

# Leukotriene receptor antagonist addition to intranasal steroid: systematic review and meta-analysis\*

Kachorn Seresirikachorn<sup>1,2</sup>, Joaquim Mullol<sup>3</sup>, Kanda Limitlaohaphan<sup>4</sup>, Vararuthai Asvapoositkul<sup>5</sup>, Kornkiat Snidvongs<sup>1,2</sup>

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<sup>1</sup> Department of Otolaryngology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

<sup>2</sup> Endoscopic Nasal and Sinus Surgery Excellence Center, King Chulalongkorn Memorial Hospital, Bangkok, Thailand

<sup>3</sup> Rhinology Unit & Smell Clinic, ENT Department, Hospital Clinic, IDIBAPS, Universitat de Barcelona, CIBERES, Barcelona, Catalonia, Spain

<sup>4</sup> Relief and Community Health Bureau, The Thai Red cross Societies, Bangkok, Thailand

<sup>5</sup> Bangkok Metropolitan Administration General Hospital, Bangkok, Thailand

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## Abstract

**Background:** Intranasal corticosteroids (INCS) and leukotriene receptor antagonist (LTRA) have different mechanisms of action. The combination of INCS and LTRA (INCS+LTRA) are utilized to control the allergic rhinitis (AR) symptoms. The effects of this combination have not been made evident yet.

**Methodology:** Randomized controlled trials studying the effects of INCS+LTRA vs INCS in monotherapy on rhinoconjunctivitis symptoms in patients with AR were included. Data were pooled for meta-analysis. The outcomes were nasal symptoms, ocular symptoms, disease-specific quality of life (QOL), and adverse events.

**Results:** Six studies (358 participants) met the inclusion criteria. There were no differences between INCS+LTRA and INCS monotherapy on composite nasal symptom score, total daytime symptom score, total night time symptom score, disease-specific QOL and adverse events. The results favoured the effects of INCS-LTRA on ocular symptoms.

**Conclusions:** The effects of the INCS+LTRA combination are not different from INCS in monotherapy in the improvement of both nasal symptoms and patient's QOL. The combination may, however, be better on improving ocular symptoms.

**Key words:** corticosteroids, leukotriene receptor antagonist, allergic rhinitis, asthma

## Introduction

With multiple anti-inflammatory activities, intranasal corticosteroid (INCS) is an effective medicine for treating allergic rhinitis (AR). INCS may be prescribed to AR patients with moderate to severe or persistent symptoms having nasal obstruction as major symptom<sup>(1, 2)</sup>. INCS binds to a specific cytoplasmic glucocorticoid receptor then activates anti-inflammatory gene transcription and represses pro-inflammatory gene transcription<sup>(3)</sup>. As a result, the lymphocyte activation and cytokine production are inhibited, which decrease the migration of inflammatory cells to the nasal mucosa<sup>(4, 5)</sup>. The anti-inflammatory effects of INCS effectively control the allergic response and relieve the clinical symptoms, including itching, sneezing, rhinorrhea, nasal obstruction, and ocular symptoms.

Leukotriene is a pro-inflammatory mediator which plays a key role in the pathogenesis of AR. In addition to eosinophil chemotaxis, leukotriene release causes vasodilation, increased vascular permeability, smooth muscle constriction and mucus hypersecretion in the airways<sup>(6-8)</sup>. Therefore, the effects of leukotriene on the nasal vasculature, such as vascular permeability and vasodilation play a role in producing symptoms of the mucosal swelling<sup>(9)</sup>. The related clinical symptoms include nasal obstruction, hypersecretion, bronchoconstriction, and bronchial hyperresponsiveness<sup>(7)</sup>. Clinical studies found that topical leukotriene D4 increased blood flow and nasal airway resistance without causing sneezing, rhinorrhea, and nasal itching<sup>(10, 11)</sup>. Leukotriene receptor antagonist (LTRA) binds to cysteinyl leukotriene 1 (CysLT1) receptor and reduces eosinophilic

inflammation in upper-airway inflammatory diseases such as rhinitis and nasal polyposis<sup>(8,12)</sup> and eosinophil chemotaxis<sup>(13)</sup>. CysLTs-induced productions of IL-5 and IL-13 from group 2 innate lymphoid cells (ILC2s) were completely inhibited by CysLT1 antagonist<sup>(14)</sup>. As a result, LTRA reduces nasal inflammation, especially nasal congestion<sup>(9)</sup>. While LTRA decreased T-helper 1 (Th1) cells and increased T-regulatory (Treg) cells in peripheral blood, INCS decreased Th1 cells and Th2 and increased Treg cells in nasal mucosa<sup>(15)</sup>. In addition, eosinophil cationic protein (ECP), histamine, and cysteinyl-leukotrienes (CysLTs) were significantly decreased greater by INCS and INCS+LTRA treatments than LTRA monotherapy. This trend was reflected with combination therapy<sup>(15)</sup>.

Although INCS and LTRA have different mechanisms of action, the combination of an LTRA with an INCS may provide additional effects on the improvement of nasal symptoms of AR. Combination therapy is an option which may be offered to patients with AR who do not respond to monotherapy<sup>(1,2)</sup>. Potentially, this combination of INCS and LTRA (INCS+LTRA) may also be more effective in controlling the symptoms of AR patients with/without asthma. This systematic review aimed to assess the effects of INCS+LTRA vs INCS in monotherapy in relieving rhinoconjunctivitis symptoms of AR.

## Materials and methods

### Eligibility criteria

This systematic review followed The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)<sup>16</sup>. Randomized controlled trials (RCTs) studying the effects of INCS+LTRA versus INCS in monotherapy in patients with AR were included. The diagnostic criteria of AR followed the Allergic Rhinitis and Impact on Asthma (ARIA) guidelines<sup>(1)</sup>. RCTs studying INCSs and LTRAs, at any dose, frequency, and duration were included in the analysis. The selected outcomes were nasal symptoms, ocular symptoms, disease-specific QOL, and adverse events. RCTs published in a language other than English were excluded. RCTs with mixed populations of AR and non-AR were excluded unless the outcomes for patients with AR could be isolated.

### Information sources and search strategy

Electronic systematic searches for RCTs were conducted with no publication year, or publication status restrictions. The last search was performed on 19 May 2020. Literature searches were performed using Ovid MEDLINE, Ovid EMBASE, CENTRAL, and Web of Science. References of the included studies were searched for identifying any missing published or unpublished trials. The searched term used was (Leukotriene receptor antagonist OR Leukotriene receptor blocking agent OR antileukotriene OR Montek OR Montelukast OR Singulair) AND (Triamcinolone Acetonide OR Nasacort OR Nasonex OR Mometasone Furoate OR Rhinocort OR Budesonide OR Pulmicort OR Flonase OR

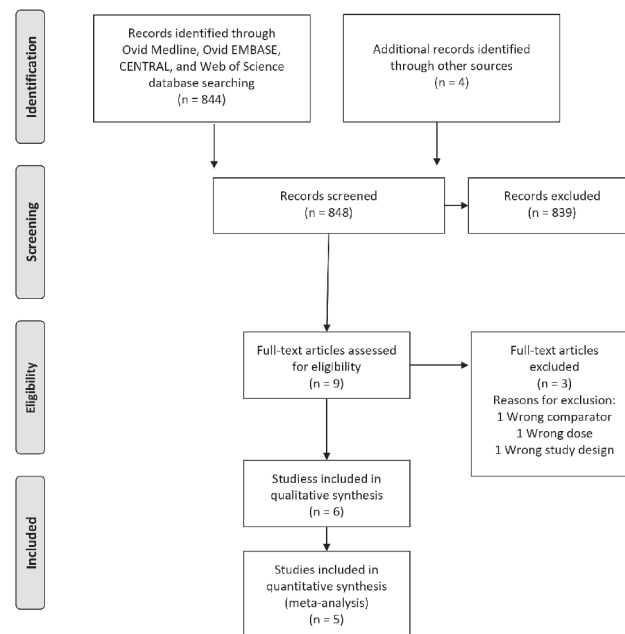


Figure 1. Flow diagram of study selection for the systematic review and meta-analysis.

Fluticasone OR Dexamethasone OR Betamethasone OR Omnis OR Ciclesonide OR Veramyst OR Flunisolide OR Nasalide OR Beclomethasone OR hydrocortisone) AND (allergic rhinitis).

### Study selection and data collection

Two review authors (KL and VA) independently performed trial selection by title and abstract screening based on predetermined eligibility criteria. The full-text articles of the selected RCTs were reviewed. Two authors (KSe and KL) extracted details of the included studies. When insufficient information or conflicting data were found during the data collection, the corresponding author was approached for further information. Any disagreements over data were resolved by the fifth author (KSn) if necessary. The collected data included: study type, number of participants, mean age, gender, primary outcomes and secondary outcomes. The primary outcomes were nasal symptoms, ocular symptoms, and disease-specific QOL. The secondary outcomes were adverse events. Data of patients with comorbid asthma were extracted separately when possible, for subgroup analysis.

### Risk of bias in included studies

The quality of included RCTs was assessed by evaluating the risks of bias as guided by the Cochrane Handbook for Systematic Reviews of Interventions<sup>(17)</sup>. Five domains were assessed: random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, and selective reporting. The included studies had a low risk of bias when the methods used for each domain were clearly described. When

Table 1. Characteristics of included studies.

First author	Year	Study Type	Disease phenotype	Patients Age (years old)	Number of patients	LTRA drug	LTRA dose (mg/d)	INCS drug	INCS dose (µg/d)	Duration of treatment (weeks)
Di lorenzo <sup>(19)</sup>	2004	RPCT, DB	Moderate to severe SAR	12-50	100	Montelukast	10	Fluticasone propionate	200	6
Modgill <sup>(20)</sup>	2010	RCT	AR	15-55	90	Montelukast	10	Fluticasone propionate	400	4
Esteitie <sup>(21)</sup>	2010	RPCT, DB	PAR	18-55	54	Montelukast	10	Fluticasone propionate	200	2
Tatar <sup>(22)</sup>	2013	RCT	Moderate to severe persistent AR	17-67	56	Montelukast	10	Mometasone furoate	200	4
Goh <sup>(23)</sup>	2014	RPCT, DB	Moderate to severe SAR	>12	128	Montelukast	10	Fluticasone propionate	200	8
Chen <sup>(24)</sup>	2019	RCT	Moderate to severe SAR	18-60	41	Montelukast	10	Budesonide	256	2

LTRA, leukotriene receptor antagonist; INCS, intranasal corticosteroid; mg/d, milligram per day; µg/d, microgram per day; RPCT, Randomized placebo-controlled trial; RCT, Randomized controlled trial; DB, Double-blind; SAR, seasonal allergic rhinitis; PAR, perennial rhinitis.

the described methods for each domain showed a high risk of bias, that study was classified as high risk. When there was not enough information to determine the risk, the RCT was defined as unclear risk of bias.

### Data synthesis and statistical analysis

Data were pooled for meta-analysis. Odds ratios (OR) and 95% confidence intervals (CI) were used for dichotomous data. Standardized Mean Differences (SMD) and 95% CIs were used for continuous data. The heterogeneity or the discrepancy in the estimates of treatment effects from different trials was assessed by the  $I^2$  statistic. An  $I^2$  of less than 40%, 40–60%, or >60% represented low, moderate, and substantial heterogeneity, respectively. A fixed-effect method was used when statistical heterogeneity was low. When the statistical heterogeneity was high, a random-effect method was used for a more conservative estimate of the difference. Statistical assessments were performed using Review Manager (RevMan) version 5.3<sup>(18)</sup> (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

## Results

### Study selection

There were 848 studies identified and retrieved, 844 studies were from electronic searches, and 4 studies were from manual searches. During the title and abstract screening, 839 studies were excluded due to irrelevant references. Three studies were excluded after full-text screening (Figure 1). Six studies were finally included<sup>(19–24)</sup> in the qualitative synthesis. A randomized controlled trial by Tatar et al.<sup>(22)</sup> did not compare between the groups and did not report the standard deviation. Therefore,

the data from this study could not be pooled for meta-analysis. Finally, a total of 5 studies were included for the meta-analysis<sup>(19–21,23,24)</sup>. Characteristics of the included studies are shown in Table 1. A flow chart of the study retrieval and selection is presented in Figure 1.

### Participants

In these 6 studies, there were a total of 358 participants. The mean age was 28.9 years, being 41.6% male. The diagnosis of AR was confirmed by skin tests or serum-specific IgE in 298 patients. Three RCTs studied paediatric and adult patients<sup>(19,20,23)</sup> while three RCTs studied only adult patients<sup>(21,22,24)</sup>. Two RCTs studied patients with seasonal AR (SAR)<sup>(19,24)</sup>, while two studied perennial AR (PAR), one with persistent disease<sup>(21,22)</sup>. Concerning severity, four RCTs studied moderate to severe AR<sup>(19,22–24)</sup>. One trial included AR patients with comorbid mild asthma, but the data were not reported separately<sup>(21)</sup>. Patients with asthma were excluded from five trials<sup>(19,20,22–24)</sup>.

### Intervention

One RCT used mometasone furoate 200µg per day<sup>(22)</sup>, three used fluticasone propionate 200µg per day (50 µg /actuation, two actuations into each nostril once a day)<sup>(19,21,23)</sup>, one used fluticasone propionate 400µg per day (200 µg into each nostril once a day)<sup>(20)</sup>, and one used budesonide 256µg per day (64 µg into each nostril twice daily)<sup>(24)</sup>. All RCTs used oral montelukast (10mg/day) as the LTRA<sup>(19–24)</sup>. Treatment duration ranged from 2 to 8 weeks. None of the RCTs conducted a long-term study.

### Outcomes

**Nasal symptom score.** The nasal symptom was scored using



Figure 2. Improvement in the composite nasal symptom score: Intranasal corticosteroid plus leukotriene receptor antagonist vs intranasal corticosteroid in monotherapy. Abbreviations: SMD, standardized mean difference; IV, inverse variance; Random, Random effects; CI, confidence interval; df: degrees of freedom; INCS, intranasal corticosteroid; LTRA, leukotriene receptor antagonist.

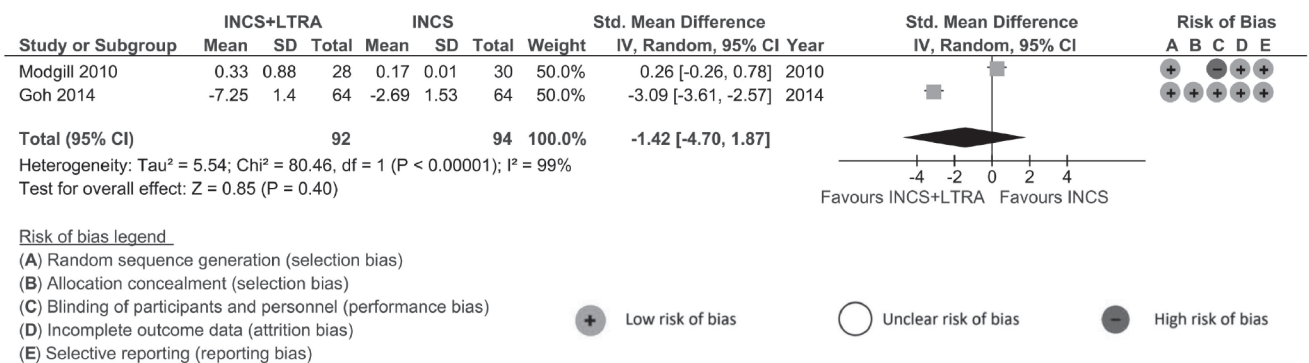


Figure 3. Improvement in the total daytime symptom score: Intranasal corticosteroid plus leukotriene receptor antagonist vs Intranasal corticosteroid. Abbreviations: SMD, standardized mean difference, IV: inverse variance, Random: Random effects, CI: confidence interval, df: degrees of freedom, INCS: Intranasal corticosteroid, LTRA: leukotriene receptor antagonist.

a 4-point scale (0 none, 1 mild, 2 moderate, and 3 severe)<sup>(19,21-23)</sup>. One study used a 10 cm visual analog scale (0 cm = no symptoms and 10 cm = most severe and bothersome symptom)<sup>(24)</sup>. The scoring system was not described in one study<sup>(20)</sup>. Four RCTs assessed composite nasal symptom score<sup>(19,20,22,24)</sup>. There was no significant statistical difference in the composite nasal symptom score between the INCS+LTRA and INCS in monotherapy (SMD -0.91, 95%CI -2.52 to 0.70,  $p=0.27$ , 3 RCTs)<sup>(19,22,24)</sup>. An  $I^2$  of 94% represented substantial heterogeneity of the 3 RCTs<sup>(19,21,24)</sup>. There were no significant differences between the INCS+LTRA and INCS in monotherapy in total daytime symptom score (SMD -1.42, 95%CI -4.70 to 1.87,  $p=0.40$ , 2 RCTs)<sup>(20,23)</sup> and total nighttime symptom score (SMD -0.55, 95%CI -3.46 to 2.35,  $p=0.71$ , 2 RCTs)<sup>(20,23)</sup>. An  $I^2$  of 99% represents substantial heterogeneity of the 2 RCTs<sup>(20,23)</sup>. The data are displayed in Figures 2-4. The individual nasal symptom score was assessed in five RCTs<sup>(19-22,24)</sup>. One RCT did not report the standard deviation for each individual nasal symptom score and could not be imputed<sup>(22)</sup>. There were no significant differences between INCS+LTRA and INCS in monotherapy in nasal congestion (SMD -0.98; 95%CI -2.37 to 0.42,  $p=0.17$ , 4 RCTs)<sup>(19-21,24)</sup>, rhinorrhea (SMD -0.73;

95%CI -2.26 to 0.81,  $p=0.35$ , 4 RCTs)<sup>(19-21,24)</sup>, itching (SMD -0.73; 95%CI -2.99 to 1.53,  $p=0.53$ , 3 RCTs)<sup>(19,20,24)</sup> and sneezing (SMD -0.19; 95% CI -1.76 to 1.38,  $p=0.81$ , 4 RCTs)<sup>(19-21,24)</sup>. The heterogeneity was substantial for nasal congestion, rhinorrhea, nasal itching, and sneezing ( $I^2$  of 93%, 94%, 97%, and 96%, respectively). Reduction of nasal symptoms in the subgroup of patients with comorbid asthma could not be assessed as patients with asthma were excluded from most studies.

**Ocular symptom score.** The assessed ocular symptoms were tearing, ocular itching, redness, and puffiness. The ocular symptom was scored by a 4-point scale (0 none, 1 mild, 2 moderate, and 3 severe). One RCT assessed total ocular symptom score<sup>(23)</sup>. The results favoured the effects of INCS+LTRA over the INCS in monotherapy. The difference was statistically significant (SMD -2.87, 95%CI -3.75 to -1.99,  $p<0.00001$ , 1 RCT)<sup>(23)</sup>.

**Disease-specific QOL.** Three RCTs assessed disease-specific QOL score<sup>(21-23)</sup>. The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)<sup>(25)</sup> was used in two RCTs only<sup>(21,23)</sup>. The RQLQ questionnaire comprises 25 questions distributed in 6 domains (activity



Figure 4. Improvement in the total nighttime symptom score: intranasal corticosteroid plus leukotriene receptor antagonist vs intranasal corticosteroid. Abbreviations: SMD, standardized mean difference; IV, inverse variance; Random, Random effects; CI, confidence interval; df, degrees of freedom; INCS, intranasal corticosteroid; LTRA, leukotriene receptor antagonist.

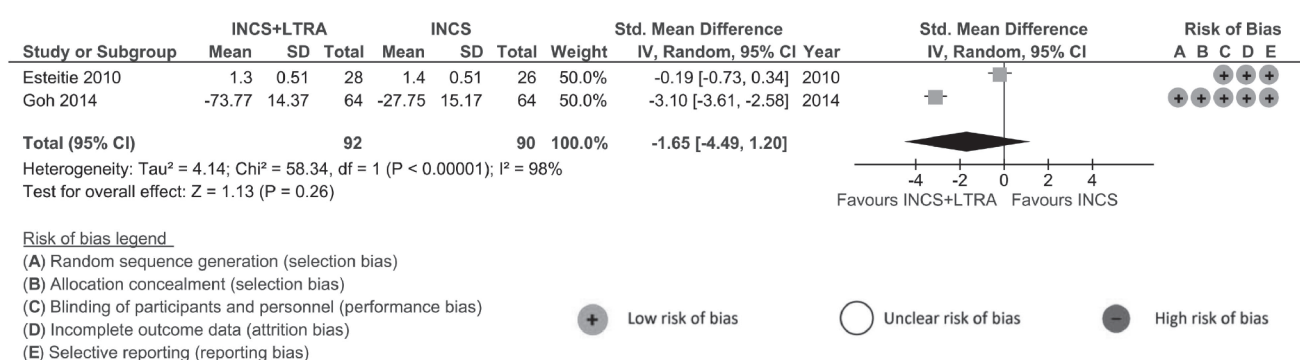


Figure 5. Improvement in the disease-specific quality of life score: Intranasal corticosteroid plus leukotriene receptor antagonist vs Intranasal corticosteroid. Abbreviations: SMD, standardized mean difference; IV, inverse variance; Random, Random effects; CI, confidence interval; df, degrees of freedom; INCS, Intranasal corticosteroid; LTRA, leukotriene receptor antagonist.

limitations, practical problems, nose symptoms, eye symptoms, non-hay fever symptoms, and emotional problems). Each item was rated on a 7-point scale from 0 (no impairment) to 6 (severely impaired). A high score corresponds to the low quality of life. The miniRQLQ comprised 14 questions distributed in five domains (activity limitations, practical problems, nasal symptoms, eye symptoms, and other symptoms) and was used in one trial<sup>(22)</sup>. This trial did not report; however, the standard deviation for the disease-specific QOL score and could not be imputed<sup>(22)</sup>. There was no significant difference between the INCS+LTRA and INCS in monotherapy (SMD -1.65; 95%CI -4.49 to 1.20,  $p=0.26$ , 2 RCTs)<sup>(21,23)</sup>. The data are displayed in Figure 5.

### Adverse events

The number of patients with adverse events was reported by four RCTs<sup>(19,21,22,24)</sup>. There was no significant difference in adverse events between the INCS+LTRA and INCS in monotherapy (Risk Ratio 1.50, 95%CI 0.54 to 4.18,  $p=0.44$ ).

### Risk of bias in the included studies

From the included studies, 50% and 40% had a low risk of bias

in random sequence generation and allocation concealment respectively, while 50% had a high risk of bias in the blinding of outcome assessment. All studies (100%) had a low risk of bias in incomplete outcome data, while 83% had a low risk of bias in selective reporting. Overall, the included studies had selection bias and performance bias, whereas they had low risks in attrition bias and reporting bias (Figure 6).

### Discussion

The use of LTRA+INCS combination for treating AR has been a controversial issue in recent years. The results of this study failed to demonstrate the benefits of INCS+LTRA compared to INCS in monotherapy on the improvement in nasal symptoms and disease-specific QOL. In line with our findings, when the olfactory function was assessed by Dalgic et al., LTRA did not add benefits to INCS<sup>(26)</sup>. However, the combination had beneficial effects on extra nasal symptoms. Based on one RCT, the INCS+LTRA combination significantly decreased ocular symptoms compared to the INCS in monotherapy. Goh et al.<sup>(23)</sup> randomized 128 patients with AR to receive fluticasone propionate nasal spray together with either montelukast tablets or



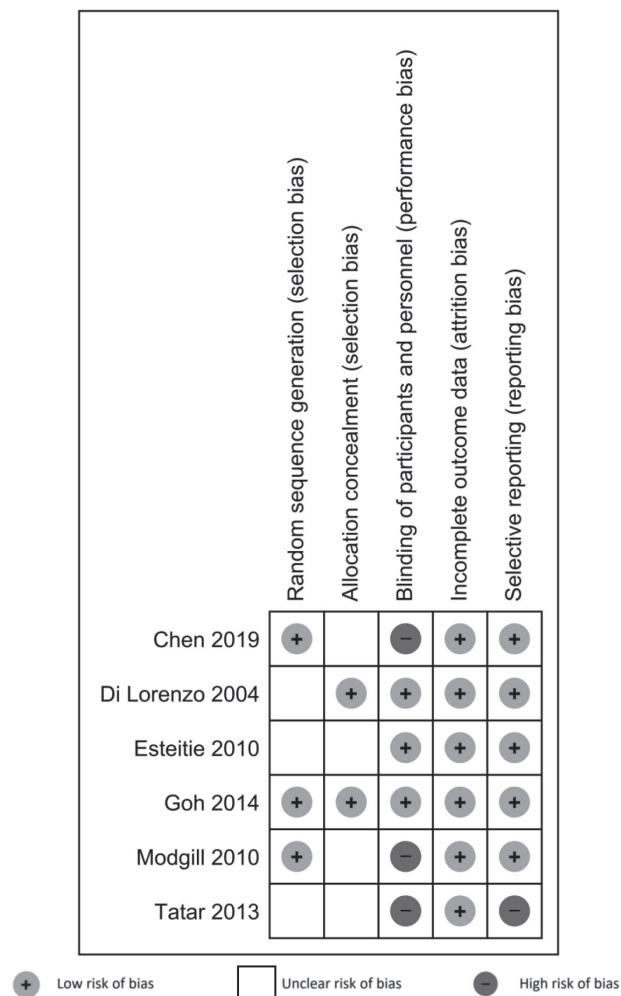


Figure 6. Risk of bias summary: each risk of bias item for each included study.

placebo. The combination demonstrated greater effects in both ocular symptom scores and the eye domain of the RQLQ questionnaires. Likewise, previous articles reported that the combination controlled asthmatic symptoms better than the INCS in monotherapy<sup>(27-30)</sup>. The INCS+LTRA combination improved lower airway symptoms by the effects on bronchial smooth muscle contraction, vasodilatation, and mucus hypersecretion<sup>6</sup>. In contrast to the results of the present study, a previous meta-analysis by Feng et al.<sup>(31)</sup> favoured the INCS+LTRA effects vs INCS in monotherapy on nasal symptoms improvement, including total nasal symptom, rhinorrhea, and sneezing scores. That meta-analysis was published in Chinese, had different inclusion criteria, included some non-randomized trials<sup>(31)</sup> and even did not include one important RCT<sup>(22)</sup>. Seidman et al.<sup>(2)</sup>, in a clinical practice guideline, does not recommend the use of INCS+LTRA combination after the failure of INCS in monotherapy for the management AR and it is not recommended either by the International Consensus Statement

on Allergy and Rhinology: Allergic Rhinitis (ICAR:AR) regarding its effectiveness<sup>(32)</sup>. In practice, INCS in monotherapy or the formulation MP-AzeFlu of INCS should be an initial treatment for patients with moderate to severe persistent AR or nasal obstruction<sup>(32,33)</sup>. The findings of our meta-analysis do not recommend the use of INCS+LTRA combination in AR patients who fail after INCS in monotherapy. The INCS+LTRA combination may, however, be considered to improve persistent extra nasal symptoms, including ocular symptoms. The clinical guidelines recommend against LTRA monotherapy for the management of AR because LTRA was more expensive and equally as effective as or less effective than oral antihistamines for AR<sup>(34)</sup>; moreover, it is less effective than INCS<sup>2</sup>. LTRA combined with oral H1 antihistamine might be considered when failure of antihistamine monotherapy<sup>(2,32,35)</sup>. In this situation, the formulation MP-AzeFlu of INCS is better evidence-based option validated by previous studies<sup>(36)</sup>, meta-analysis<sup>(37,38)</sup>, and clinical guidelines<sup>(33,39)</sup>. Besides, a double-dosing of INCS is another option to be considered, this being favoured by a meta-analysis in adult patients<sup>(40)</sup>. Other drug combinations such as nasal decongestants with INCS have not proved any beneficial effect in a meta-analysis<sup>(40)</sup>. The limitation of our study was the quality and heterogeneity of the included studies. Most studies had risks of bias in several ways. The common biases were allocation concealment and blinding. Two RCTs included in the meta-analysis had a high risk of bias in blinding of participants and personnel<sup>(20,24)</sup>. The Substantial heterogeneity was found for the outcomes of total daytime and nighttime symptoms scores. Thus, the overall effect may be invalid. There was homogeneity among the three randomized controlled trials reporting no difference between the effects of INCS+LTRA vs INCS in monotherapy<sup>(19-21)</sup>. It is worth noting that these three RCTs had significant risks of bias and the study, which favored the use of INCS+LTRA had moderate to high quality<sup>(23,24)</sup>. Although the reduction of ocular symptoms was shown, these findings were based on only one trial, being this beneficial effect quite inconclusive. This analysis did not assess the effects in patients with asthma because they were excluded from five trials<sup>(19,20,22-24)</sup>. Well-conducted randomized controlled trials are required for further evidence-based recommendations.

### Conclusion

Evidence from five randomized controlled trials in patients with AR did not show benefit of the INCS+LTRA combination when compared to INCS in monotherapy. Nasal symptoms and disease-specific QOL were not different between the two treatments. Although observed, the reduction of ocular symptoms by INCS + LTRA was inconclusive because it was based on a single trial. However, the INCS+LTRA combination was safe and well-tolerated. When INCS fails to improve allergic rhinitis, the INCS+ azelastine combination should be a better option.

When oral H1 antihistamine fails, oral H1 antihistamine +LTRA combination might be considered. LTRA should not be used as monotherapy for the treatment of AR.

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## Authorship contribution

KSe: study design, search, study selection, data collection, data analysis, drafting the article, and final approval. JM: expert opinion, revising the article, and final approval. KL: search, study selection, data collection, revising the article, and final approval

VA: search, study selection, and final approval. KSn: conception, study design, data analysis, drafting the article, and final approval

## Conflict of interest

JM has been a member of the advisory board or speaker bureau or received research grants from Allakos, ALK, AstraZeneca, Genentech, GlaxoSmithKline, Menarini, Mitsubishi-Tanabe, MSD, Mylan-MEDA Pharma, Novartis, Sanofi-Genzyme & Regeneron, UCB, Uriach Group. KSN received Honoraria for speaking at symposia from Merck Sharp & Dohme and Menarini. KSE, KL and VA declare that they have no conflict of interest.

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**Kornkiat Snidvongs**  
**Department of Otolaryngology**  
**Medical School**  
**Chulalongkorn University**  
**1873 Rama 4 Road**  
**Pathumwan, Bangkok 10330**  
**Thailand**

**Tel: (+66) 2-256-4103**  
**Fax: (+66) 2-252-7787**  
**E-mail: drkornkiat@yahoo.com**