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Review

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# KAAACI Allergic Rhinitis Guidelines: Part 1. Update in Pharmacotherapy

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## ABSTRACT

The prevalence of allergic rhinitis (AR) and the socioeconomic burden associated with the medical cost and quality of life (QOL) of AR have progressively increased. Therefore, practical guidelines for the appropriate management of AR need to be developed based on scientific evidence while considering the real-world environment, values, and preferences of patients and physicians. The Korean Academy of Asthma, Allergy and Clinical Immunology revised clinical guidelines of AR to address key clinical questions of the management of AR. Part 1 of the revised guideline covers the pharmacological management of patients with AR in

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Korea. Through a meta-analysis and systematic review, we made 4 recommendations for AR pharmacotherapy, including intranasal corticosteroid (INCS)/intranasal antihistamine (INAH) combination therapy, oral antihistamine/INCS combination therapy, leukotriene receptor antagonist treatment in AR patients with asthma, and prophylactic treatment for patients with pollen-induced AR. However, all recommendations are conditional because of the low or very low evidence of certainty. Well-designed and strictly executed randomized controlled trials are needed to measure and report appropriate outcomes.

**Keywords:** Rhinitis, allergic; asthma; guideline; drug therapy

## INTRODUCTION

Allergic rhinitis (AR) is an immunoglobulin E (IgE)-mediated inflammatory disease of the nasal mucous membranes caused by inhaled allergens, which provoke nasal symptoms including nasal congestion, rhinorrhea, sneezing, and nasal itching. AR is one of the most common allergic diseases worldwide and is estimated to affect nearly 1 in every 5 adults and 1 in every 3 adolescents in Korea.[1,2] The prevalence of AR has progressively increased and has conferred a substantial economic burden associated with AR management. The Korean National Health Insurance Corporation reported an increase, from 2015 to 2019, in the number of patients with AR and the associated medical costs (15,057,265 to 16,103,366 cases and 1,352 to 1,711 billion won, respectively).[3] Besides the direct medical costs, AR increases the socioeconomic burden because of the adverse impacts of AR on the quality of life (QOL), including low sleep quality, daytime somnolence and fatigue, irritability, depression, and impairment of cognitive or physical function. AR is associated with loss of workdays and schooldays as well as decreased performance.[4] The economic burden of AR is similar to that of asthma and chronic obstructive pulmonary disease (COPD), and the AR-induced loss in productivity is higher than that of asthma and COPD.[5]

Appropriate treatment of AR improves symptoms, QOL, and school and work performance and can substantially reduce the socioeconomic burden. Although several clinical practice guidelines for AR management have been developed, there are significant variations in their application, and many physicians are dissatisfied with the current AR guidelines.[6] Therefore, it is necessary to develop scientific evidence-based practice guidelines for AR management while considering the real-world environment, values, and preferences of patients and physicians. Accordingly, the Korean Academy of Asthma, Allergy and Clinical Immunology (KAAACI) had revised previous guidelines.[7]

By providing the level of evidence and specifying the benefits to promote effective treatment and reduce treatment-related harm, this guideline has been developed to help physicians who manage AR patients in Korea. The target audience of this guideline includes primary care physicians and allergy specialists who manage patients with AR. Pharmacological and non-pharmacological treatment options are covered, and the diagnostic approach to AR and the treatment of other types of rhinitis (*e.g.*, non-allergic, vasomotor, and infectious rhinitis) are beyond the scope of the current guideline.

The guideline reported herein consists of 2 parts: Part 1 covers disease definition, guideline scope, and methodology as well as evidence-based recommendations for pharmacotherapy, and Part 2 pertains to the non-pharmacological treatment of AR.


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## METHODS

This guideline has been developed *de novo* and comprises recommendations based on a systematic review of the selected literature for key questions and from the results of analysis, synthesis, and summary of the evidence. The members of the guideline development committee of KAAACI included experts in allergy and immunology who had specialized in internal medicine, otorhinolaryngology, or pediatrics. The committee members participated in the formulation of key questions, literature searches, systematic review, data extraction, evidence synthesis, and generation of recommendations. At least 2 committee members were assigned to review and write each key question. A methodology specialist coordinated and guided the committee members throughout the entire process of guideline development. All committee members have no potential conflicts of interest. Details of the *de novo* process of guideline development have been summarized in the supplementary materials (**Supplementary Data S1**).

## KEY QUESTIONS AND RECOMMENDATIONS

All key questions and recommendations for the pharmacological management of AR are summarized in **Table 1**, and the details of the evidence supporting each recommendation are described below.

### Key Question 1: Is intranasal corticosteroid and intranasal antihistamine (INCS/INAH) combination therapy more effective than INCS monotherapy for symptom relief in patients with AR?

*Background*

International guidelines recommend INCS as the first-line treatment for patients with moderate-to-severe and/or persistent AR.[4] However, patients often report inadequate symptom relief or difficulties in treatment adherence.[8] Furthermore, although the effects of INCS appear within a few days, maximal effects are attained only after a few weeks in patients with perennial rhinitis.[9] Recently, combination therapy with INCS/INAH has been recommended as an alternative therapeutic option for AR management.[4,10] This population, intervention, comparison, and outcome (PICO) question are intended to initiate a review of the increased efficacy or risk of INCS/INAH combination therapy compared to INCS monotherapy in patients with AR.

**Table 1.** Summary of recommendations for pharmacological management of allergic rhinitis

| Key questions | Recommendations | Quality of evidence | Strength of recommendation |
|---|---|---|---|
| Is INCS/INAH combination therapy more effective than INCS monotherapy for symptom relief in patients with AR? | We suggest an INCS/INAH combination therapy in patients with AR who show inadequate therapeutic effects with INCS monotherapy. | Low quality | Conditional |
| Is OAH/INCS combination therapy more effective for relieving symptoms than INCS monotherapy in patients with AR? | We suggest that, in patients with AR, either OAH/INCS combination therapy or INCS monotherapy can be selected, considering the patient's values and preferences as well as the benefits and harms of treatment. | Low quality | Conditional |
| Do LTRAs reduce rhinitis-related symptoms and medication use in AR patients with asthma? | We suggest LTRA treatment for improving rhinitis-related symptoms in AR patients with asthma. | Low quality | Conditional |
| Is prophylactic treatment before the start of pollen dispersal more effective for relieving symptoms than treatment after the onset of symptoms in patients with pollen-induced AR? | For patients with pollen-induced AR, we suggest prophylactic treatment that commences 2 weeks before pollen dispersal in consideration of the patient's values and preferences as well as the benefits and harms of treatment. | Very low quality | Conditional |

INCS, intranasal corticosteroid; INAH, intranasal antihistamine; AR, allergic rhinitis; OAH, oral antihistamine; LTRA, leukotriene receptor antagonists.


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*Recommendation*

We suggest using INCS/INAH combination therapy in patients with AR with insufficient therapeutic effect with INCS monotherapy (conditional recommendation, low quality of evidence).

*Summary of evidence*

We initially identified and retrieved 19,685 studies, of which 19,643 were excluded after screening the title and abstract. The remaining 42 studies were assessed for eligibility, and 29 were excluded after the full-text screening. A total of 13 randomized controlled trials (RCTs) were identified to compare the INCS/INAH combination therapy with INCS monotherapy.[11-23] Of these, 10 RCTs were included in the meta-analysis for evaluating the difference in symptom score (total nasal symptom score [TNSS], total ocular symptom score [TOSS], rhinoconjunctivitis quality of life questionnaires [RQLQ], and total symptom score [TSS]), and 12 RCTs were included in the meta-analysis for evaluating adverse events (treatment emergent adverse events [TEAEs], dysgeusia, epistaxis, and serious adverse events [SAEs]).[24]

In 7 studies, the TNSS in patients who received INCS/INAH combination therapy was significantly lower than that in patients with INCS monotherapy (mean difference [MD], −0.44; 95% confidence interval [CI], −0.61 to −0.27; $P < 0.00001$; $I^2 = 8\%$).[11,12,14,18,21,24] Furthermore, 2 studies showed a significant decrease in the TOSS after azelastine/fluticasone combination therapy than after fluticasone monotherapy (MD, −0.62; 95% CI, −1.05 to −0.19; $P = 0.005$; $I^2 = 36\%$).[12,14,24] Moreover, the RQLQ was described in 4 studies, and INCS/INAH combination therapy induced a more significant improvement over that of INCS monotherapy (MD, −0.24; 95% CI, −0.42 to −0.06; $P = 0.009$; $I^2 = 79\%$).[11,12,14,15,24] In 3 studies, the TSS slightly decreased with the INCS/INAH combination therapy compared to INCS monotherapy, although this difference was not statistically significant (MD, −0.66; 95% CI, −2.02 to 0.71; $P = 0.34$; $I^2 = 98\%$).[15,19,22,24]

In a meta-analysis of adverse events, the risk of TEAEs increased significantly in the INCS/INAH combination therapy group compared with that in the INCS monotherapy group (relative risk [RR], 1.52; 95% CI, 1.28 to 1.81; $P < 0.00001$; $I^2 = 1\%$).[11-14,16,24] However, in both treatments, the incidence of TEAEs was low (131/1,000 patients for INCS/INAH combination therapy and 93/1,000 patients for INCS monotherapy, respectively). Moreover, dysgeusia induced by nasal spray passing along the back of the throat occurred more frequently with combination therapy than monotherapy (RR, 7.40; 95% CI, 3.60 to 15.23; $P < 0.00001$; $I^2 = 0\%$).[11,12,14,16,19,21,24] However, the incidence of dysgeusia in both treatments was low (19/1,000 patients for combination therapy and 3/1,000 patients for monotherapy, respectively). The incidence of epistaxis, which is a side effect of drugs used as a nasal spray, did not differ significantly between the two groups and was low (RR, 0.97; 95% CI, 0.55 to 1.69; $P = 0.91$; $I^2 = 0\%$; INCS/INAH combination: 17/1,000, INCS alone: 18/1,000).[12,14,16,19,22,24] Furthermore, the incidence of SAEs did not differ significantly between the two groups (RR, 1.72; 95% CI, 0.47 to 6.38; $P = 0.42$; $I^2 = 0\%$).[11-14,16,21,24] In total, 4 specific SAEs were reported in the combination therapy, 2 each of spontaneous abortion and gastritis/gastric ulcers.[17,18] However, the researchers reported that these events were unrelated to combination therapy, and other researchers did not specifically mention the other two SAEs. One SAE (tonsil abscess) was reported with INCS monotherapy, and the researchers reported that this SAE was unrelated to INCS monotherapy.[16]

*Remark*

In a meta-analysis of 13 RCTs, INCS/INAH combination therapy was more effective than INCS monotherapy for reducing symptoms and improving QOL in patients with AR; however,


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adverse events, including dysgeusia, occurred more frequently with INCS/INAH combination therapy.[24] Therefore, to balance the risk-benefit, the committee suggests that INCS/INAH combination therapy be used in patients for whom INCS monotherapy provides inadequate therapeutic effect or for those who want quick and effective symptom relief.

## Key Question 2: Is oral antihistamine (OAH)/INCS combination therapy more effective in relieving symptoms than INCS monotherapy in patients with AR?

*Background*

Domestic and international guidelines recommend that clinicians prescribe INCS monotherapy as the first-line treatment for patients with moderate-to-severe and/or persistent AR. Antihistamines are recommended as a possible treatment option in intermittent AR and mild persistent AR. However, a combination of an OAH and INCS is often used in routine clinical practice for the treatment of AR, regardless of the frequency and severity of AR.[25] This PICO question was to review whether OAH/INCS combination therapy is more effective and safer than INCS monotherapy in patients with AR.

*Recommendation*

We suggest that in patients with AR, either OAH/INCS combination therapy or INCS monotherapy can be selected, considering the patient's values and preferences as well as the benefits and harms of treatment (conditional recommendation, low quality of evidence).

*Summary of evidence*

We identified 19,123 potentially relevant studies, and 29 were assessed for eligibility after reviewing the information provided in the title and abstract of the publications. The full-text screening was performed, and 8 RCTs were finally selected for the meta-analyses.[15,26-32] Among them, 6 studies evaluated differences in symptom scores, and 4 studies described adverse events.

The meta-analysis results revealed no significant difference in the TNSS between OAH/INCS combination therapy and INCS monotherapy (standard mean difference [SMD], −0.16; 95% CI, −0.40 to 0.07; $P = 0.16$; $I^2 = 0\%$). With regard to individual nasal symptom scores, our pooled results from 2 studies did not show any significant difference in each nasal symptom. However, Du *et al.*[33] analyzed the data from 5 studies and demonstrated that OAH/INCS combination therapy was more effective than INCS monotherapy for only rhinorrhea (95% CI, −0.07 to 0; $I^2 = 0\%$; $P$ for overall effect < 0.05), but not nasal congestion, sneezing, or itching. Of the 4 studies that used the RQLQ,[15,26,28,30] compared to INCS monotherapy, OAH/INCS combination therapy induced significant improvement in total mean scores of RQLQ (SMD, −0.26; 95% CI, −0.51 to −0.02; $P = 0.04$; $I^2 = 78\%$); however, the difference did not exceed −0.50, which is the criterion for a clinically significant difference.[34] The change in the TOSS was reported in only one study, and there was no significant difference between combination therapy and monotherapy.

TEAEs tended to occur more frequently with OAH/INCS combination therapy than INCS monotherapy (RR, 1.34; 95% CI, 0.74 to 2.43; $P = 0.30$; $I^2 = 66\%$); however, the incidence of TEAEs was low in both groups (346/1,000 patients for combination therapy and 258/1,000 patients for monotherapy, respectively), and there was no significant difference between the two groups. No SAEs were reported in all 4 studies included in the analysis. Sleepiness, a side effect of antihistamine, occurred more frequently with OAH/INCS combination therapy than with INCS monotherapy (RR, 6.41; 95% CI, 1.28 to 32.14; $P = 0.02$; $I^2 = 9\%$). Although the


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OAH/INCS combination therapy tended to yield a higher frequency of dry mouth than INCS monotherapy, there was no statistically significant intergroup difference (RR, 3.02; 95% CI, 0.32 to 28.58; $P = 0.33$; $I^2 = 0\%$).

*Remark*

In terms of efficacy, OAH/INCS combination therapy does not improve the overall symptom of AR and allergic conjunctivitis over INCS monotherapy alone; however, combination therapy slightly improves the RQLQ and is effective for rhinorrhea among various AR symptoms. In addition, considering that INCSs are not effective within 2 hours,[10] OAH/INCS combination therapy can exert a rapid therapeutic effect if a fast-acting OAH, such as (levo)cetirizine or fexofenadine, is added. With regard to safety, OAH/INCS combination therapy tends to cause more TEAEs or dry mouth compared to INCS monotherapy. However, no significant intergroup difference was found and the incidence of adverse events in both treatments was low. However, sleepiness was significantly more likely to cause harm in combination therapy than in monotherapy.

Furthermore, clinicians should consider treatment adherence when choosing and prescribing drugs. The administration routes of the INCS and OAH are different, which may decrease patient compliance. Therefore, the committee has drawn up a conditional recommendation based on the current evidence, the likelihood of adverse drug events, and compliance.

## Key Question 3: Do leukotriene receptor antagonists (LTRAs) reduce rhinitis symptoms and medication use in AR patients with asthma?

*Background*

Cysteinyl leukotrienes induce smooth muscle contraction, airway edema, inflammatory cell infiltration, and mucus over-secretion, and are one of the important mediators for AR and asthma.[35] LTRAs, including montelukast, pranlukast, and zafirlukast, inhibit the cysteinyl leukotriene receptor 1 and are often used in patients with rhinitis or asthma. However, most patients with asthma concomitantly have rhinitis, and 10%–40% of patients with rhinitis have asthma.[36] LTRA is the only drug that can be used for AR simultaneously with asthma-control agents. This PICO question was to review whether LTRA is effective and safe in AR patients with asthma.

*Recommendation*

We suggest LTRA treatment for improving rhinitis symptoms in AR patients with asthma (conditional recommendation, low quality of evidence).

*Summary of evidence*

We identified 19,110 potentially relevant studies, of which 19,047 were excluded after reviewing the title and abstract of the publications. The remaining 63 studies were assessed for eligibility, of which 60 were excluded after the full-text screening. Only 3 randomized double-blind placebo-controlled studies were finally selected for the meta-analysis.[37-39] These studies analyzed the changes in the daytime total nasal symptom score (D-TNSS) and the night total nasal symptom score (N-TNSS) after the administration of LTRA and placebo drugs. The meta-analysis showed that LTRA treatment significantly reduced the D-TNSS more than placebo (MD, −0.44; 95% CI, −0.63 to −0.25; $P < 0.001$; $I^2 = 0\%$). Furthermore, the N-TNSS significantly decreased after treatment with LTRA compared to placebo (MD, −0.21; 95% CI, −0.35 to −0.07; $P = 0.0001$; $I^2 = 0\%$).


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In addition, headache was the most common adverse event in all 3 studies, followed by sore throat, indigestion, epistaxis, rash, and backache.[37-39] However, the incidence of adverse events in the LTRA-treated group did not differ significantly from that in the placebo-treated group, and no SAEs were reported in all 3 studies.

Despite the low incidence of adverse events, post-marketing surveillance suggested an association between LTRA use and suicide risk in young adults. In March 2020, the US Food and Drug Administration (FDA) warned the risk of serious neuropsychiatric adverse events (*e.g.*, agitation, depression, sleeping problem, and suicidal thoughts and actions) caused by montelukast.[40] However, one subsequent case-control study reported no significant association between LTRA and psychiatric adverse events after adjusting for confounding variables.[41]

*Remark*

According to the Global Initiative for Asthma (GINA) report, LTRAs can be used as an initial regulator in patients with mild persistent asthma who cannot use inhaled corticosteroids. However, LTRAs have a less anti-inflammatory or preventive effect than inhaled corticosteroids in the treatment of asthma.[36] In addition, the symptoms of both diseases can be controlled simultaneously with LTRA in patients with asthma and rhinitis. In the meta-analysis, the use of LTRA significantly reduced the D-TNSS and N-TNSS compared to the placebo in AR patients with asthma. However, few studies were included in the analysis, and the degree of symptom reduction was small. Moreover, LTRA use is associated with concerns about psychiatric adverse events. Therefore, if LTRA use is necessary because INCS cannot be used as the first-line treatment, careful consideration of the risk-benefit balance is recommended.

## Key Question 4: Is prophylactic treatment before the commencement of pollen dispersal more effective in relieving symptoms than treatment after the onset of symptoms in patients with pollen-induced AR?

*Background*

Prophylactic treatment that begins before the pollen season is often administered to prevent symptoms of pollen-induced AR. However, there is no consensus on the timing and effectiveness of prophylactic treatment, and there is no clear clinical evidence for the benefits and harms of prophylactic treatment. This PICO question was asked to review whether prophylactic treatment before the commencement of pollen dispersal is more effective in relieving symptoms in patients with pollen-induced AR.

*Recommendation*

Prophylactic treatment beginning 2 weeks before the start of pollen dispersal could attenuate symptoms of AR during peak pollen dispersion (3–4 weeks after the commencement of pollen dispersal). For patients with pollen-induced AR, we suggest prophylactic treatment in consideration of the patient's values and preferences as well as the benefits and harms of treatment (conditional recommendation, very low quality of evidence).

*Summary of evidence*

We identified 19,110 potentially relevant studies, and 42 were assessed for eligibility after reviewing the information provided in the title and abstract of the publications. After the full-text screening, 9 RCTs that compared the efficacy of treatment before and after the commencement of pollen dispersal were finally selected for inclusion in the meta-analysis.[42-50] The studies in the analysis included 7 for Japanese cedar,[43,44,46,50]1 for cypress,[42]


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and 1 for birch.[45] Six studies for antihistamine,[45-50] 2 for LTRA,[42,44] and 1 for INCS[43] were evaluated. In general, the included studies had a high risk of bias.

Symptoms of AR (runny nose, nasal congestion, itching, sneezing, and the degree of interference with daily life) were evaluated on a 4-point scale (0–3) or a 5-point scale (0–4). The symptom scores of AR with prophylactic treatment during the pollen season were lower compared to those with treatment initiated after the commencement of pollen dispersal. The differences in scores for symptoms of AR were higher in the early pollen season; however, the scores gradually became similar in the late pollen season. The prophylactic treatment significantly reduced the mean TNSS (MD, −0.65; 95% CI, −1.38 to 0.08) 3–4 weeks after the onset of the pollen dispersal season. Scores for sneezing and nasal congestion were significantly lower at 1–2 weeks (MD, −0.31; 95% CI, −0.55 to −0.08 and MD, −0.76; 95% CI, −1.54 to 0.02, respectively) and 3–4 weeks (MD, −0.48; 95% CI, −0.86 to −0.08 and MD, −0.81; 95% CI, −1.52 to −0.10, respectively) after the beginning of the pollen dispersal season when compared with patients who did not receive pretreatment. Prophylactic treatment showed a significant reduction in scores for the runny nose (MD, −0.56; 95% CI, −1.17 to 0.06) 1–2 weeks after the commencement of the pollen dispersal season than in non-pretreated patients.

Six studies described adverse events.[43-46,49,50] One study reported no adverse event with INCS use.[43] A study of LTRA reported sleepiness, but did not specify whether this was in the pretreated or non-pretreated group.[44] Somnolence caused by antihistamines was reported in both pre- and post-treated groups.[45,46,49,50] According to the results of a meta-analysis that compared somnolence with cetirizine and placebo, the risk ratio of somnolence was 2.52 (95% CI, 1.78–3.57).[51] However, the incidence of adverse events did not differ significantly between fexofenadine and placebo and between OAH/INCS and INCS in other meta-analyses.[52,53] The pre-treated group had a more extended period of drug administration (up to 2 weeks more) than the post-treated group; therefore, the incidence of adverse events could be increased, whereas the symptoms are mild, and the incidence is relatively low.

In studies that compared the effects of prophylactic treatment and placebo before the onset of the pollen season in patients with pollen-induced AR, antihistamines,[54-58] LTRA,[55,59] and INCS[54,60] improved symptoms compared to placebo. However, the analysis did not reveal which drugs are more effective.

*Remark*

All studies included in this analysis were conducted in Japan, and most participants had AR caused by Japanese cedar; therefore, the results of prophylactic treatment have limited generalizability to the whole cohort of patients with AR. However, prophylactic treatment approximately 2 weeks before onset does not differ significantly in cost, and the effect of symptom reduction can be obtained through prophylactic treatment. We suggest that prophylactic treatment before symptom occurs should be initiated at least 1–2 weeks before pollen dispersal in patients with pollen-induced AR who have repeatedly experienced a worsening of symptoms during the pollen season and want to avail of proactive prophylaxis for AR.


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## CONCLUSIONS

This guideline has been developed to assist physicians in selecting treatments for AR based on a systematic review of the evidence of desirable and undesirable outcomes. In Part 1 of this guideline, we made 4 recommendations for AR pharmacotherapy, including INCS/INAH combination therapy, OAH/INCS combination therapy, LTRA treatment in AR patients with asthma, and prophylactic treatment for patients with pollen-induced AR. Owing to the low or very low evidence of certainty, all recommendations are conditional. Well-designed and strictly executed RCTs are needed to measure and report outcomes appropriately. Considering the regional differences in epidemiology and clinical settings, specific recommendations for Korean patients with AR are required and should be based on evidence generated from Korean populations. Moreover, further research on knowledge gaps is needed. As new evidence becomes available from such studies, the recommendations made herein will be revised. Part 2 of this guideline describes the non-pharmacological management of AR.

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## SUPPLEMENTARY MATERIAL

**Supplementary Data S1**
Study methods: *de novo* process

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