoephedrine tablets used/person at week 4 (0.49 vs 0.98, $p = 0.06$). While the mean changes of TNSS of both groups were similar.

The most common AEs observed in this study were somnolence followed by drowsiness. Marmouz *et al.*[19] reported that the somnolence occurs more frequently in RUP group compared with placebo. In a 1-year multicenter open-label study in PER patients, the most common RUP treatment-related AEs were headache, somnolence, and dry mouth and no adverse cardiovascular effect in extensive clinical trials involving adults or children was occurred.[9] A study compared the risk of sedation and drowsiness between LEV and desloratadine found that the first occurrence of sedation in both groups is low but significantly lower with desloratadine than LEV.[25] In other studies, common AEs of LEV include headaches, somnolence, and dry mouth similar to RUP.[26] In the present study, either LEV or RUP were administered in the morning, this may explain the higher incidence of somnolence and drowsiness than other studies in which antihistamines were administered in the evening.

This study was a randomized, single-blind, active controlled study. Only the investigators were unaware of which drug the patients were taking. Therefore, the bias might occur if the patients knew the randomization assignment. A randomized, double-blind, double-dummy, controlled study should be designed in future study.

Conclusions

In this study, we have demonstrated that the once-daily administration of RUP 10 mg for 4 weeks is as effective as LEV 5 mg in relieving the symptoms of PER.

Conflict of Interests

There are no conflicts of interest. None of the authors have a direct financial relation with any of the commercial identities mentioned in the paper.

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