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Intranasal antihistamine is superior to oral H₁ antihistamine as an add-on therapy to intranasal corticosteroid for treating allergic rhinitis

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ABSTRACT

Background: Currently, a combination of intranasal corticosteroid (INCS) plus oral H₁ antihistamine (OAH) or intranasal H₁ antihistamine (INAH) therapy is frequently used in the treatment of allergic rhinitis (AR). The superiority of the 2 combined treatments needs to be further examined.

Objective: To identify the better of the 2 therapeutic strategies for treating AR.

Methods: A literature review was performed on MEDLINE, Cochrane Library, and EMBASE databases. Following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses, meta-analyses of the total nasal symptom scores and individual nasal symptom scores were pooled based on studies that compared concomitant H₁ antihistamines plus INCS with INCS alone in the treatment of AR. The pooled results were expressed as weighted mean differences between the treatments. For each selected study, we calculated the relative clinical impact based on the total nasal symptom scores as follows:

$$100 \times (\text{Score}_{\text{Monotherapy}} - \text{Score}_{\text{Combined therapy}}) / \text{Score}_{\text{Monotherapy}}$$

Results: A total of 13 publications met our selection criteria, with 5066 patients. The pooled results revealed no significant weighted mean difference on the total nasal symptom scores between concomitant OAH plus INCS and INCS alone. As for the individual symptoms, the most common symptom that revealed remission was rhinorrhea, which was after OAH in combination with INCS. The combination therapy of INAH and INCS was superior to INCS alone. In an indirect comparison, the weighted mean relative clinical impact of INAH plus INCS was significantly higher than that of OAH plus INCS.

Conclusion: Intranasal H₁ antihistamines have an add-on effect on intranasal corticosteroids, and the combination of intranasal H₁ antihistamines plus intranasal corticosteroid is superior to that of oral H₁ antihistamines plus intranasal corticosteroid in improving nasal symptoms for patients with AR.

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Introduction

Allergic rhinitis (AR) is a chronic inflammatory disorder of the nasal mucosa, which is characterized by nasal congestion, rhinorrhea, sneezing, nasal itching, and other ocular symptoms (eg, pruritus, lacrimation, and redness).^{1,2} During the past several decades, AR has become a global problem and has an increasing prevalence especially in more developed countries. It currently affects 10% to 40% of adults and 2% to 25% of children worldwide.³ This chronic allergic disease significantly reduces school and work performance and leads to substantial social and economic burdens.^{4,5}

The pharmacotherapy of AR aims to control the disease severity, which is a challenge owing to the reoccurrence of the symptoms or insufficient response to the treatment. Recently, a regimen for the pharmacologic therapy of AR was devised according to the guidelines based on the Grading of Recommendations Assessment, Development and Evaluation.⁶ The regimen proposed an initial treatment of using H₁ antihistamines or intranasal corticosteroid. As the first-line monotherapy of AR, the effect of intranasal corticosteroid (INCS) is superior to oral H₁ antihistamine (OAH) and intranasal H₁ antihistamine (INAH).^{7,8} In this regard, the US practice guidelines recommended clinicians to prescribe monotherapy with intranasal corticosteroid as a routine for the management of AR.⁹ For those patients whose symptoms failed to be controlled, a concomitant therapy with OAH or INAH was proposed, which might lead to an improvement in the symptoms of moderate-to-severe AR.¹⁰ However, the superiority of combined oral antihistamine plus intranasal corticosteroid (OAH plus INCS) or combined intranasal antihistamine plus intranasal corticosteroid (INAH plus INCS) needs to be further examined. To the best of our knowledge, until now, only 2 clinical trials^{11,12} have reported the direct comparisons of OAH plus INCS with INAH plus INCS by analyzing a total of 138 patients, and they found that INAH plus INCS was more effective than OAH/INCS in the therapy of AR. However, many patients prefer oral drugs to nasal sprays when taking medications.⁶ Thus, more studies are needed to identify whether INAH as an add-on therapy to INCS is better than OAH, which is important to guide the appropriate therapeutic strategy for clinicians and to enhance the compliance of patients. Presently, there is no systematic review or meta-analysis available to study their efficacies. Thus, we conducted this meta-analysis to identify the better of the 2 combination therapies.

Because there are currently few studies that have performed a direct head-to-head comparison of the 2 combination treatments, indirect comparisons are necessary. Matricardi et al¹³ proposed an approach to compare the clinical benefits of different medications by calculating the relative clinical impact (RCI). Based on this methodology, we defined the RCI in this study by calculating the percentage difference between the total nasal symptom scores (TNSSs) recorded for combined therapy vs those recorded for monotherapy (INCS alone). The aim of this study was to collect all randomized controlled trials (RCTs) that evaluated the 2 combined therapies and

the monotherapy (INCS) in patients with AR and to provide an overall effect assessment regarding the clinical improvements in the nasal symptoms of AR after OAH plus INCS and INAH plus INCS.

Methods

Search Methods for Study Selection

We performed a literature review of blind, randomized, and controlled trials evaluating the combination therapy of OAH and INCS or that of INAH and INCS having been granted authorization (from 1974 to February 10, 2020) for the indications of AR in adults and children in databases of MEDLINE, Cochrane Library, and EMBASE. In addition, Clinicaltrial.gov was searched for unpublished studies. We identified studies by using Medical Subject Headings (MeSH) and free terms, which were limited to the title and abstract. Notably, 2 authors (Drs K. Du and H. Qing) independently selected the relevant RCT studies, after which, a manual search of the references listed in each eligible article or cited in each review article was performed. The electronic search strategy was logical combinations as follows:

1. (Rhinitis, Allergic [MeSH]) OR (Rhinitis, Allergic, Seasonal [MeSH]) OR (Rhinitis, Allergic, Perennial [MeSH]) OR allergic rhinitis OR seasonal rhinitis OR perennial rhinitis OR hay fever OR allergic rhinitides.
2. intranasal steroid OR intranasal corticosteroid OR fluticasone OR ciclesonide OR beclomethasone OR flunisolide OR mometasone OR triamcinolone OR dexamethasone OR budesonide.
3. (Histamine H₁ Antagonists [MeSH]) OR azelastine OR olopatadine OR MP-Azeflu OR MP29-02 OR loratadine OR desloratadine OR fexofenadine OR cetirizine OR levocetirizine.
4. (Randomized Controlled Trial [Publication Type]) OR randomized OR placebo for AR.

For the previous step, we made a logical combination of 1, 2, 3, and 4, listed above, when searching studies from the 3 databases (MEDLINE, Cochrane Library, and EMBASE). The drugs that could be used in the studies were selected according to the International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis guideline, and the effectiveness and safety of all drugs had been

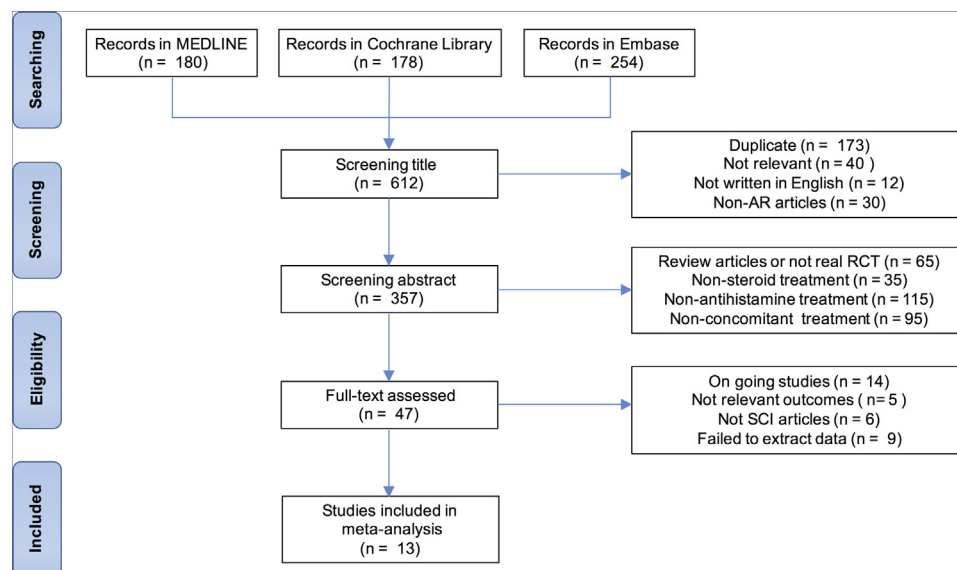


Figure 1. A PRISMA flowchart revealing the literature review and study selection process. AR, allergic rhinitis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT, randomized controlled trial; SCI, Scientific Citation Index.

Table 1
Characteristics of the Included Studies

Study	Design	Diagnosis	Group (n)	Age (y) mean (SD or range)	Daily intervention	Total duration (wk)	Outcome measure
Ratner et al ²²	Parallel	Moderate-to-severe SAR	OC (150)	42.2 (15–78)	MFNS (200 µg) + LOR (10 mg)	2	VAS
			C (150)	40.7 (13–80)	MFNS (200 µg)	2	RQLQ TNSS Individual NSS
Di Lorenzo et al ²³	Parallel	Moderate-to-severe SAR	OC (20)	32.8 (14–48)	FPANS (200 µg) + CTZ (10 mg)	6	TNSS
			C (20)	30.5 (15–50)	FPANS (200 µg)	6	Eos in secretions ECP in secretions
Barnes et al ²⁴	Crossover	SAR	OC (16)	45.9 (15.0)	FPANS (200 µg) + CTZ (10 mg)	2	TNSS
			C (11)	44.2 (15.9)	FPANS (200 µg)	2	Mini-RQLQ Nasal nitric oxide
Anolik ²⁵	Multicenter parallel	Moderate-to-severe SAR	OC (169)	26 (11–62)	MFNS (200 µg) + LOR (10 mg)	2	TNSS
			C (176)	26 (12–71)	MFNS (200 µg)	2	TSS
Kim et al ²⁶	Multicenter parallel	Moderate-to-severe SAR	OC (82)	29.8 (9.6)	CIC (200 µg) + LEVO (5 mg)	2	rTNSS and rTOSS
			C (88)	32.9 (11.3)	CIC (200 µg)	2	PANS RQLQ
Ratner et al ²⁷	Multicenter parallel	Moderate-to-severe SAR	IC (52)	36 (13–70)	AZENS (548 µg) + FPANS (200 µg)	2	RQLQ
			C (50)	37.4 (12–72)	FPANS (200 µg)	2	TNSS Individual NSS
Hampel et al ²⁸	Multicenter parallel	Moderate-to-severe SAR	IC (153)	39.5 (12–73)	AZENS (548 µg) + FPANS (200 µg)	2	TNSS
			C (151)	38.1 (12–74)	FPANS (200 µg)	2	TOSS RQLQ
Meltzer et al ²⁹	Multicenter parallel	Moderate-to-severe SAR	IC (193)	38.8 (12–73)	AZENS (548 µg) + FPANS (200 µg)	2	rTNSS
			C (189)	37 (12–72)	FPANS (200 µg)	2	rTOSS
Carr et al ³⁰	Multicenter parallel	Moderate-to-severe SAR	IC (848)	36.7 (14.4)	AZENS (548 µg) + FPANS (200 µg)	2	rTNSS and iTNNS
			C (846)	35.9 (14.3)	FPANS (200 µg)	2	rTOSS RQLQ
Meltzer et al ³¹	Parallel	Moderate-to-severe SAR	IC (98)	≥12	AZENS (548 µg) + FPANS (200 µg)	2	rTNSS
			C (84)	≥12	FPANS (200 µg)	2	rTOSS
Hampel et al ³²	Multicenter parallel	SAR	IC (299)	39.5 (15.4)	OLO (665 µg) + MOM (25 µg)	2	rTNSS and iTNNS
			C (294)	38.7 (16.3)	MOM (25 µg)	2	rTOSS and iTOSS RQLQ and PANS
Gross et al ³³	Multicenter parallel	Moderate-to-severe SAR	IC (291)	39.9 (14.9)	OLO (665 µg) + MOM (25 µg)	2	rTNSS and iTNNS
			C (293)	39.2 (14.9)	MOM (25 µg)	2	rTOSS and iTOSS RQLQ and PANS
Andrews et al ³⁴	Parallel	Moderate-to-severe SAR	IC (157)	43.4 (14.1)	OLO (665 µg) + MOM (25 µg)	2	rTNSS and iTNNS
			C (158)	44.6 (13.7)	MOM (25 µg)	2	rTOSS and iTOSS RQLQ and PANS

Abbreviations: AZENS, azelastine nasal spray; C, intranasal corticosteroids; CIC, ciclesonide; CTZ, cetirizine; ECP, eosinophil cationic protein; Eos, eosinophils; FPANS, fluticasone propionate aqueous nasal spray; IC, intranasal antihistamines plus intranasal corticosteroids; iTNNS, instantaneous total nasal symptom scores; iTOSS, instantaneous total ocular symptom scores; LEVO, levocetirizine; LOR, loratadine; MFNS, mometasone furoate nasal spray; MOM, mometasone; NSS, nasal symptom score; OC, oral antihistamines plus intranasal corticosteroids; OLO, olopatadine; PANS, physician-assessed overall nasal signs and symptoms severity; RQLQ, rhinoconjunctivitis quality-of-life questionnaires; rTNNS, reflective total nasal symptom scores; rTOSS, reflective total ocular symptom scores; SAR, seasonal allergic rhinitis; TNSS, total nasal symptom scores; TSS, total symptom score; VAS, visual analog scale.

verified in RCTs.¹⁴ First-generation H₁ antihistamines were excluded because they have been implicated in some deaths owing to overdosing in infants and young children and suicides committed by teenagers and adults.¹⁵

Criteria for Included Studies

We included RCT studies that compared concomitant OAH/INCS or concomitant INAH/INCS with monotherapy of INCS. All the studies recorded TNSSs and adverse events (AEs). The TNSSs involved 4 individual components of the nasal symptom score (NSS) (eg, rhinorrhea, nasal congestion, sneezing, and nasal

itching), and the symptoms were rated on a 4-point scale (0 = absent; 1 = mild; 2 = moderate; 3 = severe).

The study selection is of the utmost importance during meta-analyses. Underpowered studies often suffer from publication bias and contribute limited information to the meta-analyses when 2 or more adequately powered trials are available.¹⁶ Thus, we excluded trials that were interfered by other medications when making comparisons, trials partly containing patients with nonallergic rhinitis, trials with insufficient clinical data or published solely in abstract form, trials that were not included in the Scientific Citation Index, and reviewed articles.

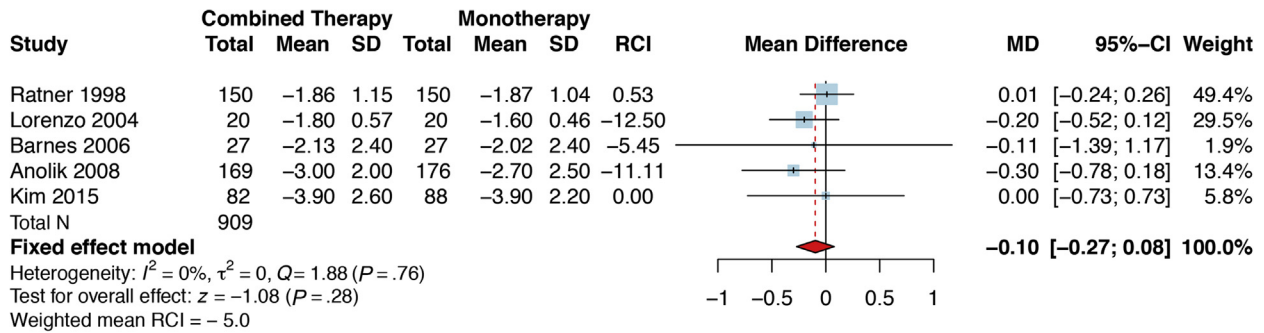


Figure 2. Relative clinical impact and meta-analysis of the RCTs comparing TNSS between combined therapy of OAH plus INCS with monotherapy of INCS. CI, confidence interval; INCS, intranasal corticosteroid; MD, mean difference; Mean, mean score for the change in TNSS after receiving respective treatment; N, a total number of subjects in the meta-analysis; OAH, oral H_1 antihistamine; RCI, relative clinical impact; RCT, randomized controlled trial; TNSS, total nasal symptom scores.

Quality Assessment

The quality of each RCT was independently rated by 2 investigators (Drs K. Du and H. Qing) based on the Cochrane Collaboration's tool for assessing risk of bias.¹⁷ Disagreement were resolved by discussions and consensus. To reduce the heterogeneity of the studies, we selected the TNSS as the only outcome measure for our meta-analyses.

Data Extraction

The following data were extracted from each selected publication: (1) treatment and dosage; (2) age and number of patients in each treatment group; (3) duration of treatment; (4) nature and value of TNSS; and (5) frequency of AEs after receiving the treatment.

Meta-Analysis and Calculation of the RCI

Data in the meta-analysis were analyzed using the meta and metafor packages of R, version 3.5.1 (<http://www.r-project.org/>). Meta-analyses were performed for the effect of each drug (eg, concomitant OAH plus INCS, concomitant INAH plus INCS, or INCS). Differences in TNSSs were expressed as weighted mean difference (WMD) with 95% confidence intervals (CIs) from baseline or decrease from placebo.^{18,19} An I^2 and τ^2 statistic were used to quantify the heterogeneity of the selected studies and can be interpreted as the percentage of the total variability in the set of fixed- or random-effect sizes owing to the true heterogeneity. The P values for heterogeneity test are according to the Q statistic, and a P value of less than .1 was considered to be statistically significant. When I^2 values were greater than 50% (corresponded to substantial heterogeneity), a random-effects model was applied, otherwise, a fixed-effects model was used. A P value of less than .05 was considered statistically significant when WMD was analyzed. Potential publication bias was evaluated by inspecting the symmetry of a funnel plot and tested with Begg's tests.^{20,21}

We used the mean difference (MD) in combined therapy and monotherapy to calculate the RCI. We analyzed the clinical effect of each combined therapy (nasal corticosteroids plus oral or intranasal H_1 antihistamines) by calculating the RCI as follows:

$100 \times (\text{Score}_{\text{Monotherapy}} - \text{Score}_{\text{Combined therapy}}) / \text{Score}_{\text{Monotherapy}}$ ¹³
The weighted mean RCI was calculated based on the combined individual RCIs, which were compared in a Mann–Whitney U test between the 2 groups.¹⁹ In addition, the comparisons for incidence of AEs between the treatment groups were made by using the chi-squared test.

Results

Study Selection

After performing the research, a total of 612 articles were identified, and 22 of these studies were initially selected. A total of 9 of these studies were excluded because they failed to report the mean values of TNSSs and SDs or 95% CIs, which interfered with the calculation of the MD and RCI. Therefore, 13 studies were finally selected for the meta-analyses.^{22–34} A flowchart of study retrieval and selection is displayed in Figure 1.

Characteristics of the Included Studies

The 13 trials enrolled a total of 5066 patients, with an age range from 11 to 80 years. Most of these trials were multicenter RCTs (8/13), and the disease severity in the 11 studies was moderate-to-severe seasonal allergic rhinitis (SAR). A total of 5 studies^{22–26} compared the concomitant therapy of OAH plus INCS with a single therapy of INCS, and 8 studies^{27–34} compared concomitant INAH plus INCS with a single therapy of INCS. The characteristics of these studies are presented in Table 1. There was 1 crossover RCT research,²⁴ and the others were all parallel RCTs. There was 1 trial²⁶ that had an open-label design, whereas all the other included studies were double-blind trials. The formulations involved in these studies were 3 INCS (ciclesonide, fluticasone, and mometasone), 3 OAH (loratadine, cetirizine, and levocetirizine tablet), and 2 INAH (olopatadine and azelastine). Among the 8 studies investigating concomitant INAH plus INCS, 3 trials^{29–31} used a fixed-dose combination of nasal sprays of MP29-02 (azelastine and fluticasone propionate) and 3 other trials^{32–34} administered GSP301 (olopatadine and mometasone) as pharmacologic interventions. The other 2 trials^{27,28} used sequential sprays of azelastine and

Table 2

Analysis of Individual Symptom Scores Comparing Oral Antihistamine Plus Intranasal Corticosteroid With Intranasal Corticosteroid Monotherapy

NSS	WMD	(95% CI)	Heterogeneity	P for overall effect	Weighted mean RCI (range)
Congestion	-0.02	(-0.05, 0.01)	$I^2 = 46\%$, $P = .12$	.22	-6.59 (-33.30 to 18.30)
Rhinorrhea	-0.04	(-0.07, 0.00)	$I^2 = 0\%$, $P = .98$	.04	-8.03 (-8.70 to 14.30)
Sneezing	0.01	(-0.02, 0.04)	$I^2 = 0\%$, $P = .56$	.61	2.15 (-29.40 to 4.20)
Itching	-0.08	(-0.20, 0.05)	$I^2 = 74\%$, $P < .01$	.24	-31.26 (-100.0 to 4.0)

Abbreviations: CI, confidence interval; NSS, nasal symptom score; RCI, relative clinical impact; WMD, weight mean difference.

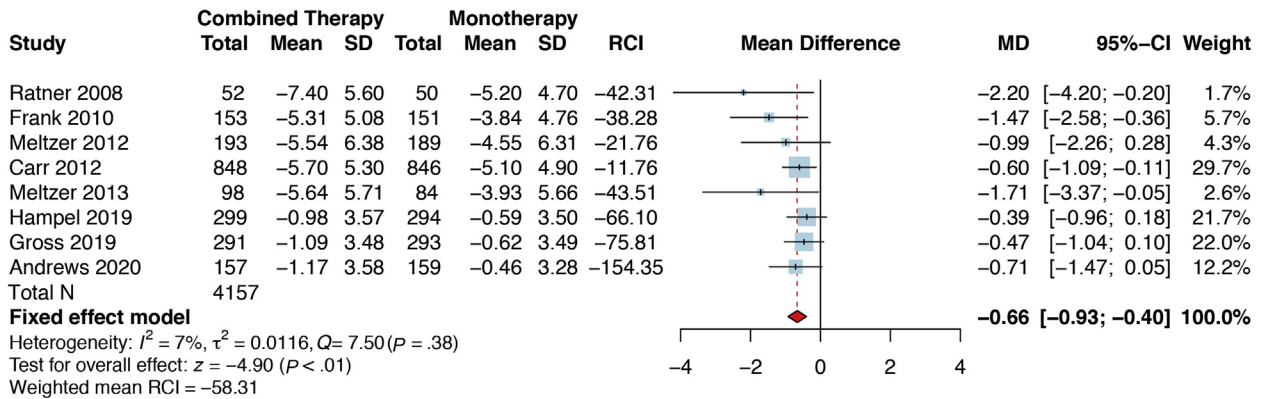


Figure 3. Relative clinical impact and meta-analysis of the RCTs comparing TNSS between combination therapy of INAH plus INCS with monotherapy of INCS. CI, confidence interval; INAH, intranasal H₁ antihistamine; INCS, intranasal corticosteroid; MD, mean difference; Mean, mean score for the change in TNSS after receiving respective treatment; N, a total number of subjects in the meta-analysis; RCI, relative clinical impact; RCT, randomized controlled trial; TNSS, total nasal symptom scores.

fluticasone. All the studies included the TNSS as an outcome measure for the clinical effectiveness of the treatment, and the TNSS was extracted for a formal meta-analysis. There were no serious AEs in any of the studies.

Combination of Oral Antihistamine Plus Intranasal Corticosteroid vs Solo Intranasal Corticosteroid

The results of the meta-analysis for the comparison between concomitant OAH and INCS vs just INCS are indicated in Figure 2. The pooled results revealed no significant difference in TNSS between combination therapy and monotherapy ($n = 909$, $WMD = -0.10$, 95% CI -0.27 to 0.08 , P for overall effect = .28; P for heterogeneity = .76, $I^2 = 0\%$). Because there was no observed heterogeneity in the meta-analysis, we did not carry out a sensitivity analysis and thus presented the pooled results using a fixed-effects model (Figure 2). Regarding individual NSSs, pooled result from the 5 studies^{22–26} revealed that concomitant therapy was more effective than monotherapy concerning rhinorrhea ($I^2 = 0\%$, P for overall effect $< .05$). As for nasal congestion, sneezing, and itching, no significant difference was observed (Table 2).

Combination of Intranasal Antihistamine Plus Intranasal Corticosteroid vs Solo Intranasal Corticosteroid

The meta-analysis of the 8 trials^{27–34} identified that the concomitant treatment with intranasal antihistamine plus intranasal corticosteroid was superior to the single treatment of intranasal corticosteroid in improving TNSS ($n = 4157$, $WMD = -0.66$, 95% CI -0.93 to -0.40 , P for overall effect $< .01$, $I^2 = 7\%$, P for heterogeneity = .38) (Figure 3). Notably, 5 of the 8 studies reported individual NSS, for which the meta-analysis is summarized in Table 3. The pooled results also revealed that the combination therapy (INAH and INCS) was better than monotherapy (INCS) regarding nasal congestion, rhinorrhea, sneezing, and itching (I^2 ranged from 0%–58%, all the P for overall effects $< .05$).

Relative Clinical Impact

To compare the treatment effect of INAH plus INCS with OAH plus INCS, we calculated the RCI (according to TNSS) for each study (Figure 2 and Figure 3). The weighted mean (range) RCIs were -58.31% (-154.35% to -11.76%) for the INAH/INCS treatment and -5% (-12.5% to 0.53%) for the OAH plus INCS treatment and revealed a significant difference ($P < .01$). The largest RCI (-154.35%) was observed in the INAH plus INCS treatment group in a study by Andrews et al.³⁴ In that study, the researchers investigated 2 types of administration (twice daily and once daily). When we performed the meta-analysis, we recorded the data from twice daily administration which revealed a significant difference. This might have contributed to the larger value of RCI in this study.

As for individual NSSs, the weighted mean RCI values of congestion, rhinorrhea, and sneezing for the INAH plus INCS treatment were significantly higher than those for the OAH plus INCS treatment (all the P values $< .01$) (Tables 2 and 3). In contrast, the weighted mean RCI value of itching in the OAH/INCS treatment group was relatively higher. However, no significant difference was found between the 2 groups ($P = .192$). Taken together, our pooled data reveal that the INAH is more effective than OAH as an add-on therapy to INCS.

Risk of Bias

The risk of bias within the included studies is summarized in Figure 4. A total of 9 studies had an unclear risk for selection bias because the randomization schedule was not described. All subjects in the trials received allocation concealment. Most of the studies had a double-blind design, but 1 study had an open-label design with an elevated risk of performance bias. All the 13 studies were judged to have low risks of detection, attrition, and reporting bias. Regarding publication bias, the funnel plots of the publications comparing treatment of OAH plus INCS with INCS or that of INAH plus INCS with INCS are indicated in Figure 5A and Figure 5B, respectively. No significant publication bias was found in our

Table 3
Analysis of Individual Symptom Scores Comparing Intranasal Antihistamine Plus Intranasal Corticosteroid With Intranasal Corticosteroid Monotherapy

NSS	WMD	(95% CI)	Heterogeneity	P for overall effect	Weighted mean RCI (range)
Congestion	-0.27	(-0.37, -0.18)	$I^2 = 43\%$, $P = .14$	$< .01$	-27.20 (-132.0 to -18.20)
Rhinorrhea	-0.14	(-0.25, 0.03)	$I^2 = 0\%$, $P = .73$	.01	-11.29 (-30.77 to -7.69)
Sneezing	-0.28	(-0.40, -0.16)	$I^2 = 39\%$, $P = .16$	$< .01$	-21.77 (-106 to -13.30)
Itching	-0.26	(-0.48, -0.04)	$I^2 = 58\%$, $P = .05$	$< .01$	-24.77 (-247.0 to -8.33)

Abbreviations: CI, confidence interval; NSS, nasal symptom score; RCI, relative clinical impact; WMD, weight mean difference.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome of assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ratner 1998	?	+	+	+	+	+	?
Lorenzo 2004	?	+	+	+	+	+	+
Barnes 2006	+	+	+	+	+	+	?
Anolik 2008	?	+	+	+	+	+	+
Kim 2015	?	+	–	+	+	+	?
Ratner 2008	?	+	+	+	+	+	+
Frank 2010	?	+	+	+	+	+	+
Meltzer 2012	+	+	+	+	+	+	+
Carr 2012	+	+	+	+	+	+	+
Meltzer 2013	+	+	+	+	+	+	+
Hampel 2019	?	+	+	+	+	+	?
Gross 2019	?	+	+	+	+	+	+
Andrews 2020	?	+	+	+	+	+	+

Figure 4. Assessment of risk of bias in each included study.

AEs were headache, ranging from 0% to 3.6% for the OAH plus INCS group, 2.6% to 3.1% for the INAH plus INCS group, and 2.6% to 5.7% for the INCS group. In addition, 2 trials compared OAH plus INCS with INCS monotherapy, and 6 trials compared concomitant INAH plus INCS with INCS monotherapy. The pooled relative risk of AEs in patients treated with OAH plus INCS vs INCS was 1.81 (95% CI, 0.99–3.32; eFig 1). For patients treated with INAH plus INCS vs INCS, the pooled relative risk of AEs was 1.68 (95% CI, 1.38–2.05; eFig 2).

Furthermore, we calculated the overall incidence of mild AEs in the OAH plus INCS, INAH plus INCS, and INCS monotherapy groups (eFig 3–5). A low weighted incidence of mild AEs was observed in all the treatment groups, which was 10% (95% CI, 7%–15%), 12% (95% CI, 11%–14%), and 7% (95% CI, 6%–8%) for the OAH plus INCS, INAH plus INCS, and INCS monotherapy groups, respectively. There was no significant difference between the OAH plus INCS and INAH plus INCS groups ($P = .34$) or between the OAH plus INCS and INCS groups ($P = .091$). However, the incidence of AEs in the INAH plus INCS group was significantly higher than that in the INCS monotherapy group ($P < .01$).

Discussion

This is the first meta-analysis to confirm that INAH was superior to OAH as an add-on therapy to INCS with regard to improvement in TNSS and individual NSS. However, no significant difference in improvement of TNSS was found between the concomitant OAH plus INCS and the INCS alone. Only the rhinorrhea symptom of patients with AR had better remission after the addition of OAH to INCS.

There exists evidence supporting the effect of oral H_1 antihistamine on improving the effectiveness of INCS since the 1990s.^{35–37} However, some limitations in those early studies may contribute to selection bias, such as small sample size, selection of patients only for ragweed SAR, and subjects mixed with non-AR.^{35,37} A recent meta-analysis revealed a different finding, which claimed that the concomitant OAH plus INCS offers no advantage over INCS alone.¹⁸ In that study, although the combined treatment group manifested improvement of nasal symptoms when compared with the INCS group, no statistical significance was found. In addition, 3 of 4 NSSs revealed better remission when receiving just the INCS therapy. The inconsistency in that study may be because of a small sample size (a total of 47 patients receiving OAH plus INCS treatment) in the pooled results.¹⁸ Compared with that study, we analyzed more clinical trials with a total number of 909 patients and confirmed that oral antihistamines did not have a better add-on effect to INCS, in terms of TNSS. The 2016 Allergic Rhinitis and Its Impact on Asthma guidelines suggest either a combination of OAH plus INCS or INCS alone as the therapeutic strategy for patients with SAR, but the potential net benefit might not justify spending of additional resources.¹⁰ Our study confirmed that a combination therapy of OAH plus INCS was not superior to monotherapy of INCS. To reduce the cost of treatment and avoid the potential adverse effects of oral drugs, combination therapy should not be a routine option. Of note, we also identified that the symptom of rhinorrhea had moderate improvement when OAH was added to INCS. Thus, for patients that prefer oral drugs, whose predominant symptom is rhinorrhea, a prescription of concomitant OAH and INCS was proposed.

The INAH has been extensively identified to improve the clinical effects of INCS in adults and children with AR.^{38,39} The US practice and guidelines of the Allergic Rhinitis and Its Impact on Asthma^{9,10} recommended a combination therapy of INAH plus INCS for patients with moderate-to-severe AR. There exists a lot of evidence supporting the use of combination therapy (INAH plus INCS) instead of monotherapy (INCS).^{40–42} However, another recent meta-analysis revealed no evident superiority of concomitant INAH plus INCS therapy over INCS alone, in terms of improvement in RCI.¹⁹ The inconsistency might be because of the insufficient number of trials at that time, and

meta-analysis of OAH plus INCS therapy. However, asymmetry of the funnel plot was present in our meta-analysis of INAH plus INCS therapy, and Begg's test indicated the possibility of publication bias.

Treatment Safety

There were no serious AEs when patients received the treatments in all the included studies. Among these studies, 8 RCTs^{25,26,28–30,32–34} observed well-tolerated AEs. The treatment-related AEs in these studies involved headache, mucosal erosion, epistaxis, somnolence, dysgeusia, and nausea. The most frequent

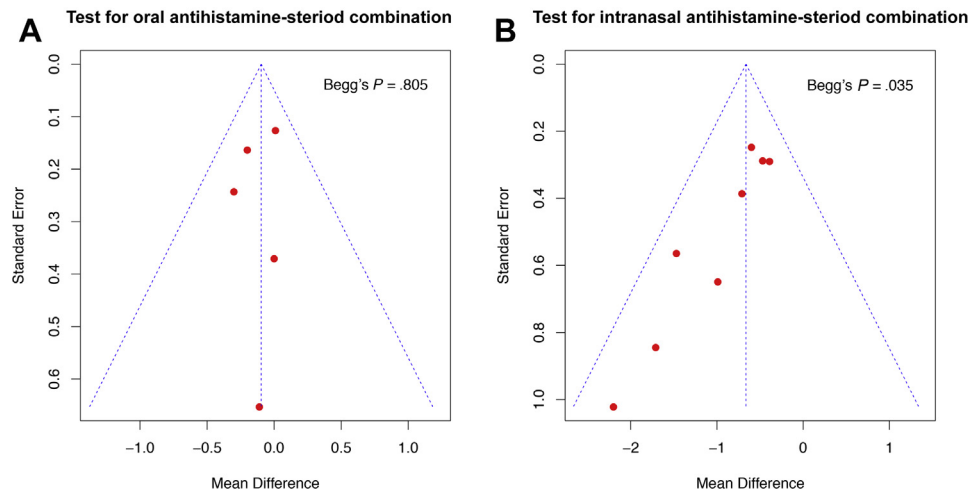


Figure 5. Funnel plots of studies comparing (A) OAH plus INCS with INCS and (B) INAH plus INCS with INCS. INAH, intranasal H₁ antihistamine; INCS, intranasal corticosteroid; OAH, oral H₁ antihistamine.

of those, only 3 trials that discussed the role of INAH plus INCS were analyzed. Therefore, more studies are needed when analyzing the efficacy of concomitant INAH and INCS therapy. In the previous 2 years, a number of RCT articles incorporating more than 100 participants in each arm have been published.^{32–34} In fact, well-powered RCT studies having a sample size of more than 100 could partly avoid publication bias and provide more information for a meta-analysis.¹⁶ In this regard, we gathered all the RCTs comparing combination therapy of INAH and INCS with monotherapy of INCS and pooled the data from a total of 8 trials.^{27–34} Notably, 6 of the 8 trials had a sample size of more than 100. As for concomitant therapy, there were following 2 types of administration used among the 8 clinical trials: 6 trials used single combination nasal sprays (MP29-02 or GSP301) and 2 trials used sequential combination nasal sprays (an intranasal corticosteroid plus an intranasal histamine H₁ antagonist). Although a single spray application might provide more uniform distribution and higher retention in the nasal cavity than sequential spray application, all the 8 studies reported similar outcomes regardless of the 2 types of administration. Our results confirmed that INAH had a significant add-on effect, compared with INCS alone, in terms of the TNSS and individual NSSs (eg, nasal congestion, rhinorrhea, nasal itching, and sneezing).

However, the comparison of OAH plus INCS with INAH plus INCS could not be performed because there were no sufficient studies directly comparing the 2 therapies. Our literature review revealed only 2 relative studies involving the 2 therapeutic modalities. Lanier et al¹¹ found that concomitant use of fluticasone and olopatadine was better than that of fluticasone and fexofenadine, in improving the symptoms of induced allergic rhinoconjunctivitis, by analyzing data from 30 patients in each treatment group. Bousquet et al¹² revealed that the onset of action of INAH plus INCS was 2 hours earlier than that of OAH plus INCS. Even so, there is still no consensus on which of the 2 combination therapies is better in treating the symptoms of AR. In this study, we had a total of 2091 patients receiving INAH plus INCS and a total of 448 patients receiving OAH plus INCS and performed an indirect comparison of RCI. Similar to past studies, the weighted mean RCI (according to TNSS) value of INAH plus INCS (–58.31%) was significantly higher than that of OAH plus INCS (–5.0%). Regarding individual NSSs, the RCI values for congestion, rhinorrhea, and sneezing, but not itching, in the INAH plus INCS group were significantly higher than those in the OAH plus INCS group. In addition, the incidence of AEs was not significantly different in the 2 groups. Taken together, our pooled

data revealed that INAH is more effective than OAH as an add-on therapy to INCS in improving the symptoms of patients with AR.

When interpreting our findings, there are some limitations that should be considered. First, this meta-analysis only encompassed 13 studies and only 5 studies investigated OAH plus INCS therapy. Among the 5 trials, 3 contained a sample size of less than 100. This may be because of the addition of INAH as a therapy only since 2000,⁴³ and it has better clinical efficacy. Second, as for the meta-analysis of INAH plus INCS, the funnel plot was skewed and Begg's test indicated a publication bias. Indeed, it needs to be considered that the significance level of the Begg's test may not equal the nominal value when the number of the involved studies is small.²¹ All the trials that investigated INAH plus INCS therapy reported a significant positive result. Thus, we speculated that there might be a possibility of publication bias owing to the fact that nonsignificant studies are less likely to be published.²¹ More studies are needed to confirm the publication bias. Finally, TNSS, as a single outcome measure in this meta-analysis, helped to decrease the heterogeneity of this study. However, TNSS is a subjective assessment of treatment outcome. The scores recorded by patients might contribute to differences in results among individuals.

In conclusion, we confirmed that, except for the remission of rhinorrhea, the combination therapy of OAH plus INCS has similar effect to INCS monotherapy in controlling the symptoms of AR. The combination therapy of INAH and INCS was found to be superior to INCS alone or the combination of OAH and INCS in reducing nasal symptoms in patients with AR.

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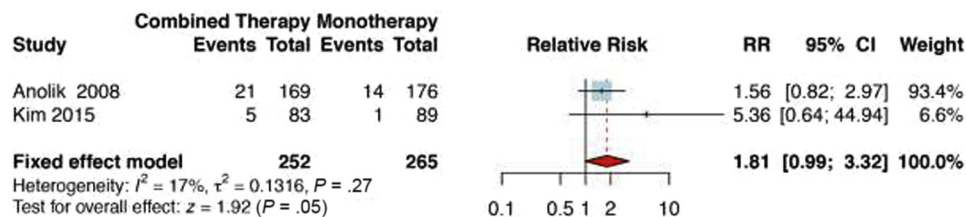
Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.anai.2020.06.038>.

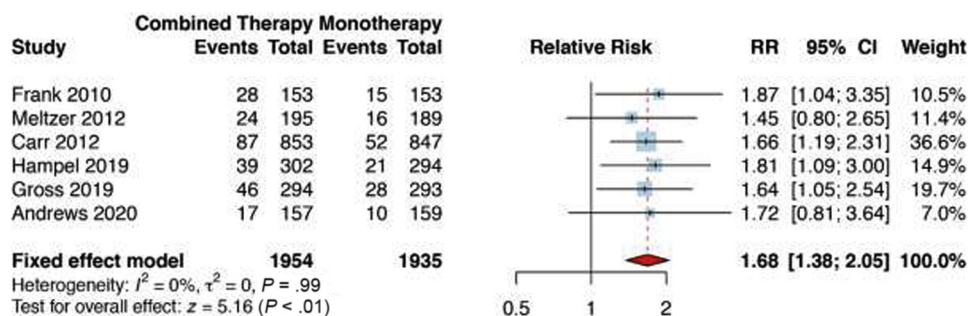
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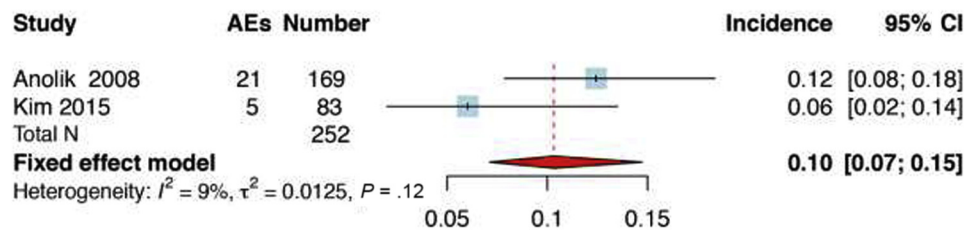
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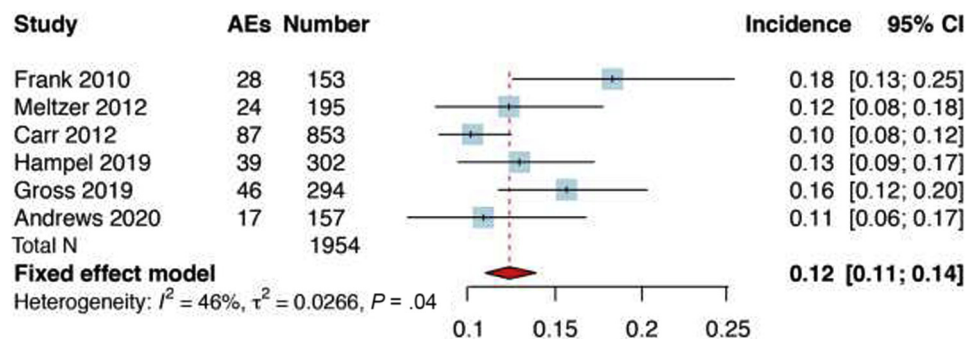
eFigure 1. Forest plot comparing the risk for adverse events in the combined therapy (OAH plus INCS) and monotherapy groups (INCS). CI, confidence interval; INCS, intranasal corticosteroid; OAH, oral H₁ antihistamine.



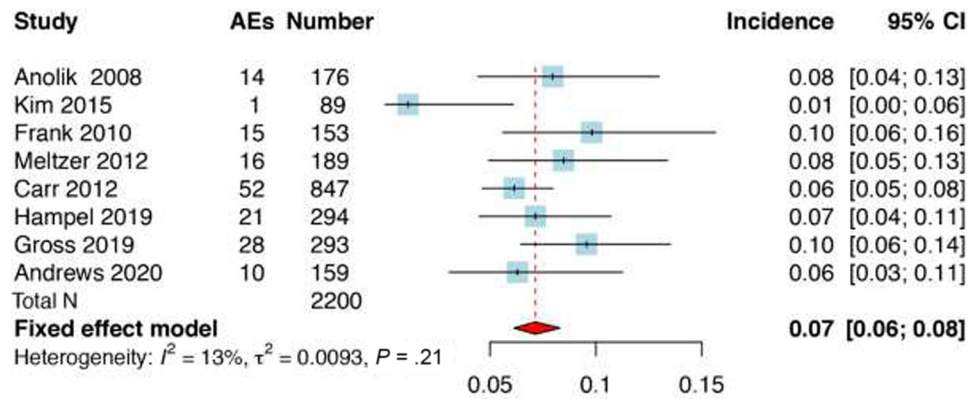
eFigure 2. Forest plot comparing the risk for adverse events in the combined therapy (INAH plus INCS) and monotherapy groups (INCS). CI, confidence interval; INAH, intranasal H₁ antihistamine; INCS, intranasal corticosteroid.



eFigure 3. Meta-analysis for the incidence of AEs in the OAH plus INCS treatment group. AEs, adverse events; CI, confidence interval; INCS, intranasal corticosteroid; OAH, oral H₁ antihistamine.



eFigure 4. Meta-analysis for the incidence of AEs in the INAH plus INCS treatment group. AEs, adverse events; CI, confidence interval; INAH, intranasal H₁ antihistamine; INCS, intranasal corticosteroid.



eFigure 5. Meta-analysis for the incidence of AEs in the INCS treatment group. AEs, adverse events; CI, confidence interval; INCS, intranasal corticosteroid.