Effects of bepotastine, a nonsedating H1-antihistamine, for the treatment of persistent cough and allergic rhinitis: a randomised, double-blind, placebo-controlled trial

Ji-Hyang Lee, Ji-Yoon Oh, Hyouk-Soo Kwon, Tae-Bum Kim, You Sook Cho and Woo-Jung Song

Department of Allergy and Clinical Immunology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea.

Corresponding author: Woo-Jung Song (swj0126@amc.seoul.kr)

Shareable abstract (@ERSpublications)
Nonsedating H1-antihistamines offer no improvement over placebo in cough outcomes, even in patients with allergic rhinitis and cough. The treatment effects observed in real-world practice may largely result from regression to the mean effects. https://bit.ly/3OPbiH4

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Abstract

Background Empirical therapy with oral histamine-1 receptor antagonists (H1RAs) is often used for patients with suspected upper airway cough syndrome. No placebo-controlled trials with nonsedating H1RAs (nsH1RAs) have evaluated validated cough outcomes. The objective of the present study was to assess the effect of an nsH1RA, bepotastine, on cough outcomes in patients with allergic rhinitis and persistent cough.

Methods A randomised, double-blind, placebo-controlled trial was conducted. Adult patients with persistent cough (>3 weeks in duration) and symptomatic allergic rhinitis were recruited and randomly assigned to receive either bepotastine or placebo at a 1:1 ratio. The primary outcome was cough-specific quality of life assessed using the Leicester Cough Questionnaire (LCQ). Secondary outcomes included cough severity visual analogue scale (VAS), throat VAS, Cough Hypersensitivity Questionnaire, Sinonasal Outcome Test-22 score and drug adverse events.

Results Between October 2021 and September 2022, 50 participants (43 females; mean age 46.28 years; median cough duration 3 months) were assigned to either the bepotastine 10 mg twice daily or placebo group in a 1:1 ratio. After 2 weeks of treatment, both bepotastine and placebo groups showed significant improvements in the LCQ scores, but there was no significant difference in the magnitude of change between the groups (3.45±2.10 *versus* 3.04±2.94, p=0.576). Secondary outcomes were also comparable.

Conclusions Despite the relatively small sample size, our study clearly demonstrated that a 2-week treatment with bepotastine did not provide therapeutic benefits for cough outcomes. These findings suggest against the use of nsH1RAs with the intention of improving cough outcomes, even in patients with persistent cough and allergic rhinitis.

Introduction

Chronic cough is a common medical condition, with a prevalence of 5–10% in general populations [1]. It is a major cause of morbidity and impairs patient quality of life (QoL) [2–4]. For decades, anatomical diagnostic protocols based on the anatomy of cough reflex pathways have been widely used in the management of chronic cough; these protocols recommend the identification and treatment of underlying conditions that provoke cough, such as rhinitis, asthma, eosinophilic bronchitis or gastro-oesophageal reflux disease (GORD) [5–8].

In East Asia and North America, cough related to upper respiratory diseases, termed upper airway cough syndrome (UACS), has been considered a major cause of chronic cough [5, 9]. In these cases, allergic rhinitis, nonallergic rhinitis, and rhinosinusitis have been associated with chronic cough; however, the mechanistic link remains disputed [10, 11].

The diagnosis of UACS often relies on the response of cough to empirical treatment, since there are no pathognomonic symptoms, signs or objective tests [11, 12]. The primary medications suggested for UACS include oral histamine-1 receptor antagonists (H1RAs), oral decongestants or intranasal corticosteroids (INCS); however, the guideline recommendations regarding the use of H1RAs vary between countries and across continents [13]. While the guidelines from European countries do not support empirical use of H1RAs targeting UACS, those from America and the Asia-Pacific region suggest the use of either sedating H1RAs (sH1RAs) or nonsedating H1RAs (nsH1RAs) as the first-line treatment when UACS is suspected. However, the use of sH1RAs may confound the diagnosis of UACS or interpretation of causal relationships between allergic rhinitis and cough because the antitussive effects of sH1RA may be due to its sedative effects on the central nervous system. Furthermore, sH1Ras have been largely replaced with nsH1RAs in the most allergic diseases due to the risk of central side-effects and falls from sH1RAs [14]. Indeed, although H1RAs are frequently prescribed for patients with chronic cough, their effects on cough remain poorly understood [15–17].

In the literature, no randomised clinical trial (RCT) of nsH1RAs has been conducted to evaluate validated cough outcomes in patients whose chief complaint is chronic cough [13]. Our previous systematic review identified nine RCTs reporting any effects of nsH1RAs on cough outcomes among patients with allergic respiratory diseases (allergic rhinitis, allergic asthma or atopic cough) that may present with cough [13]. Although significant treatment responses over placebo were suggested in nonasthmatic patients with cough and seasonal allergic rhinitis or atopic cough, the findings were inconclusive due to limited information regarding cough status and outcomes [13]. Furthermore, in most of the RCTs identified in the systematic review, cough was not assessed by validated patient-reported outcomes.

Therefore, we conducted a randomised, double-blind, placebo-controlled trial to evaluate the effect of an nsH1RA, bepotastine [18], on cough patient-reported outcomes in patients with allergic rhinitis and persistent cough.

Methods

Study design and participants

This was an investigator-initiated, randomised, double-blind, placebo-controlled, parallel-group study conducted at a tertiary allergy and cough clinic in Seoul, Korea. The study enrolled patients with persistent cough (>3 weeks in duration) and current allergic rhinitis who were aged 18–80 years. For inclusion, a subject had to have a cough severity score of >30 mm on a 100-mm visual analogue scale (VAS) and a physician-confirmed diagnosis of allergic rhinitis. The diagnosis of current allergic rhinitis was made based on the presence of one of the typical allergic rhinitis symptoms, such as rhinorrhoea, nasal obstruction, sneezing, an itchy nose, itchy eyes or post-nasal drip. Participants underwent skin-prick tests with panels of common inhalant allergens, including *Dermatophagoides farinae*, *D. pteronyssinus*, cat, dog, *Aspergillus*, *Alternaria*, mugwort, ragweed, tree pollen mix and grass pollen mix [19]. In addition, they underwent pulmonary function tests, fractional exhaled nitric oxide (F_{ENO}) measurement and complete blood count test.

Subjects were excluded if they 1) were current smokers; 2) were having current symptoms of other active respiratory disease such as fever, chills, wheezing, dyspnoea or purulent sputum that required additional treatments; 3) were being treated with allergen immunotherapy; 4) were using INCS or leukotriene receptor antagonists (LTRAs) to control allergic rhinitis or chronic rhinosinusitis; 5) had received treatment with angiotensin-converting enzyme inhibitors in the previous month; 6) had abnormal lung function including either forced expiratory volume in 1 s (FEV_1)/forced vital capacity <0.7 or FEV_1 <80% predicted; 7) had abnormal findings on a chest radiograph that might be related to cough; or 8) were diagnosed with or treated for asthma or COPD within the previous year.

The recruitment notice was posted on online and offline bulletin boards of the hospital, as well as on the internet website, to increase accessibility for potential participants. The study was approved by the institutional review board (IRB) of Asan Medical Center (IRB number 2021-0363) and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before enrolment. The trial was registered at ClinicalTrials.gov (NCT04877678).

Intervention and randomisation

The patients received a 2-week treatment with either bepotastine (10 mg twice daily, an approved dose for the treatment of allergic rhinitis [18]) or placebo. During the intervention, concomitant medications including LTRAs, nasal decongestants, INCS, systemic corticosteroids and any antitussive agents were prohibited. The allocation of participants to the treatment group was conducted using simple randomisation

by an independent research nurse. A box with active drugs and placebos at a 1:1 ratio in identical containers was provided by Daewon Pharmaceutical (Seoul, Korea). Throughout the study, the nurse randomly selected containers from the box and assigned the treatment therein to the participants. A table matching the containers to the included medication was revealed by the drug provider (Daewon Pharmaceutical) only after the completion of the study. Throughout the intervention period, the participants, researchers and participating physicians were all blinded to the treatment assignment.

Outcomes

The primary outcome was cough-specific QoL assessed using the Leicester Cough Questionnaire (LCQ). The primary objective was to evaluate whether 2-week treatment with bepotastine was superior to placebo in the improvement of LCQ scores (>2 points). Secondary outcomes included cough severity VAS, throat VAS, Cough Hypersensitivity Questionnaire (CHQ) and Sinonasal Outcome Test (SNOT)-22. The secondary objectives were to compare 1) other cough scores (the cough severity VAS and CHQ scores); 2) the SNOT-22 and throat VAS scores; and 3) adverse drug reactions (ADRs) at 2 weeks between active and placebo treatment groups. As an exploratory objective, we performed sensitivity analyses to explore the baseline clinical factors and laboratory results that might be related to better responses to bepotastine.

Sample size

The sample size in the original protocol was 78 (39 subjects per group). It was calculated to provide 80% power to detect a target difference of 2.0 [20] between the two treatment groups on the LCQ as a primary end-point with a two-sided significance level of 0.05, assuming a standard deviation of 3.3 and considering a 10% dropout rate. However, due to the challenges in recruitment during the coronavirus disease 2019 (COVID-19) pandemic, the sample size was reduced to 50 (25 subjects per group) in March 2022.

Statistical analysis

The data are presented as mean±SD, median (interquartile range) or percentages according to the type of parameters. Comparisons between groups were performed using t-tests, Mann–Whitney U-tests or Chi-squared tests, as appropriate. A two-sided p-value of <0.05 was considered statistically significant. All statistical analyses were performed using Stata 17 software (Stata Corp, College Station, TX, USA).

Results

Baseline characteristics of the study participants

Between October 2021 and September 2022, 50 patients were recruited and randomly assigned to bepotastine or placebo treatment. One patient in the placebo group did not visit at week 2, and a total of 49 patients completed the study (figure 1). The baseline demographics and clinical characteristics of the participants were comparable between the two trial groups (table 1). The number of participants with chronic cough (>8 weeks) was 16 (64%) and 17 (68%) in the bepotastine and placebo groups, respectively. There was no significant difference in the baseline cough duration or cough severity and throat VAS, LCQ or CHQ scores between the two groups. Nasal symptoms and the severity of allergic rhinitis were also similar: in both groups, sneezing was the most common nasal symptom (92% in the bepotastine group and 88% in the placebo group). The results of diagnostic tests including pulmonary function tests, F_{ENO}, blood eosinophil counts and skin-prick tests were also comparable between the bepotastine and placebo groups,

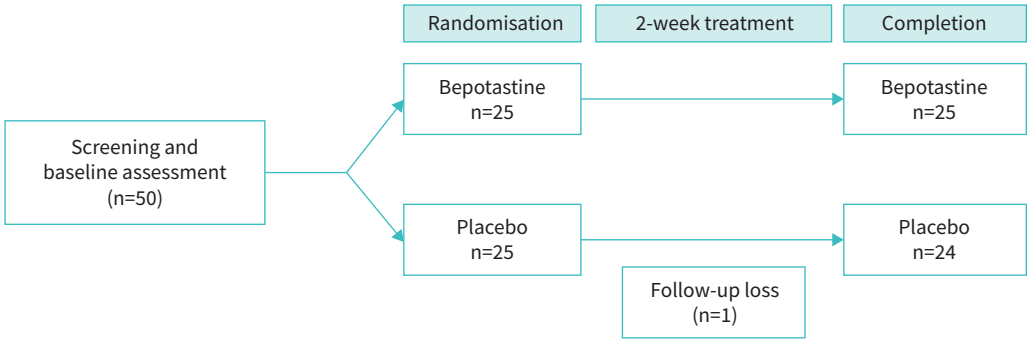

FIGURE 1 Overview of study design. After screening and baseline assessment, 50 participants were randomised to a 2-week treatment with either bepotastine (10 mg twice daily) or placebo. One subject in the placebo group was lost to follow-up, and 49 subjects completed the study.

TABLE 1 Baseline characteristics of the participants

	Bepotastine	Placebo	p-value
Participants	25	25	
Demographics			
Age, years	48.64±10.92	43.92±13.46	0.180
Female	20 (80.0)	23 (92.0)	0.417
BMI, kg·m^{-2}	23.17±4.15	24.85±5.23	0.215
Ex-smoker/never-smoker	4/21	2/23	0.667
Characteristics of cough			
Previous history of persistent cough (⩾3 weeks)	24 (96.0)	24 (96.0)	1.000
Chronic cough (duration ⩾8 weeks)	16 (64.0)	17 (68.0)	0.765
Onset of cough (remote), months	36 (12–102)	18 (10–66)	0.599
Onset of cough (remote), months	53.75±57.91	53.81±75.82	0.998
Onset of cough (recent), months	3 (1.25–4.13)	2.5 (1.63–9.50)	0.689
Onset of cough (recent), months	9.20±19.19	20.23±60.41	0.389
Cough severity VAS	58.60±13.96	58.20±11.98	0.914
Throat VAS	57.40±21.17	58.00±17.02	0.913
LCQ score	12.49±1.96	12.94±2.22	0.453
CHQ score	11.40±3.86	11.76±3.22	0.722
Characteristics of allergic rhinitis			
Previous history of allergic rhinitis diagnosis	18 (72.0)	17 (68.0)	0.758
Symptoms of allergic rhinitis			
Sneezing	23 (92.0)	22 (88.0)	1.000
Rhinorrhoea	20 (80.0)	19 (76.0)	0.733
Nasal obstruction	13 (52.0)	19 (76.0)	0.077
Itchy nose	15 (60.0)	14 (56.0)	0.774
Itchy eyes	15 (60.0)	12 (48.0)	0.395
Post-nasal drip	7 (28.0)	6 (24.0)	0.747
Severity of allergic rhinitis			
Mild, intermittent	2	2	0.934
Mild, persistent	2	2	
Moderate to severe, intermittent	6	8	
Moderate to severe, persistent	15	13	
SNOT-22 score	64.40±18.74	57.60±21.32	0.237
Diagnostic tests			
Pre-BD FEV_1, % pred	88.79±10.11	91.96±11.66	0.316
Pre-BD FVC, % pred	88.63±11.49	91.48±8.23	0.321
Pre-BD FEV_1/FVC ratio	0.82±0.06	0.83±0.09	0.803
F_{ENO}, ppb	19.46±9.41	16.44±7.42	0.217
Blood eosinophil count, cells·μL^{-1}	190±144.48	228±218.38	0.472
SPT positivity	10 (40.0)	16 (64.0)	0.089
SPT positivity to perennial allergen[#]	10 (40.0)	12 (48.0)	0.569
SPT positivity to seasonal allergen[¶]	4 (16.0)	11 (44.0)	0.031
SPT positivity to both perennial and seasonal allergens	4 (16.0)	7 (28.0)	0.306

Data are presented as n, mean±SD, n (%) or median (interquartile range), unless otherwise stated. BMI: body mass index; VAS: visual analogue scale; LCQ: Leicester Cough Questionnaire; CHQ: Cough Hypersensitivity Questionnaire; SNOT-22: Sinonasal Outcome Test-22; BD: bronchodilator; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; F_{ENO}: fractional exhaled nitric oxide; SPT: skin-prick test. [#]: includes *Dermatophagoides farinae*, *D. pteronyssinus*, cat, dog, *Aspergillus* and *Alternaria*; [¶]: includes mugwort, ragweed, tree pollen mix and grass pollen mix.

except for skin-prick test positivity to seasonal allergen (16% in the bepotastine group and 44% in the placebo group; p=0.031).

Primary outcome

After 2 weeks of treatment, the LCQ scores significantly improved in both the bepotastine and placebo groups. However, there was no significant difference in the LCQ scores between the two groups (p=0.831) (table 2 and figure 2). From baseline to week 2, the LCQ scores increased from 12.49±1.96 to 15.94±1.80 and from 12.77±2.10 to 15.81±2.45 in the bepotastine and placebo groups, respectively. The change in the LCQ score over 2 weeks was 3.45±2.10 and 3.04±2.94 in the bepotastine and placebo groups, respectively

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TABLE 2 Comparison of the therapeutic effects between bepotastine and placebo

	Bepotastine				Placebo				p-value (bepotastine *versus* placebo)	
	Pre-treatment score	Post-treatment score	Difference	p-value (pre- *versus* post-)	Pre-treatment score	Post-treatment score	Difference	p-value (pre- *versus* post-)	Post-treatment scores	Score difference (post- minus pre-treatment)
Participants	25				24					
Outcomes										
LCQ	12.49±1.96	15.94±1.80	3.45±2.10	<0.001	12.77±2.10	15.81±2.45	3.04±2.94	<0.001	0.831	0.576
Cough severity VAS	58.60±13.96	27.00±15.68	−31.60±18.01	<0.001	58.54±12.11	33.33±18.57	−25.21±23.66	<0.001	0.203	0.292
Throat VAS	57.40±21.17	29.40±17.93	−28.00±25.04	<0.001	57.50±17.19	30.42±17.32	−27.08±22.98	<0.001	0.841	0.894
CHQ	11.40±3.86	8.12±3.59	−3.28±4.17	0.001	11.92±3.19	8.25±4.30	−3.67±4.54	0.001	0.909	0.757
SNOT-22	64.40±18.74	45.69±22.36	−18.72±27.19	0.002	58.33±21.45	37.38±23.86	−20.96±18.56	<0.001	0.215	0.739

Data are presented as n or mean±SD, unless otherwise stated. LCQ: Leicester Cough Questionnaire; VAS: visual analogue scale; CHQ: Cough Hypersensitivity Questionnaire; SNOT-22: Sinonasal Outcome Test-22.

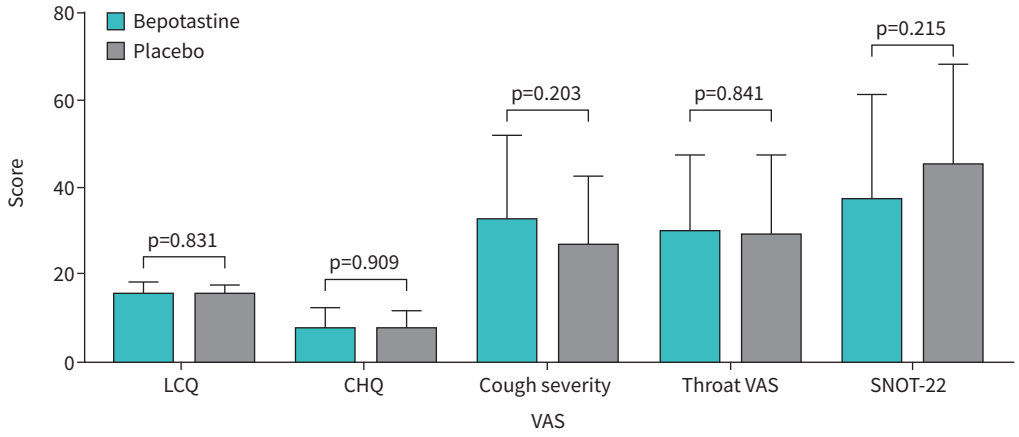

FIGURE 2 Comparison of clinical outcomes after the 2-week intervention in the bepotastine group and the placebo group. Data are presented as mean±SD. LCQ: Leicester Cough Questionnaire; CHQ: Cough Hypersensitivity Questionnaire; VAS: visual analogue scale; SNOT-22: Sinonasal Outcome Test-22.

(p=0.576) (figure 3a). The proportion of patients who showed remarkable improvement in LCQ scores (>4 points) was also similar between the groups: 36% in the bepotastine group and 32% in the placebo group (p=0.845).

Secondary outcomes

There were no significant between-group differences in the following secondary outcomes at the end of the 2-week treatment: cough severity VAS (27.00±15.68 *versus* 33.33±18.57, p=0.203) throat VAS (29.40±17.93 *versus* 30.42±17.32, p=0.841), CHQ (8.12±3.59 *versus* 8.25±4.30 p=0.909) and SNOT-22 (45.69±22.36 *versus* 37.38±23.86, p=0.215) (table 2 and figures 2 and 3). In all participants, the change in the LCQ score was correlated with the changes in the secondary outcomes: cough severity VAS (r=−0.702, p<0.001), throat VAS (r=−0.744, p<0.001), CHQ (r=−0.621, p<0.001) and SNOT-22 (r=−0.514, p=0.003).

Sensitivity analysis

We explored baseline clinical factors associated with better LCQ responses to bepotastine, but did not find any parameters that were statistically significant (table 3). In an analysis confined to 33 participants with chronic cough (>8 weeks in duration), there was no significant difference between the two groups. In addition, skin-prick test positivity, allergic rhinitis symptoms or severity or F_{ENO} levels were not significantly associated with better bepotastine responses. However, in a subgroup of patients with low blood eosinophil counts, bepotastine treatment led to a numerically greater improvement in the LCQ score than placebo (post-treatment score 16.58±1.23 *versus* 15.31±1.93, p=0.078) (table 3).

Adverse reactions

Four (16%) patients in the bepotastine group and three (12.5%) patients in the placebo group reported any ADR that occurred during the study (table 4). The proportion of patients experiencing ADRs and the type of ADRs were not significantly different between the two groups. None were serious and none led to treatment discontinuation.

Discussion

The present study evaluated the therapeutic benefits of bepotastine (*versus* placebo) on validated subjective cough outcomes in patients with both allergic rhinitis and persistent cough (>3 weeks). The 2-week treatment with bepotastine did not lead to any meaningful improvement in cough outcomes. To our knowledge, this is the first RCT to evaluate efficacy of nsH1RAs on validated cough patient-reported outcomes in patients with allergic rhinitis and cough. We observed statistically significant but similar improvement in all subjective cough outcomes in both the bepotastine and placebo groups, suggesting that the cough improvement observed with nsH1RA treatment in nonrandomised trials or real-world practice is largely due to regression to the mean effects or spontaneous improvement of cough.

Mechanistically, cough associated with nasal diseases could at least be partly explained by enhanced activity of the cough centre induced by trigeminal afferent nerve input [21, 22]. However, the clinical evidence and benefits were unclear [11]. In patients with seasonal allergic rhinitis, a heightened cough

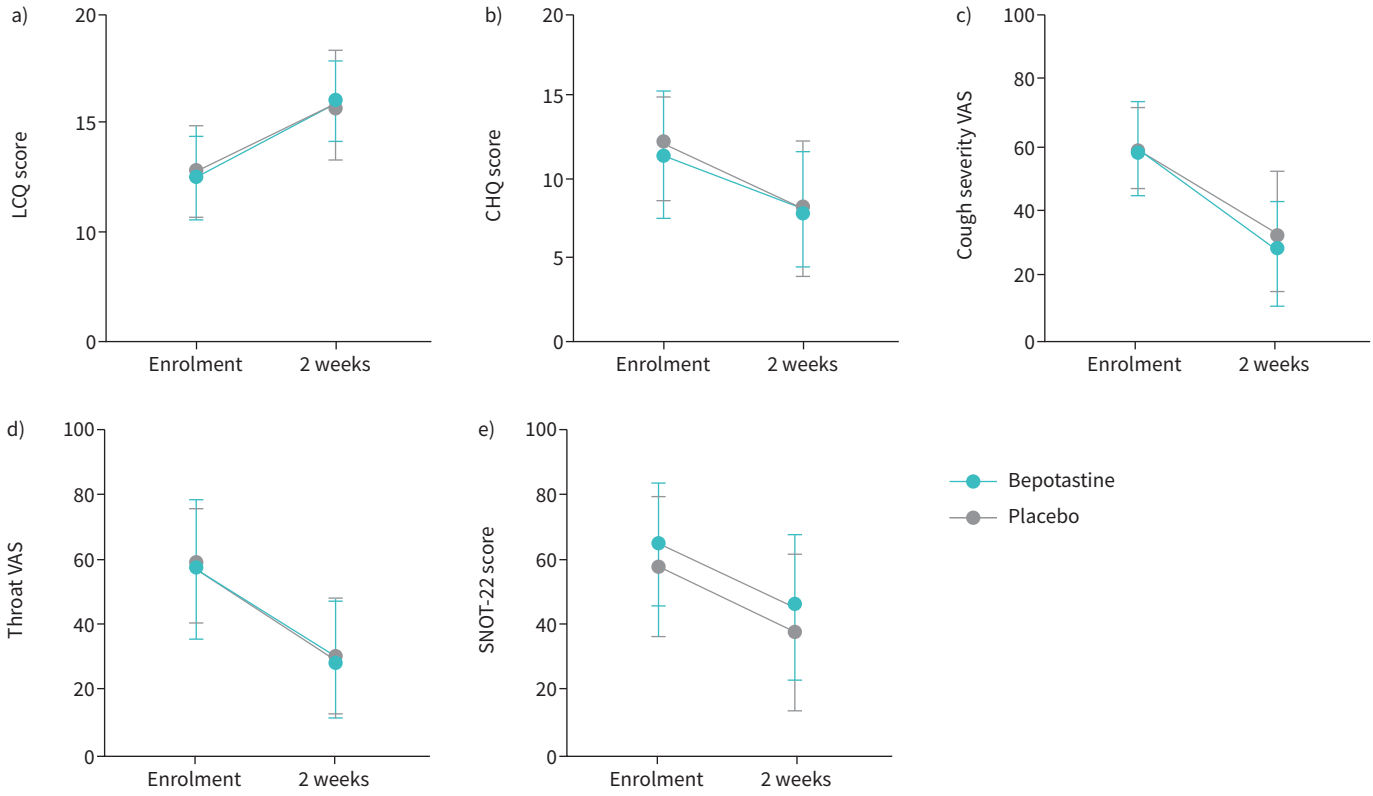

FIGURE 3 Changes in clinical outcomes before and after the intervention in the bepotastine group and the placebo group. Data are presented as mean±SD. a) Leicester Cough Questionnaire (LCQ) score, b) Cough Hypersensitivity Questionnaire (CHQ) score, c) cough severity visual analogue scale (VAS), d) throat VAS and e) Sinonasal Outcome Test (SNOT)-22 score.

reflex sensitivity to capsaicin has been observed irrespective of the pollen season [23]. A population-based longitudinal study reported the presence of rhinitis (defined as having hay fever or any other condition that made the patient's nose runny or stuffy apart from colds) as a risk factor for the development of chronic cough in 5 years [24]. However, nsH1RA treatment did not significantly affect cough reflex sensitivity in both healthy controls and patients with acute cough [25, 26]. Our RCT involving patients with allergic rhinitis and cough, who are considered to be the major population indicated for nsH1RAs, found no significant benefits of nsH1RA treatment (*versus* placebo) on cough patient-reported outcomes. Our findings indicate limited roles of allergic nasal inflammation or H1-pathways in the pathogenesis of persistent cough, at least in the short term.

In a previous systematic review [13], we identified an RCT by Ciprandi *et al.* [27] involving nonasthmatic adults with cough associated with *Parietaria judaica* pollen-allergic rhinoconjunctivitis during the pollen season. They reported significant benefits of loratadine treatment in improving subjective cough frequency and intensity scores (*versus* placebo; reduction by 44.0±7.33% and 65.67±8.33%, respectively); however, the trial had a small sample size (n=20) and did not use a validated cough outcome, which limited the validity and impact of the findings. Meanwhile, the findings are not directly comparable with ours, because the population in the study by Ciprandi *et al.* [27] was confined to a specific pollen-associated allergic rhinoconjunctivitis and cough which occurred during the pollen season, while our study broadly included subjects with current allergic rhinitis based on clinical history and symptoms. However, in our sensitivity analyses according to the presence of skin-prick test positivity or typical histaminergic nasal symptoms (itchy nose, itchy eyes, or sneezing), bepotastine treatment was not superior to the placebo. Our findings suggest limited roles of nsH1RAs in the management of patients with cough, even in the presence of allergic rhinitis signs or symptoms, although the treatment might be beneficial in a selected group of patients with co-occurring seasonal nasal allergies and cough.

In our sensitivity analysis, participants without eosinophilic inflammation (blood eosinophil counts <150 cell·μL^{-1}) tended to respond better to bepotastine than to placebo; however, the difference in

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TABLE 3 Comparison of Leicester Cough Questionnaire scores in the sensitivity analyses by baseline parameters

	Participants (bepostatine/ placebo)	Bepostatine			Placebo			p-value (bepotastine *versus* placebo)	
		Pre-treatment	Post-treatment	Difference	Pre-treatment	Post-treatment	Difference	For post-treatment scores	For score difference (post- minus pre-)
Patients with chronic cough (⩾8 weeks)	33 (16/17)	12.26±2.02	15.83±2.04	3.57±2.25	12.72±2.09	15.42±2.25	2.71±3.02	0.596	0.361
Patients sensitised with any inhalant allergen proven by SPT	25 (10/15)	12.48±2.49	15.40±2.34	2.92±2.94	12.50±2.41	15.21±2.46	2.71±3.22	0.846	0.868
Patients with typical histaminergic allergic rhinitis symptoms (itchy nose, itchy eyes, sneezing)	47 (24/23)	12.58±1.95	16.03±1.79	3.45±2.15	12.87±2.09	15.83±2.50	2.97±2.98	0.760	0.524
Patients with moderate to severe allergic rhinitis	41 (21/20)	12.16±1.95	15.78±1.79	3.62±2.15	12.92±2.21	15.91±2.57	2.99±3.00	0.853	0.439
Patients with uncontrolled rhinitis (SNOT-22 score ⩾50)	32 (18/14)	12.32±1.90	16.02±2.01	3.71±2.04	12.16±2.27	15.19±2.69	3.03±3.38	0.322	0.488
Patients with F_{ENO} <25 ppb	39 (17/22)	12.86±1.90	16.39±1.64	3.54±2.05	12.65±2.12	15.62±2.45	2.97±3.06	0.267	0.515
Patients with blood eosinophils <150 cells·μL^{-1}	25 (10/15)	12.64±1.82	16.58±1.23	3.94±1.38	12.65±2.42	15.31±1.93	2.66±3.27	0.078	0.256

Data are presented as n or mean±SD, unless otherwise stated. SPT: skin prick test; SNOT-22: Sinonasal Outcome Test-22; F_{ENO}: fractional exhaled nitric oxide.

TABLE 4 Adverse drug reactions

	Bepotastine	Placebo	p-value
Participants	25	24	
Any adverse drug reaction	4 (16.0)	3 (12.5)	0.726
Dizziness	4 (16.0)	1 (4.2)	0.171
Fatigue	2 (8.0)	0	0.157
Headache	2 (8.0)	0	0.157
Dry mouth	1 (4.0)	1 (4.2)	0.976
Constipation	0	1 (4.2)	0.302
Others	0	2 (8.3)	0.141

Data are presented as n or n (%), unless otherwise stated.

post-treatment score did not achieve statistical significance (LCQ score 16.58±1.23 *versus* 15.31±1.93, p=0.078). Our previous systematic review found the potential that cough in patients without asthma may respond better to nsH1RA treatment than those with asthma [13]. These findings may be plausible because nsH1RA plays no role in the management of eosinophilic airway inflammation or asthma. Additionally, these findings suggest that screening for asthma or eosinophilic airway inflammation should be prioritised when considering the use of nsH1RA for patients with persistent cough.

This study has several limitations. First, it was conducted at a single tertiary centre, which may limit the generalisability of the results. However, we utilised online and offline bulletin boards of the hospital as well as an internet website to recruit patients from the community. Second, the study did not confine itself to subjects with chronic cough (>8 weeks in duration). A shorter cough duration might increase the probability of spontaneous improvement of the cough. However, we set the minimum duration at >3 weeks because we deemed that those patients with a longstanding cough (lasting several months or more) were likely to have aetiologies other than allergic rhinitis alone. Third, allergic sensitisation was not confirmed by skin-prick tests in all participants, and the proportion of subjects with positive skin-prick test results for seasonal allergens differed between the treatment groups. This may be partly due to the limited number of inhalant allergens used in the present study. However, the inhalant panel may explain the majority of allergic sensitisation among Korean adults [19]. Fourth, we set no criteria for GORD in patient screening; thus, untreated GORD might have confounded the treatment outcomes. However, we observed similar and substantial improvements in cough outcomes either with bepotastine or placebo treatment over 2 weeks (*e.g.* LCQ score improvement by 3.0–3.5 points) and speculate that the confounding effects due to untreated GORD were minimal. Fifth, the objective cough frequency was not measured. In the study design stage, we had planned to optionally apply a smartphone-based monitoring tool to patients who were willing to measure their cough frequency, but decided not to use it because the feasibility and validity were not confirmed before conducting this clinical trial. Finally, the number of participants was reduced from 78 to 50 due to the COVID-19 pandemic. With 50 subjects, we could achieve a statistical power of 68% to explain the results. Although an increased number of participants is unlikely to change the conclusion, given the comparable outcomes between the two treatment groups, further study may be necessary to confirm the conclusion with sufficient statistical power.

Despite these limitations, our study clearly demonstrated that a 2-week treatment with bepotastine did not provide therapeutic benefits for cough outcomes. These findings suggest against the use of nsH1RAs with the intention of improving cough outcomes in patients with persistent cough and allergic rhinitis.

Provenance: Submitted article, peer reviewed.

This study is registered at www.clinicaltrials.gov with identifier number NCT04877678. Individual de-identified participant data will be available upon request to the corresponding author for academic purposes.

Ethics statement: The study was approved by the Institutional Review Board of Asan Medical Center (IRB number 2021-0363) and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before enrolment.

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Conflict of interest: W-J. Song is deputy chief editor of this journal. The other authors declare that they have no competing interests.

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