As-needed intranasal corticosteroid spray for allergic rhinitis: a systematic review and meta-analysis*

Minh P. Hoang[1,2,3], Wirach Chitsuthipakorn[4,5], Kachorn Seresirikachorn[1,2], Kornkiat Snidvongs[1,2]

[1] Department of Otolaryngology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[2] Endoscopic Nasal and Sinus Surgery Excellent Center, King Chulalongkorn Memorial Hospital, Bangkok, Thailand
[3] Department of Otolaryngology, Hue University of Medicine and Pharmacy, Hue University, Hue, Vietnam
[4] Center of Excellence in Otolaryngology-Head & Neck Surgery, Rajavithi Hospital, Bangkok, Thailand
[5] Department of Otolaryngology, College of Medicine, Rangsit University, Bangkok, Thailand

Rhinology 60: 4, 242 - 251, 2022
https://doi.org/10.4193/Rhin21.355

***Received for publication:**
October 4, 2021
Accepted: March 16, 2022

Abstract

Background: As-needed intranasal corticosteroid spray (INCS) is commonly used by patients with allergic rhinitis (AR) who have suboptimal symptom control. This systematic review aimed to assess the effectiveness of as-needed INCS for treating AR.

Methodology: Systematic searches for randomized controlled trials studying the effects of as-needed INCS compared to regular INCS, as-needed antihistamine, or placebo were performed. Primary outcomes were total nasal symptom score (TNSS) and disease-specific quality of life (DSQoL).

Results: Eight studies (882 participants) met the criteria. Regular use of INCS showed greater improvements than as-needed INCS in TNSS, DSQoL, nasal peak inspiratory flow, sneezing, and nasal congestion scores with small effect sizes. There were no differences between regular and as-needed INCS usage for ocular symptoms, symptom-free days, nasal itching, and rhinorrhea scores. As-needed INCS was superior to as-needed antihistamine and placebo with medium effect sizes. There were no differences in risk of adverse events between the groups in all three comparisons.

Conclusions: Regular use of INCS improved total nasal symptoms score and DSQoL better than as-needed INCS. However, as-needed INCS improved TNSS better than as-needed antihistamine and placebo. The effects of as-needed INCS were closer to regular INCS usage than to placebo or as-needed AH usage.

Key words: allergic rhinitis, corticosteroid, quality of life, rhinorrhea, sneezing, itching

Introduction

As the most potent anti-inflammatory agent [(1)], intranasal corticosteroid spray (INCS) is one of the first-line therapies for treating allergic rhinitis (AR). Patients with AR benefit from INCS, especially those with nasal blockage or moderate-to-severe AR (in overall symptoms) [(2)]. INCS activates anti-inflammatory gene transcription and suppresses proinflammatory gene transcription. Subsequently, it inhibits cytokine production and inflammatory cells infiltration [(3)]. With these genomic effects, INCS is potent in controlling allergic response and clinically effective in alleviating nasal symptoms. Although clinical benefits of INCS were revealed, a study that analyzed medication-taking behavior in a real-world setting showed that only 11.3% of patients reporting data from 7 to 100 days strictly adhered to medication [(4)].

As-needed use of inhaled corticosteroid plus long-acting β-agonists is recommended as an option for the step-two treatment of asthma [(5)]. The link between the upper and lower airways has been observed which leads to a concept of united airway disease [(6)]. The as-need INCS as a treatment step for AR has gained more attention from researchers and studies on the as-need INCS are increasing [(7)]. In general, INCS is recommended for long-term daily use because its accumulation effects reach the maximum level after at least two weeks of usage. The onset

of action is around six to 24 hours after the first application [8,9] and clinical symptoms can be diminished on the first day. As a result, patients do not always comply with the treatment or stop using the medication when the symptoms are under control [10]. Wang et al. [11] showed that the patients in low adherence group (28%) still had a significant improvement in total nasal symptoms when compared to the baseline. Debate on the effectiveness of as-needed INCS versus regular INCS is still ongoing [12].

Herein, we conducted a systematic review and meta-analysis to assess the therapeutic role of as-needed INCS in treating AR. The objectives of this study were to evaluate the effectiveness and the safety of as-needed INCS.

Materials and methods

Eligibility criteria

The inclusion criteria were: 1) randomized controlled trials (RCTs) or quasi-randomized controlled trials assessing the effects of as-needed INCS in treating patients with AR without language restrictions, 2) patients of any age, 3) clinical symptoms of AR, 4) diagnostic criteria of AR confirmed by allergy tests following the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines [13], and 5) any type and any dosage of corticosteroid. The exclusion criteria were studies of 1) acute or chronic rhinosinusitis, 2) cystic fibrosis, 3) immunotherapy started within the prior year, 4) aspirin-exacerbated respiratory disease. Regular use was defined as undertaking therapeutic doses of INCS as prescribed on a daily basis. As-needed use was defined as irregular medication use only on the days when symptoms required it. Although being recorded, medication compliance was not used to exclude the low-compliance participants in the regular-use-INCS group. Comparisons were 1) as-needed INCS versus regular INCS, 2) as-needed INCS versus as-needed antihistamine (AH), and 3) as-needed INCS versus placebo. Outcome measures were not used to exclude the studies.

Information sources and search strategy

The study protocol was registered on the PROSPERO database with the identification number CRD42021269606. This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [14]. Electronic systematic searches on seven databases: PubMed, EMBASE, Web of Science, Scopus, CENTRAL, ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform, were performed without any restrictions and included publications up to August 5, 2021. Manual searches were performed to retrieve the additional studies from other sources. The search strategy is described in Table S1 in the Supplement.

Study selection and data extraction

Two reviewers (MPH and KSe) independently screened publications for inclusion in this review. After the title and abstract screening, full texts of the selected articles were retrieved to assess the eligibility. Disagreements over the study selection were resolved by a consensus after discussion among the authors. Two independent reviewers (MPH and KSe) performed the data extraction. The extracted data included participants, interventions, comparators, and outcomes at all visits. Primary outcomes were total nasal symptom score (TNSS) and disease-specific quality of life (DSQoL). Secondary outcomes were total ocular symptom score (TOSS), individual nasal symptom score, nasal patency, symptom-free days, and adverse events. The pre-intervention value, post-intervention value, and change score of each outcome were extracted. If the mean and standard deviation (SD) were not provided in the manuscript, data extraction was carried out using available figures. If an SD of the mean change from the baseline was not provided, the SD was imputed using an SD of the value at each time point with the correlation within group of 0.5 [15]. When a change value could not be extracted, the post-intervention value was used for data analysis. If a study reported outcomes at multiple time points, the longest available data were extracted and pooled in the meta-analysis. In the case of missing or inappropriate data for statistical imputation, we contacted corresponding authors for further clarification. In the case of multiple records of the same trial (published articles, conference abstracts, or post-hoc analyses), we collected the data from all sources and analyzed them as only one trial.

Risk of bias assessment

Internal validity of each included study was assessed using the Revised Cochrane risk-of-bias tool for randomized trials (RoB2) [16]. Risks of bias were evaluated in the following domains: randomization process, deviation from intended interventions, missing outcome data, measurement of the outcome, selection of the reported result, and overall bias [16]. Two reviewers (MPH and WC) independently rated whether the risk of bias of each domain was low, some concerns, or high, using signaling questions. Discussion among the authors resolved conflicts during the judgment. A "low risk of bias" was determined if the low-risk-bias method for each domain was clearly described. A "high risk of bias" was judged if a high risk was indicated in the description. A "some concerns" was indicated when there was inadequate information or uncertainty over the potential for bias. Risk-of-bias plots were generated using the Risk-of-bias VISualization (robvis) package [17].

Data synthesis and statistical analysis

Risk ratio (RR) and 95% confidence interval (CI) were used for dichotomous data. Mean difference (MD) or standardized mean difference (SMD), SD and 95% CI were used for continuous data. Standard error, median, interquartile range, or 95% CI were imputed if the SD was not reported [18]. The I^2 statistic was com-

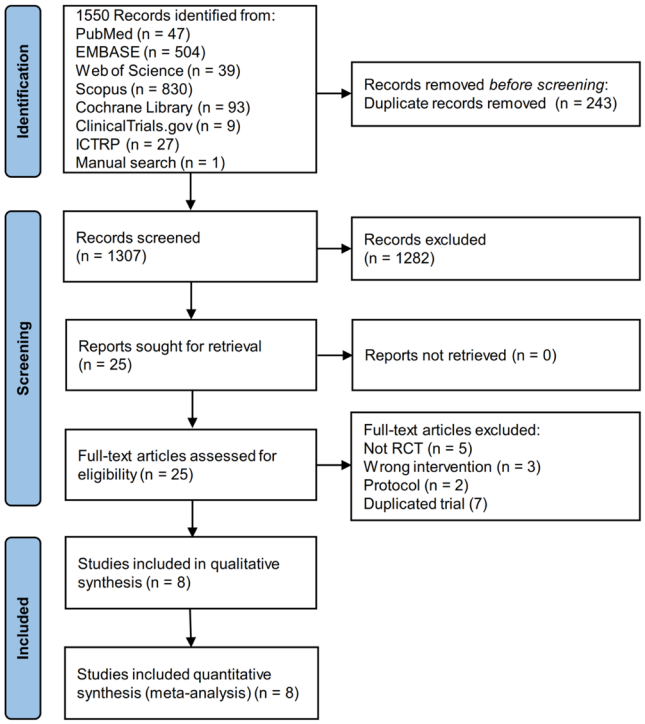


Figure 1. PRISMA flow diagram of study selection.

puted to assess the discrepancies in treatment effects among different studies. An I^2 of <40%, 40-60% and >60% represented low, moderate, and substantial heterogeneity, respectively. When heterogeneity was low, a fixed-effect model was used. A random-effects model was used if heterogeneity was high for a more conservative estimate of the differences. Egger's test and funnel plots were used to evaluate publication bias and small study effect for quantitative syntheses of at least ten studies. Subgroup analyses by AR subtype (perennial vs seasonal), age (adult vs pediatric population), dosage (high vs standard dosage), and INCS systemic bioavailability (old- vs new-generation formulation) were conducted for primary outcomes. New-generation INCS was defined as INCS with <1% systemic bioavailability, including mometasone furoate, fluticasone furoate, fluticasone propionate, and ciclesonide. Leave-one-out sensitivity analysis was performed to assess the influence of each individual study on the overall estimate of primary outcomes. Indirect comparisons and relative rankings of treatments regarding primary outcomes were performed using the mvmeta command in Stata software. All statistical assessments were conducted using Review Manager (RevMan) version 5.4.1 and Stata 17.0 (StataCorp, College Station, TX, USA).

Results

Study selection

Data searches yielded a total of 1,550 records. After removing duplicate records, the title and abstract of the remaining records were screened. Twenty-five records underwent the full-text screening, of which 17 studies were excluded. Finally, eight studies were included in the qualitative and quantitative analysis [7,19-25]. Characteristics and outcomes of the included trials are displayed in Table 1. A flowchart of study retrieval and study selection is illustrated in Figure 1.

Participants

Eight hundred and eighty-two patients were included from eight studies [7,19-25]. The mean age of each study ranged from 11.6 to 42.8 years. Four hundred and five patients (46%) were male. Six studies enrolled adult participants [7,19-22,25], one study recruited only pediatric patients [24], and the other had a mixed population [23]. Seven trials evaluated patients with seasonal AR [19-25] and one trial assessed perennial AR [7]. Severity of the disease was classified as mild-to-moderate in one study [24], moderate-to-severe in one study [7], and mild-to-severe in one study [25]. The other five studies provided inadequate information of disease severity [19-23].

Intervention

An old-generation formulation (beclomethasone dipropionate) of INCS was used in two studies [19,20]. The other six studies used three new-generation formulations (fluticasone propionate [21-24], mometasone furoate [25], or fluticasone furoate [7]). All included studies defined 'as-needed use' as irregular medication use only on the days when symptoms are required. The duration of treatment ranged from four to 12 weeks. While patients in the INCS-as-needed group were advised to use one therapeutic-dose INCS in six studies [7,21-25], the other two studies by Juniper et al. instructed that the patients could increase the amount of beclomethasone dipropionate from 400 to 800 µg/day until symptoms were controlled and then patients could later reduce the dose [19,20].

Five studies provided a quantification of "as-needed" usage [7,19,21-23]. The number of days of as-needed usage was 55% [21], 58% [22], and 62% [23] of the treatment period. Mean cumulative doses of as-needed-INCS groups were 26% [19] and 51% [7] those of regular-INCS groups (Table S2 in the Supplement).

As-needed INCS versus regular INCS

Five studies evaluated the as-needed INCS vs regular INCS [7,19,20,24,25].

Total nasal symptom score (TNSS)

TNSS was assessed by five RCTs [7,19,20,24,25]. A 4-point scale [7,24] and a 7-point scale [19,20,25] were used for each symptom with a total of four symptoms. Duration of treatment ranged from six to 12 weeks. The effects on TNSS reduction favored the regular INCS over the as-needed INCS (SMD 0.37; 95% CI 0.13, 0.61; p<0.01) [7,19,20,24,25]. An I^2 of 37% represented low heterogeneity (Figure 2).

Table 1. Characteristics of the included studies.

Study name	Disease phenotype	Patients	Patient (n)	INCS	INCS dosage (μg/d)	As-need INCS (n)	Regular INCS (n)	As-need AH (n)	Placebo (n)	Outcomes					Duration of treatment (weeks)
										TNSS	INSS	TOSS	DSQoL	SFD	NPIF	
Juniper[19] 1990	SAR	Adults	60	BD	800	29	30	NA	NA	Yes	Yes	Yes	Yes	No	No	7
Juniper[20] 1993	SAR	Adults	60	BD	800	30	30	NA	NA	Yes	Yes	Yes	Yes	No	No	6
Jen[21] 2000	SAR	Adults	52	FP	200	26	NA	NA	26	Yes	Yes	Yes	Yes	No	No	4
Kaszuba[22] 2001	SAR	Adults	88	FP	200	44	NA	44 FEX	NA	Yes	Yes	Yes	Yes	No	No	4
Dykewicz[23] 2003	SAR	Mixed	241	FP	200	122	NA	NA	119	Yes	Yes	No	No	No	No	4
Wartna[24] 2017	SAR, mild to moderate	Children	150	FP	100-200*	46	45	41 LEV	NA	Yes	Yes	Yes	No	Yes	No	12
Sakamoto[25] 2019	SAR, mild to severe	Adults	123	MF	200	62	61	NA	NA	Yes	Yes	Yes	Yes	Yes	No	8
Thongngarm[7] 2021	PAR, moderate to severe	Adults	108	FF	110	53	55	NA	NA	Yes	Yes	No	Yes	No	Yes	6

Disease-specific quality of life

Four studies used the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) [7,19,20,25]. The DSQoL improvement favored the regular INCS over the as-needed INCS (SMD 0.37; 95% CI 0.10, 0.64; p<0.01) [7,19,20,25]. An I^2 of 36% represented low heterogeneity (Figure 3).

Subgroup analysis by allergic rhinitis subtype

Subgroup analysis showed that TNSS reduction favored the regular use of INCS over the as-needed INCS in the seasonal AR (SMD 0.38; 95% CI 0.06, 0.71; p=0.02, I^2=53%) [19,20,24,25], but there was no significant difference in the perennial AR (SMD 0.36; 95% CI -0.02, 0.74; p=0.07) [7]. Likewise, the regular INCS was superior to the as-needed INCS in the DSQoL improvement in the seasonal AR group (SMD 0.46; 95% CI 0.11, 0.81; p<0.01; I^2=42%) [19,20,25], not in the perennial AR group (SMD 0.17; 95% CI -0.21, 0.55; p=0.38) [7] (Figures S1-S2 in the Supplement).

Subgroup analysis by age

The effect on TNSS improvement favored the regular INCS over the as-needed INCS in adult participants (SMD 0.45; 95% CI 0.24, 0.67; p<0.01; I^2=0%) [7,19,20,25], but no difference was found in pediatric participants (SMD -0.01; 95% CI -0.42 to 0.40; p=0.96) [24] (Figure S3 in the Supplement). All four RCTs that reported DSQoL enrolled only adult patients [7,19,20,25]. Therefore, the subgroup analysis was not performed.

Subgroup analysis by dosage of INCS

Both high- [19,20] and standard- [7,24,25] dosage of INCS improved TNSS when used regularly significantly better than intermittently. The effect on DSQoL improvement favored regular use over as-needed use in the high-dosage-INCS subgroup [19,20], not in the standard-dosage-INCS subgroup [7,25] (Figures S4-S5 in the Supplement).

Subgroup analysis by INCS systemic bioavailability

Both old- [19,20] and new- [7,24,25] generations of INCS improved TNSS when used regularly significantly better than intermittently. The effect on DSQoL improvement favored regular use over as-needed use in the old-generation INCS subgroup [19,20]. Although non-significance on DSQoL, there was a trend toward greater benefits for regular use in the new-generation INCS subgroup [7,25] (Figures S6-S7 in the Supplement).

Footnote: *aged <12 years 100 μg/day, aged ≥12 years 200 μg/day

Abbreviations: SAR, seasonal allergic rhinitis; PAR, perennial allergic rhinitis; INCS, intranasal corticosteroid spray; BD, Beclomethasone dipropionate; FP, Fluticasone propionate; MF, Mometasone furoate; FF, Fluticasone furoate; AH, antihistamine; FEX, Fexofenadine; LEV, Levocetirizine; TNSS, total nasal symptom score; INSS, individual nasal symptom scores; TOSS, total ocular symptom score; DSQoL, disease-specific quality of life; SFD, symptom-free days; NPIF, nasal peak inspiratory flow; NA, not available.

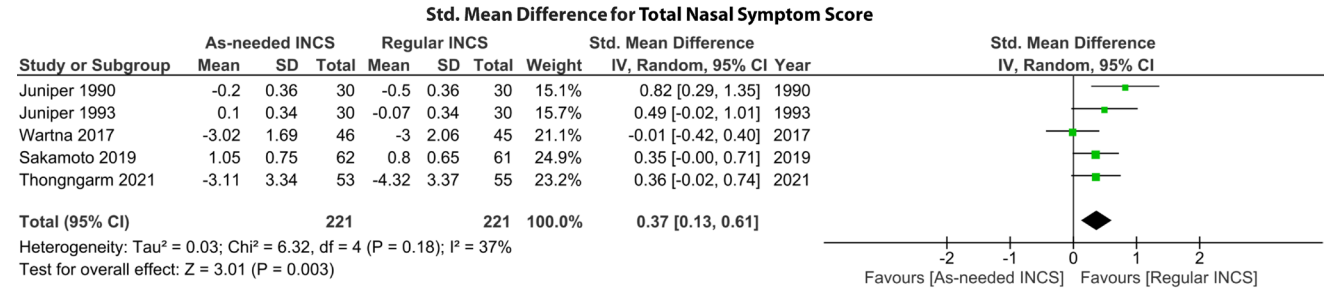


Figure 2. Improvement on total nasal symptom score at endpoint: as-needed intranasal corticosteroid spray vs. regular intranasal corticosteroid spray. INCS, intranasal corticosteroid spray; IV, inverse variance; CI, confidence interval; df, degrees of freedom; Random, random-effects model; Std. mean difference, standardized mean difference.

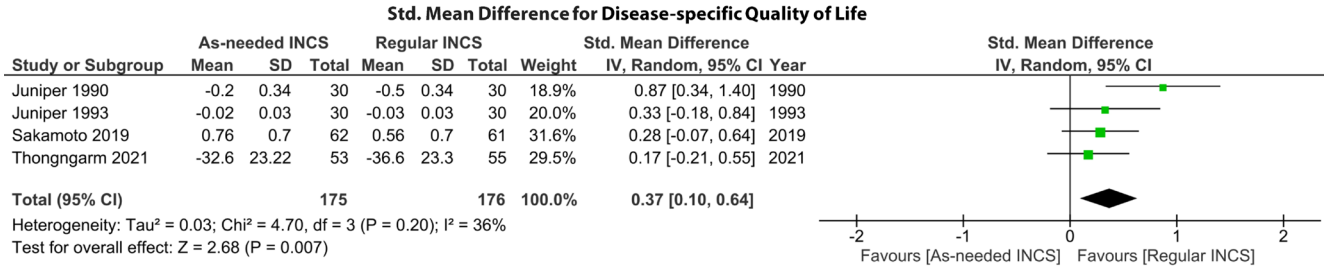


Figure 3. Improvement on disease-specific quality of life at endpoint: as-needed intranasal corticosteroid spray vs. regular intranasal corticosteroid spray. INCS, intranasal corticosteroid spray; IV, inverse variance; CI, confidence interval; df, degrees of freedom; Random, random-effects model; Std. mean difference, standardized mean difference.

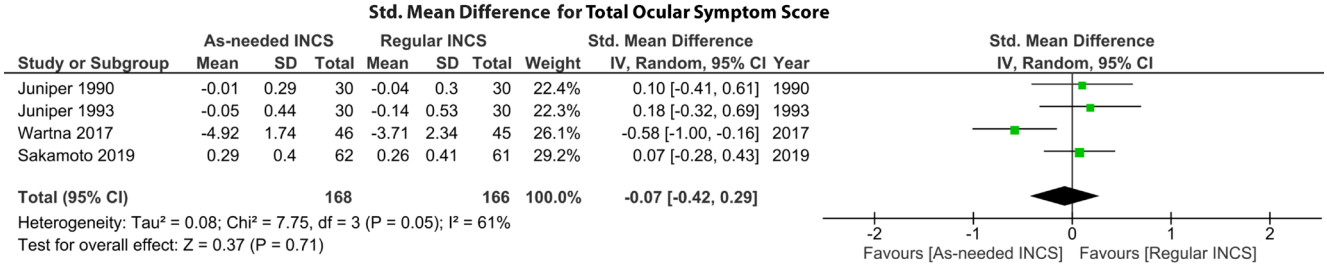


Figure 4. Improvement on total ocular symptom score at endpoint: as-needed intranasal corticosteroid spray vs. regular intranasal corticosteroid spray. INCS, intranasal corticosteroid spray; IV, inverse variance; CI, confidence interval; df, degrees of freedom; Random, random-effects model; Std. mean difference, standardized mean difference.

Sensitivity analysis

After performing the leave-one-out meta-analysis, sensitivity analyses for the improvement on TNSS and DSQoL at endpoint were consistent with the overall estimate of the pooled analyses favoring the regular use of INCS (Figures S8-S9 in the Supplement).

Total ocular symptom score

TOSS was assessed by 4 RCTs [19,20,24,25]. A 4-point scale [19,20,24] and a 7-point scale [25] were used for each symptom. One study assessed three symptoms [24] and three studies assessed four symptoms [19,20,25]. There was no difference in the TOSS improvement between the regular and as-needed use of INCS (SMD -0.07; 95% CI -0.42, 0.29; p=0.71; I^2=61%) . There was substantial heterogeneity (Figure 4).

Individual nasal symptom scores

Five studies compared the individual nasal symptom scores with a 4-point scale between the regular and as-needed use of INCS [7,19,20,24,25]. The mean and SD were neither reported nor imputed in two studies [24,25]. When individual symptoms were analyzed, the effect of symptom reduction favored the regular INCS over the as-needed INCS in sneezing (SMD 0.71; 95% CI 0.04, 1.38; p=0.04; I^2=82%) [7,19,20] and nasal congestion (SMD 0.47; 95% CI 0.07, 0.86; p=0.02; I^2=52%) [7,19,20]. There were no differences in nasal itching (SMD -0.01; 95% CI -0.27, 0.25; p=0.96; I^2=0%) [7,19,20] and rhinorrhea (SMD 0.27; 95% CI -0.11, 0.65; p=0.16; I^2=50%) [7,19,20] (Figure S10A-S10D in the Supplement).

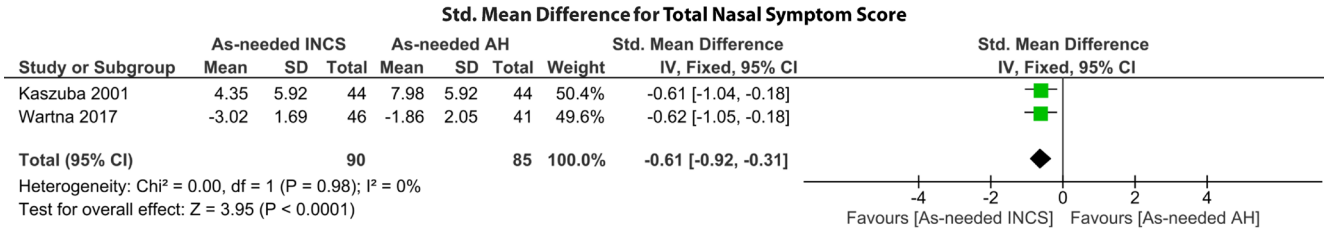


Figure 5. Improvement on total nasal symptom score at endpoint: as-needed intranasal corticosteroid spray vs. as-needed antihistamine. INCS, intranasal corticosteroid spray; AH, antihistamine; IV, inverse variance; CI, confidence interval; df, degrees of freedom; Fixed, fixed-effect model; Std. mean difference, standardized mean difference.

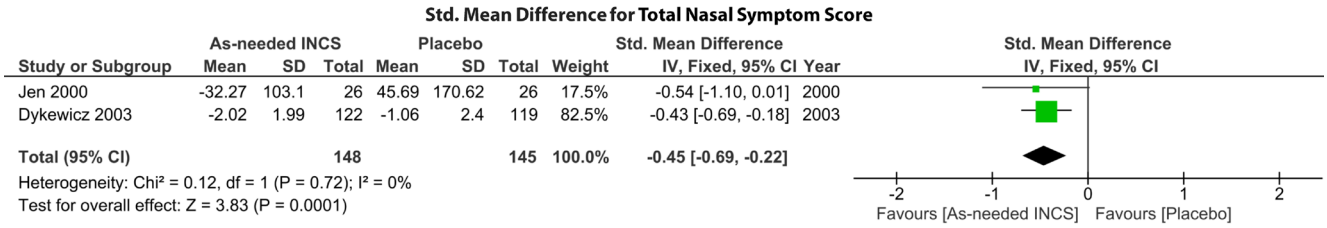


Figure 6. Improvement on total nasal symptom score at endpoint: as-needed intranasal corticosteroid spray vs. placebo. INCS, intranasal corticosteroid spray; IV, inverse variance; CI, confidence interval; df, degrees of freedom; Fixed, fixed-effect model; Std. mean difference, standardized mean difference.

Objective measurements for nasal patency

Improvement of nasal peak inspiratory flow favored the regular use over the as-needed INCS in one study (MD 19.20; 95% CI 5.24, 33.16; p<0.01) [7].

Symptom-free days

Two studies measured symptom-free days and compared between the regular and as-needed use of INCS. The effect was not significantly different between the two groups (MD 1.94; 95% CI -16.71, 20.59; p=0.84; I^2=82%) [24,25] (Figure S11 in the Supplement).

As-needed INCS versus as-needed AH

Two studies compared the as-needed INCS to the as-needed AH (fexofenadine [22] and levocetirizine [24]). The as-needed INCS reduced the TNSS significantly greater than the as-needed AH (SMD -0.61; 95% CI -0.92, -0.31; p<0.01; I^2=0%) [22,24]. There was no heterogeneity (Figure 5). There was no difference in the TOSS improvement between the groups (SMD -0.15; 95% CI -0.87, 0.56; p=0.68; I^2=82%) [22,24] (Figure S12 in the Supplement). One study reported individual symptom-free days of each symptom [24]. The as-needed INCS reduced all individual nasal symptom scores significantly greater than the as-needed AH as follows: sneezing (MD -0.62; 95% CI -1.08, -0.16; p<0.01) [22]; nasal congestion (MD -0.33; 95% CI -0.61, -0.05; p=0.02) [22]; and rhinorrhea (MD -0.75; 95% CI -1.37, -0.13; p=0.02) [22]. One study assessed DSQoL using RQLQ [22]. The as-needed INCS reduced the RQLQ score significantly greater than the as-needed AH (MD -0.62; 95% CI -1.08, -0.16; p<0.01) [22]. Symptom-free days favored the as-needed INCS over the as-needed AH (MD -15.00; 95% CI -24.76, -5.24; p<0.01) in one study [24].

As-needed INCS versus placebo

Two studies compared the as-needed INCS versus placebo [21,23]. The as-needed INCS improved TNSS greater than placebo (SMD -0.45; 95% CI -0.69, -0.22; p<0.01; I^2=0%) [21,23]. As measured by DSQoL, using RQLQ, there was no statistical difference between as-needed INCS and placebo (MD -0.35; 95% CI -0.90, 0.20; p=0.21) [21]. The effects of individual symptom reduction favored the as-needed INCS over placebo in all symptoms: sneezing (MD -0.24; 95% CI -0.41, -0.07; p<0.01) [23]; nasal congestion (MD -0.44; 95% CI -0.38, -0.04; p=0.01) [23]; nasal itching (MD -0.29; 95% CI -0.44, -0.14; p<0.01) [23]; and rhinorrhea (MD -0.24; 95% CI -0.41, -0.07; p<0.01) [23].

Indirect comparisons and relative rankings of treatments

We performed the indirect comparison and ranked the treatments following the pooled data of total effects on primary outcomes. Regular INCS ranked among the most beneficial for TNSS and DSQoL. Regular INCS was superior to as-needed INCS with small effect sizes of less than 0.5. As-needed INCS was superior to as-needed AH and placebo with medium effect sizes (See Figures S13-S14 in the Supplement).

Adverse events

Six of the eight included studies assessed the safety of INCS

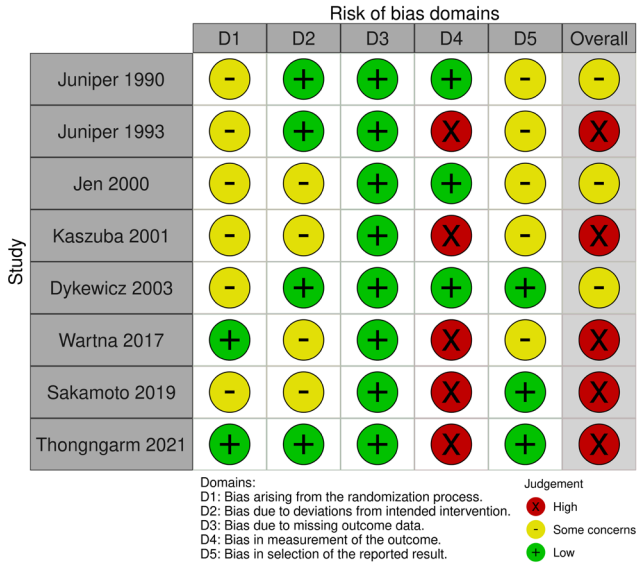


Figure 7. Each risk of bias item and overall risk of bias for each included study.

[7,19,20,23-25]. There were no significant differences in adverse events (epistaxis, common cold, headache, and sore throat) between the as-needed INCS and the regular INCS, or between the as-needed INCS and placebo. No adverse events were reported in the comparison of as-needed INCS versus as-needed AH. Data are displayed in Table 2.

Quality of the included studies

In general, all eight RCTs had low risk of bias in missing outcome data. Some concerns for randomization process, deviation from intended interventions, and selection of the reported results were found in 75%, 50%, and 63% of the included RCTs, respectively. Sixty-three percent of the included studies had high risk of bias for measurement of outcome (Figure 7). Neither Funnel plot nor Egger's test was performed due to the limited number of the included studies.

Discussion

This systematic review and meta-analysis demonstrated that the regular use of INCS was more effective than the as-needed INCS in improving TNSS, DSQoL, and nasal patency. These findings align with the traditional concept that the maximal benefits of INCS on clinical improvement can be achieved after the continuous usage for up to two weeks [8,26]. This concept was confirmed by a randomized, double-blind, placebo-controlled trial conducted by Vasar et al. [27]. They demonstrated that the participants who received fluticasone furoate nasal spray 110 µg once daily significantly improved the daily reflective TNSS. The improvement started on the first day and the overall response increased up to two weeks until it reached the maximal therapeutic outcome. Unlike the common cold medications, corticosteroid agents were used primarily to control chronic symptoms of AR. Therefore, the aim of corticosteroid agents is for the long-term control of symptoms and quality of life.

The first comparison between the regular use versus the as-needed of INCS was investigated by a double-blind, double-dummy RCT by Juniper et al. [19] which showed that the regular use of INCS brought more benefits than the as-needed INCS. Likewise, a study by Sakamoto et al. [25] also supported the regular use of INCS during the pollen season for patients with Japanese cedar pollinosis. Nevertheless, the effects at the eighth week follow-up were not different between the regular and as-needed INCS. Other studies by Juniper et al. [20], Wartna et al. [24], and Thongarm et al. [7] reported no differences in symptom improvements between the regular and as-needed INCS usage. It is noted that the participants of these four studies [7,20,24,25] were unblinded to their interventions. Although the statistical difference between the regular and as-needed INCS usage was not demonstrated by many studies, it could not be concluded that the effects of the two interventions were similar. The sample size of those studies may be too small to detect the difference. However, our meta-analysis which assessed the pooled data from 442 patients

Table 2. Risk ratio of adverse events.

Adverse events	Number of studies	Number of patients	Number of events	Number of patients	Number of events	Risk ratio (95% CI)	p value
		As-needed INCS		Regular INCS			
Epistaxis[7,19,25]	3	143	2	143	8	0.29 (0.07 - 1.17)	0.08
Common cold[7]	1	53	5	55	8	0.65 (0.23 – 1.86)	0.42
Headache[7]	1	53	1	53	1	1.04 (0.07 - 16.17)	0.98
		As-needed INCS		Placebo			
Epistaxis[23]	1	122	2	119	0	4.88 (0.24 - 100.55)	0.30
Sore throat[23]	1	122	4	119	1	3.90 (0.44 - 34.40)	0.22
Headache[23]	1	122	16	119	15	1.04 (0.54 - 2.01)	0.91

Abbreviations: INCS, intranasal corticosteroid spray; CI, confidence interval.

showed statistical significance with low heterogeneity among five studies.

Regular usage of INCS aims to achieve a long-term control of clinical symptoms and target persistent inflammation. Minimal persistent inflammation has been revealed in both the patients with seasonal and perennial allergic rhinitis. Although symptoms and quality of life are known associated with immunological and functional parameters of allergic inflammation [28], the poor correlation between symptomatology and objective measures of inflammation was evident when minimal persistent inflammation outlasts symptoms. Ricca et al. [29] assessed inflammatory markers in six patients who were sensitized only to Betula alba. Persistent inflammation was evident even after the pollen season and the patients were free of symptoms. Similarly, Ciprandi et al. [30] detected ICAM-1/CD54 expression on the conjunctival and nasal epithelium in asymptomatic patients with allergic rhinitis caused by mites. Management of this underlying inflammatory condition requires long-term, continuous administration of potent anti-inflammatory agents such as INCS [31]. Regular usage of INCS is suggested for this purpose while the as-needed INCS does not provide continuous inhibition of persistent inflammation. There was no consistently statistical difference in levels of total eosinophils and eosinophil cationic protein in nasal lavage between as-needed INCS and placebo groups in each follow-up time point during the study period [21]. Subgroup analysis favored the regular use of INCS over the as-needed INCS in the seasonal AR, but not the perennial AR subgroup. Thongngarm 2021 was the only included study that investigated patients with perennial AR [7]. Although the study group was assigned into the as-needed group in a six-week RCT, the study participants received fluticasone furoate nasal spray, two sprays once daily for one week, before using as-needed INCS for five more weeks. The study authors showed no difference in the symptom improvement between the two groups. Nevertheless, when using the TNSS on the seventh day as a baseline, the improvement in TNSS from week 2 to week 6 favored the INCS-regular group than the INCS-as-needed group. In addition, the INCS-regular group had a significantly greater improvement in PNIF at week 5 compared with the as-needed group. Thus, the evidence supporting the regular use of INCS was revealed for both seasonal and perennial AR.

The management strategy in asthma and rhinitis has been changed and headed toward a patient-centered approach [10,12,32]. In practice, many patients with AR take over-the-counter drugs without consulting the physicians or use on-demand medication and stop the medication when the symptoms are under control [2,10,32]. The data from 2,871 questionnaire respondents collected from a mobile application, including overall allergic rhinitis symptoms, daily visual analogue scale, and medication usage, showed that a significant proportion of patients (47% to 50.1%) did not use AR medications on a daily basis [33]. Many patients only use or step-up their medication(s) when the symptoms are not under control [2]. Adherence to medications was assessed in 7,000 respondents using "The Allergy Diary" application. Non-adherence to treatment was observed in all AR medications [4]. Although physicians recommended their patients to use medications regularly even with minimal nasal symptoms, the physicians did not follow the same instructions when they became a patient. Instead, they used medications on demand [34]. The lack of adherence around 32 to 40% [32] was pervasive in long-term prescribed treatment [2].

Based on the results of our meta-analyses, we suggest regular use of INCS with the optimal therapeutic effects for long-term control of the overall AR symptoms and improve AR-related quality of life. The long-term, regular use of INCS prevents minimal persistent inflammation in patients with allergic rhinitis. Therefore, adherence to medication is essential. Patients need to comply with their prescribed treatment. Communication between physicians and patients should be encouraged to emphasize the importance of adherence to medication.

As-needed use implies on-demand usage only on the days when symptoms require it. This meaning is valid, and it is homogeneous among all included studies. When healthcare providers instruct a patient to use as-needed INCS, we suggest emphasizing that INCS should be used "on the days when symptoms require it". Our meta-analyses demonstrated that the as-needed INCS improved nasal symptoms better than both the as-needed AH and placebo with medium effect sizes. Although inferior to regular usage, the effect size of regular INCS usage over as-needed usage is not particularly great. As-needed INCS is closer to regular INCS usage than it is to placebo or as-needed AH usage. Furthermore, mean cumulative doses of as-needed-INCS were around 25%-50% those of regular-INCS groups. As-needed use of new-generation INCS may have an advantage of lower corticosteroid exposure and fewer adverse events, particularly in children and adolescent groups. The as-needed INCS showed some benefits which outweighed the harms. As the onset of action of INCS is around 6-24 hours [9], the overall nasal symptoms can be relieved within one day. A combination of INCS with intranasal antihistamine showed a rapid onset of around 15 minutes [35,36], suggesting an alternative on-demand use. These findings may explain why most patients were satisfied with the as-needed INCS and this reflects the low adherence to INCS in the real-life situation.

To the best of our knowledge, this is the first systematic review and meta-analysis which assessed the effects of as-needed INCS versus regular usage of INCS. Our study had limitations in several aspects. The included studies had overall high risks of bias or some concerns. Five of the eight included RCTs used participant-reported outcomes without blinding the participants which could lead to a bias for measuring outcome. The TNSS and TOSS used in the included studies had different scales

for scoring. Instantaneous scores were not reported in any RCTs. Most participants in the included studies had seasonal AR. Only one RCT studied the patients with perennial AR.

Conclusion

Regular use of INCS provided greater benefits than the as-needed INCS in total nasal symptoms score and disease-specific quality of life. However, the magnitude of mean difference was modest and as-needed use may have an advantage of lower corticosteroid exposure and fewer adverse events. As-needed INCS was more effective than placebo and as-needed AH as the treatment for AR. Further studies investigating the effectiveness of as-need INCS in the pediatric population and perennial AR are warranted.

Acknowledgements

The authors thank Dr Robert M. Naclerio and Dr Fuad M. Baroody (The University of Chicago) for providing the data of their study.

Funding

This is an unfunded project.

Authorship contribution

MPH: conception, study design, search, study selection, data collection, bias assessment, data analysis, drafting the article, and final approval. WC: bias assessment, revising the article, and final approval. KSe: search, study selection, data collection, revising the article, and final approval. KSn: conception, study design, data analysis, drafting the article, and final approval.

Conflict of interest

Kornkiat Snidvongs received Honoraria for speaking at symposia from Organon, Mylan, and Menarini. Minh P. Hoang, Wirach Chitsuthipakorn, and Kachorn Seresirikachorn declare that they have no conflict of interest.

References

1. Snidvongs K, Thanaviratananich S. Update on Intranasal Medications in Rhinosinusitis. Curr Allergy Asthma Rep. 2017; 17(7): 47.
2. Bousquet J, Schunemann HJ, Togias A, et al. Next-generation Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines for allergic rhinitis based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) and real-world evidence. J Allergy Clin Immunol. 2020; 145(1): 70-80 e73.
3. Mullol J, Obando A, Pujols L, Alobid I. Corticosteroid treatment in chronic rhinosinusitis: the possibilities and the limits. Immunol Allergy Clin North Am. 2009; 29(4): 657-668.
4. Menditto E, Costa E, Midao L, et al. Adherence to treatment in allergic rhinitis using mobile technology. The MASK Study. Clin Exp Allergy. 2019; 49(4): 442-460.
5. Domingo C, Rello J, Sogo A. As-needed ICS-LABA in Mild Asthma: What Does the Evidence Say? Drugs. 2019; 79(16): 1729-1737.
6. Compalati E, Ridolo E, Passalacqua G, Braido F, Villa E, Canonica GW. The link between allergic rhinitis and asthma: the united airways disease. Expert Rev Clin Immunol. 2010; 6(3): 413-423.
7. Thongngarm T, Wongsa C, Phinyo P, Assanasen P, Tantilipikorn P, Sompornrattanaphan M. As-Needed Versus Regular Use of Fluticasone Furoate Nasal Spray in Patients with Moderate to Severe, Persistent, Perennial Allergic Rhinitis: A Randomized Controlled Trial. J Allergy Clin Immunol Pract. 2021; 9(3): 1365-1373 e1366.
8. Derendorf H, Meltzer EO. Molecular and clinical pharmacology of intranasal corticosteroids: clinical and therapeutic implications. Allergy. 2008; 63(10): 1292-1300.
9. Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: allergic rhinitis executive summary. Otolaryngol Head Neck Surg. 2015; 152(2): 197-206.
10. Bousquet J, Bedbrook A, Czarlewski W, et al. Guidance to 2018 good practice: ARIA digitally-enabled, integrated, person-centred care for rhinitis and asthma. Clin Transl Allergy. 2019; 9: 16.
11. Wang K, Wang C, Xi L, et al. A randomized controlled trial to assess adherence to allergic rhinitis treatment following a daily short message service (SMS) via the mobile phone. Int Arch Allergy Immunol. 2014; 163(1): 51-58.
12. Bousquet J, Klimek L, Kuna P, Mullol J, Toppila-Salmi S. The Debate: Regular Versus As-Needed Use of Intranasal Corticosteroids for a Patient-Centered Approach. J Allergy Clin Immunol Pract. 2021; 9(3): 1374-1375.
13. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy. 2008; 63 Suppl 86: 8-160.
14. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021; 372: n71.
15. Higgins JPT, Thomas J, Chandler J, et al. Cochrane handbook for systematic reviews of interventions: John Wiley & Sons; 2019.
16. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019; 366: l4898.
17. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Synth Methods. 2021; 12(1): 55-61.
18. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014; 14: 135.
19. Juniper EF, Guyatt GH, O'Byrne PM, Viveiros M. Aqueous beclomethasone diproprionate nasal spray: regular versus "as required" use in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol. 1990; 86(3 Pt 1): 380-386.
20. Juniper EF, Guyatt GH, Archer B, Ferrie PJ. Aqueous beclomethasone dipropionate in the treatment of ragweed pollen-induced rhinitis: further exploration of "as needed" use. J Allergy Clin Immunol. 1993; 92(1 Pt 1): 66-72.
21. Jen A, Baroody F, de Tineo M, Haney L, Blair C, Naclerio R. As-needed use of fluticasone propionate nasal spray reduces symptoms of seasonal allergic rhinitis. J Allergy Clin Immunol. 2000; 105(4): 732-738.
22. Kaszuba SM, Baroody FM, deTineo M, Haney L, Blair C, Naclerio RM. Superiority of an intranasal corticosteroid compared with an oral antihistamine in the as-needed treatment of seasonal allergic rhinitis. Arch Intern Med. 2001; 161(21): 2581-2587.
23. Dykewicz MS, Kaiser HB, Nathan RA, et al. Fluticasone propionate aqueous nasal spray improves nasal symptoms of seasonal allergic rhinitis when used as needed (prn). Ann Allergy Asthma Immunol. 2003; 91(1): 44-48.
24. Wartna JB, Bohnen AM, Elshout G, et al. Symptomatic treatment of pollen-related allergic rhinoconjunctivitis in children: randomized controlled trial. Allergy. 2017; 72(4): 636-644.
25. Sakamoto K, Takahashi G, Yonaga T, Tanaka

S, Matsuoka T, Masuyama K. Comparison of regular and as-needed use of mometasone furoate hydrate nasal spray for the treatment of Japanese cedar pollinosis. Yamanashi Med J. 2019; 34(1): 17-26.
26. Corren J. Intranasal corticosteroids for allergic rhinitis: how do different agents compare? J Allergy Clin Immunol. 1999; 104(4 Pt 1): S144-149.
27. Vasar M, Houle PA, Douglass JA, et al. Fluticasone furoate nasal spray: effective monotherapy for symptoms of perennial allergic rhinitis in adults/adolescents. Allergy Asthma Proc. 2008; 29(3): 313-321.
28. Ciprandi G, Klersy C, Cirillo I, Marseglia GL. Quality of life in allergic rhinitis: relationship with clinical, immunological, and functional aspects. Clin Exp Allergy. 2007; 37(10): 1528-1535.
29. Ricca V, Landi M, Ferrero P, et al. Minimal persistent inflammation is also present in patients with seasonal allergic rhinitis. J Allergy Clin Immunol. 2000; 105(1 Pt 1): 54-57.
30. Ciprandi G, Buscaglia S, Pesce G, et al. Minimal persistent inflammation is present at mucosal level in patients with asymptomatic rhinitis and mite allergy. J Allergy Clin Immunol. 1995; 96(6 Pt 1): 971-979.
31. Canonica GW, Compalati E. Minimal persistent inflammation in allergic rhinitis: implications for current treatment strategies. Clin Exp Immunol. 2009; 158(3): 260-271.
32. Bender BG. Motivating patient adherence to allergic rhinitis treatments. Curr Allergy Asthma Rep. 2015; 15(3): 10.
33. Bousquet J, Devillier P, Arnavielhe S, et al. Treatment of allergic rhinitis using mobile technology with real-world data: The MASK observational pilot study. Allergy. 2018; 73(9): 1763-1774.
34. Bousquet J, Murray R, Price D, et al. The allergic allergist behaves like a patient. Ann Allergy Asthma Immunol. 2018; 121(6): 741-742.
35. Bousquet J, Meltzer EO, Couroux P, et al. Onset of Action of the Fixed Combination Intranasal Azelastine-Fluticasone Propionate in an Allergen Exposure Chamber. J Allergy Clin Immunol Pract. 2018; 6(5): 1726-1732 e1726.
36. Patel P, Salapatek AM, Tantry SK. Effect of olopatadine-mometasone combination nasal spray on seasonal allergic rhinitis symptoms in an environmental exposure chamber study. Ann Allergy Asthma Immunol. 2019; 122(2): 160-166 e161.

Kornkiat Snidvongs
Department of Otolaryngology
Faculty of Medicine
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

This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Table S1. Search strategies.

Search strategy 1: MEDLINE (47), EMBASE (504)	
exp Rhinitis/	As needed.mp
Rhinitis Allergic Perennial/	As-needed.mp
Rhinitis, allergic, seasonal/	On demand.mp
hayfever.mp.	As required.mp
hay fever.mp.	As-required.mp Symptomatic treatment.mp
fever, hay.mp.	Prn.mp
seasonal allergic rhinitis.mp.	or 40-46
allergic rhinitides.mp.	Intervention Studies.mp.
allergic rhinitis.mp.	Experimental stud*.mp.
rhiniti*.mp.	exp Clinical Trial/
pollinosis.mp.	Trial.mp.
pollenosis.mp.	Clinical Trial.mp.
pollen-induced rhinitis.mp.	exp Controlled Clinical Trial/
exp Nasal obstruction/	Controlled Clinical Trial.mp.
Conjunctivitis/	Randomized Controlled Trial.mp.
Conjunctivitis, Allergic/	Randomised Controlled Trial.mp
conjunctivit*.mp.	exp Placebos/
rhino-conjunctivit*.mp.	Placebos.mp.
allergic rhinoconjuntivitis.mp	exp Random Allocation/
or/1-19	Random Allocation.mp.
intranasal corticosteroid*.mp.	exp Double-Blind Method/
INCS*.mp.	Double-Blind Method.mp.
exp Beclomethasone/	Double-Blind design.mp.
Beclomethasone dipropionate.mp.	exp Single-Blind Method/
exp Budesonide/	Single-Blind Method.mp.
Budesonide dipropionate.mp.	Single-Blind design.mp.
exp Fluticasone/	Triple-Blind Method.mp.
Fluticasone propionate.mp.	Random*.mp.
Fluticasone furoate.mp.	Search:.tw
exp Mometasone Furoate/	Review.pt.
exp Triamcinolone Acetonide/	Systematic review.tw.
Flunisolide.mp.	Meta analysis.mp,pt.
Ciclesonide.mp.	Case series.mp.
Nasonex.mp.	Or 48-73
Pulmicort.mp.	20 and 39 and 47 and 74
dymista.mp.	
flixonase.mp.	
rhinocort.mp.	
or 21-38	

Search strategy 2: Cochrane Library (93), Web of Science (39), Scopus (830), ClinicalTrials.gov (9), ICTRP (27)	
#1	"Rhinitis" OR "allergic rhinitis" OR "seasonal allergic rhinitis" OR "perennial allergic rhinitis" OR "hayfever" OR "hay fever" OR "pollinosis" OR "pollenosis" OR "pollen-induced rhinitis" OR "Conjunctivitis" OR "allergic rhinoconjuntivitis" OR "rhino-conjunctivitis"
#2	"intranasal corticosteroid" OR "INCS" OR "Beclomethasone" OR "Beclomethasone dipropionate" OR "Budesonide" OR "Budesonide dipropionate" OR "Fluticasone" OR "Fluticasone propionate" OR "Fluticasone furoate" OR "Mometasone Furoate" OR "Triamcinolone Acetonide" OR "Flunisolide" OR "Ciclesonide" OR "Nasonex" OR "Pulmicort" OR "dymista" OR "flixonase" OR "rhinocort"
#3	"As needed" OR "As-needed" OR "On demand" OR "As required" OR "As-required" OR "Symptomatic treatment" OR "Prn"
#4	#1 AND #2 AND #3

Table S2. Definition and quantification of as-needed INCS.

Study, year	Definition of "as-needed"	Quantification* of "as-needed" use
Juniper, 1990	Only use INCS as soon as symptoms start. Increase the dose (not over the maximum daily dose) until symptoms are controlled and then reduce the dose.	Mean as-needed BD dose: 105.7±68.3 (μg/day) Mean regular BD dose: 405.6±10.8 (μg/day)
Juniper, 1993	Only use INCS as soon as symptoms start. Increase the dose (not over the maximum daily dose) until symptoms are controlled and then reduce the dose.	Not reported
Jen, 2000	Use therapeutic-dose INCS once a day only on the days when symptoms require it.	Percentage of days that patient used medication As-needed FP: 55.4 (22.5) % Placebo: 51.8 (20.7) %
Kaszuba, 2001	Use therapeutic-dose INCS once a day only on the days when symptoms require it.	Percentage of days that patient used medication As-needed FP: 58.2 (20.4) % As-needed FEX: 61.8 (18.6) %
Dykewicz, 2003	Use therapeutic-dose INCS once a day only on the days when symptoms require it with average usage ≤75% of the treatment period.	Percentage of days that patient used medication As-needed FP: 61.8 (30.4) % Placebo: 70.1 (28.3) %
Wartna, 2017	Use therapeutic-dose INCS once a day only on the days when symptoms require it.	Not reported
Sakamoto, 2019	Use therapeutic-dose INCS once a day only on the days when symptoms require it.	Not reported
Thongngarm, 2021	Use therapeutic-dose INCS once a day only on the days when symptoms occur exceeding patients' threshold.	Cumulative dose As-needed FF: 2.0±0.84 mg Regular FF: 3.92±0.65 mg

* Data are presented as mean±SD. Abbreviations: INCS, intranasal corticosteroid spray; BD, Beclomethasone dipropionate; FP, Fluticasone propionate; MF, Mometasone furoate; FF, Fluticasone furoate; FEX, Fexofenadine

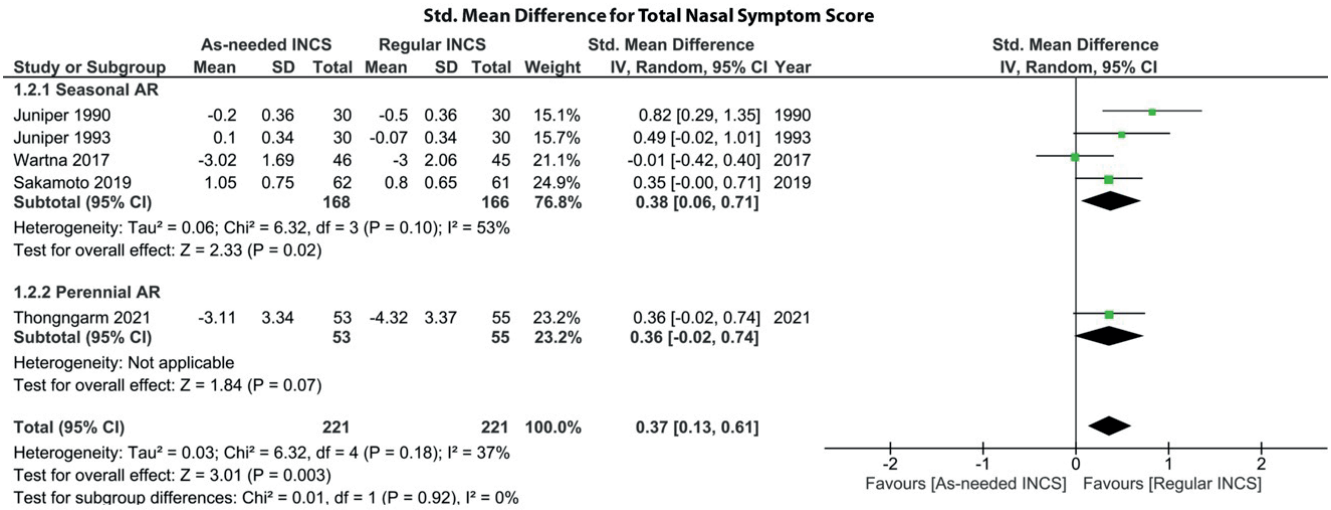


Figure S1. Improvement on total nasal symptom score at endpoint and subgroup analysis by allergic rhinitis subtype: as-needed intranasal corticosteroid spray vs. regular intranasal corticosteroid spray.

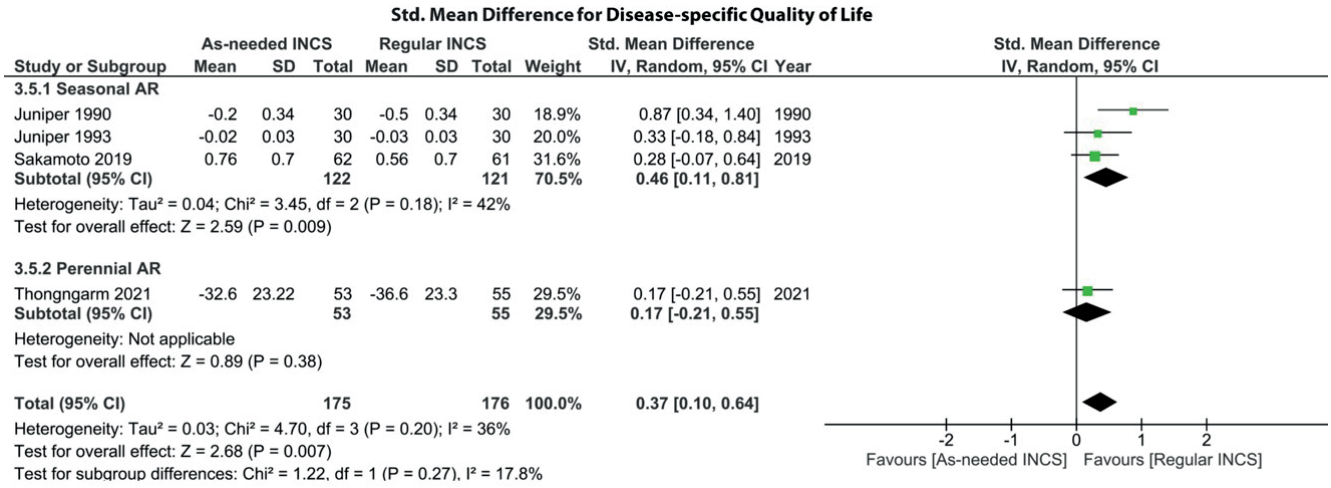


Figure S2. Improvement on disease-specific quality of life at endpoint and subgroup analysis by allergic rhinitis subtype: as-needed intranasal corticosteroid spray vs. regular intranasal corticosteroid spray.

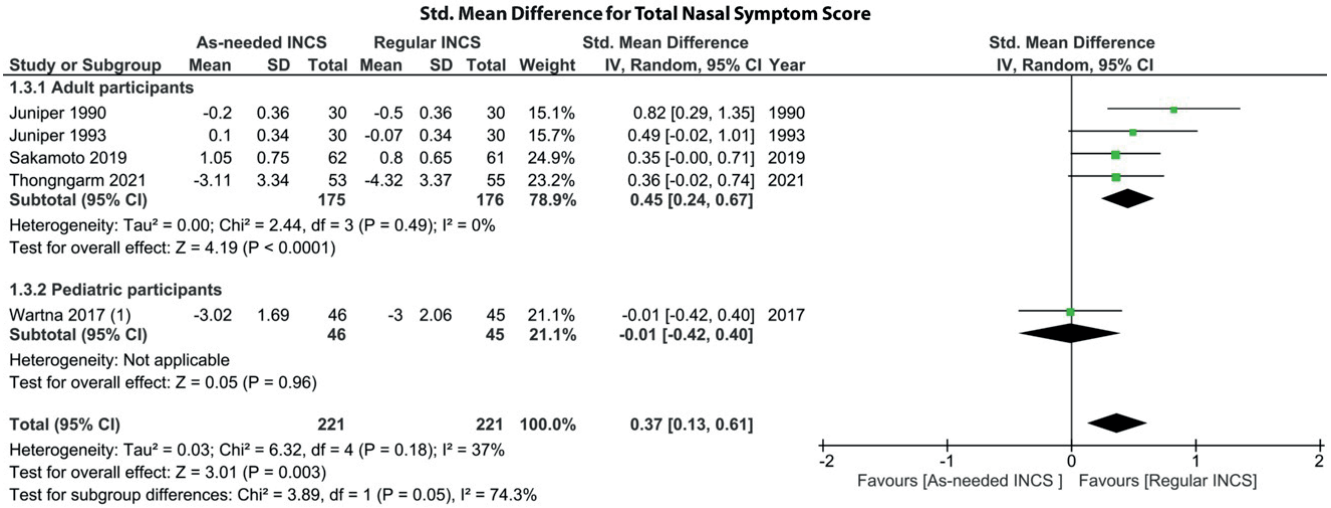


Figure S3. Improvement on total nasal symptom score at endpoint and subgroup analysis by age: as-needed intranasal corticosteroid spray vs. regular intranasal corticosteroid spray.

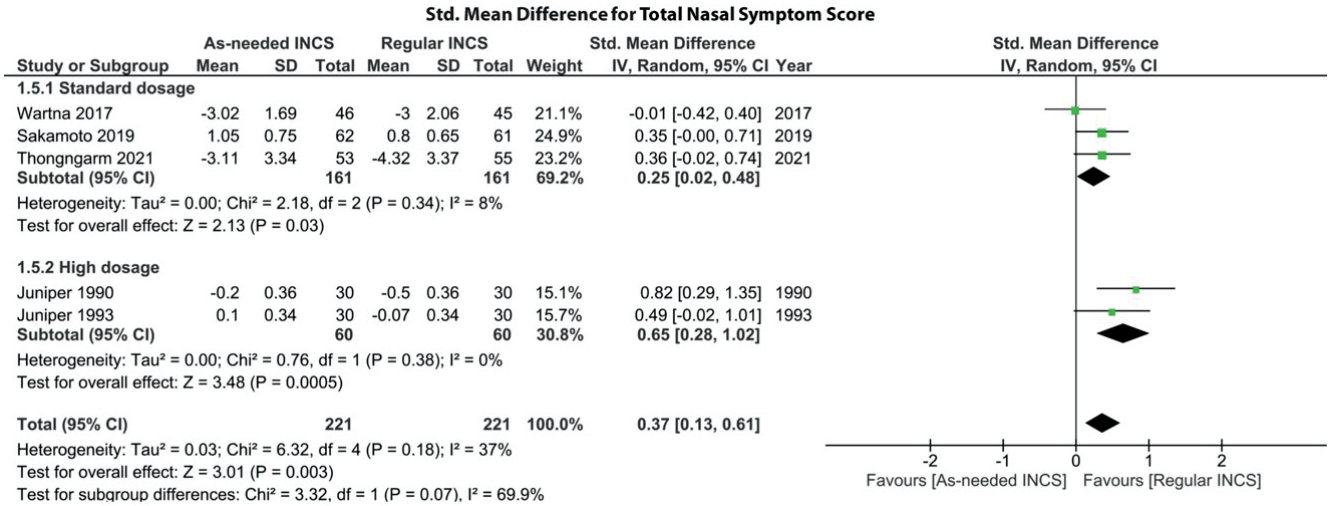


Figure S4. Improvement on total nasal symptom score at endpoint and subgroup analysis by dosage of INCS: as-needed intranasal corticosteroid spray vs. regular intranasal corticosteroid spray.

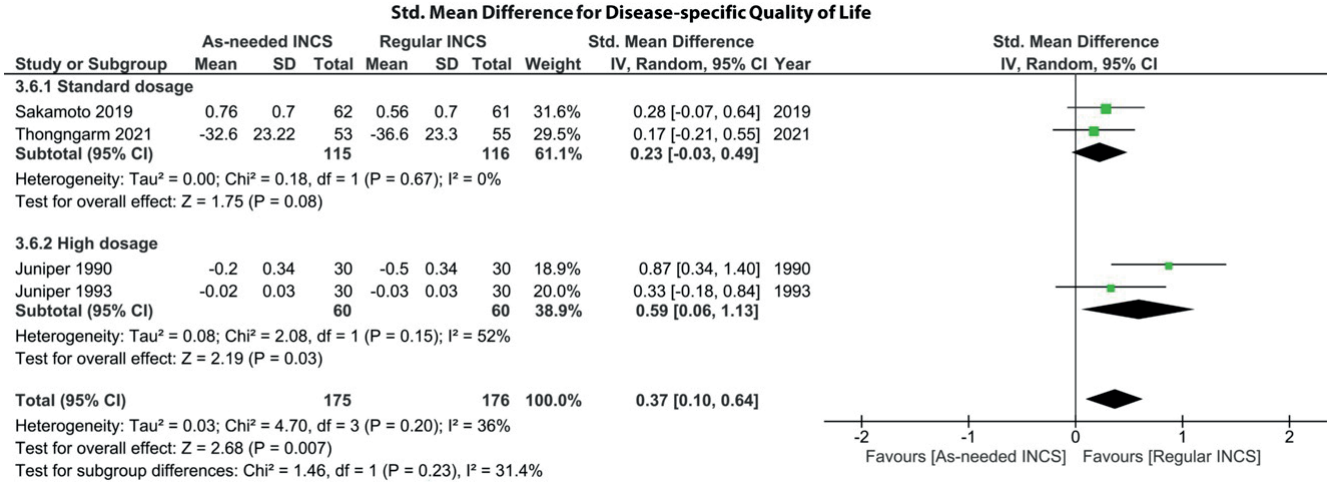


Figure S5. Improvement on disease-specific quality of life at endpoint and subgroup analysis by dosage of INCS: as-needed intranasal corticosteroid spray vs. regular intranasal corticosteroid spray.

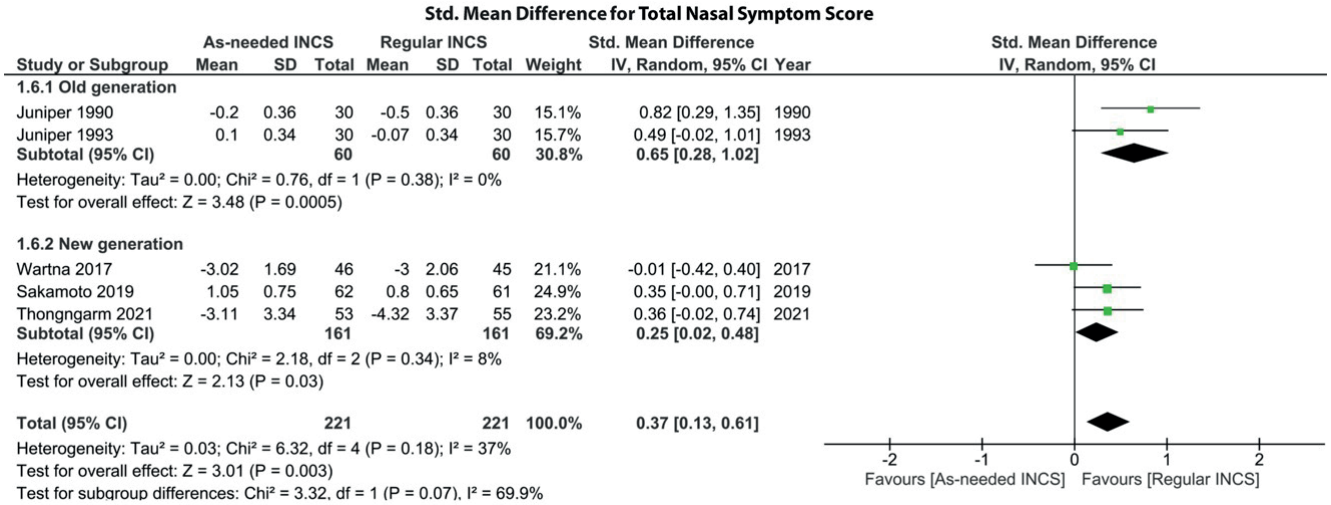


Figure S6. Improvement on total nasal symptom score at endpoint and subgroup analysis by INCS systemic bioavailability: as-needed intranasal corticosteroid spray vs. regular intranasal corticosteroid spray.

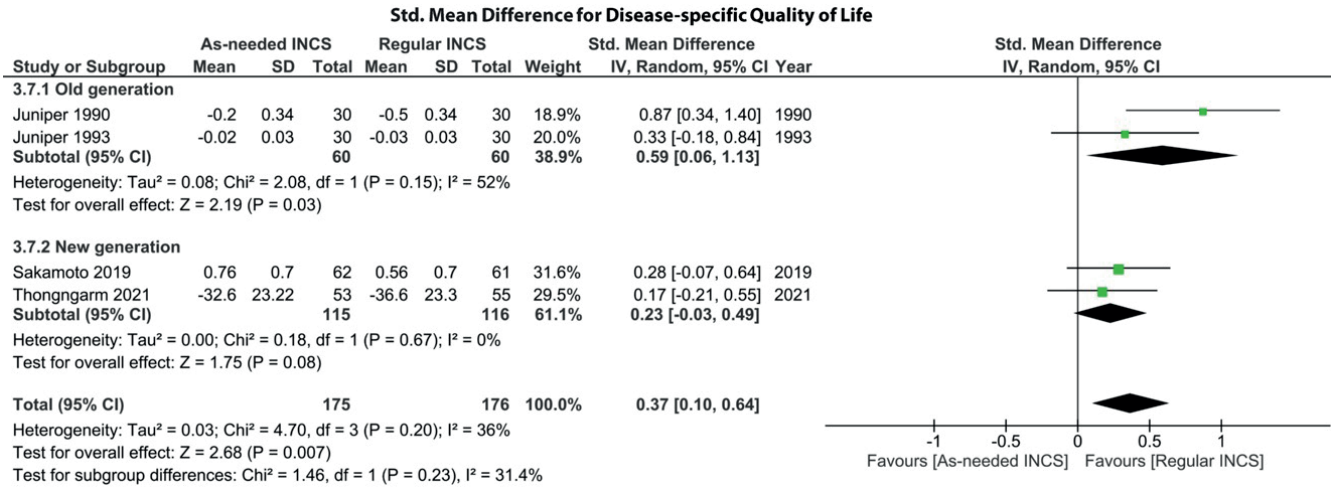


Figure S7. Improvement on disease-specific quality of life at endpoint and subgroup analysis by INCS systemic bioavailability: as-needed intranasal corticosteroid spray vs. regular intranasal corticosteroid spray.

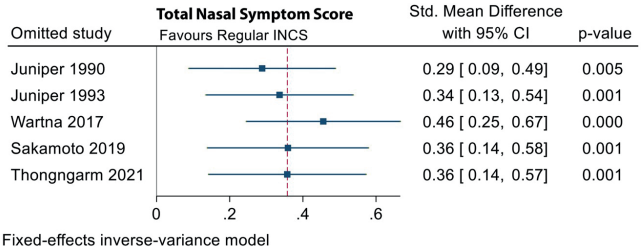


Figure S8. Sensitivity analysis for the comparison of improvement on total nasal symptom score at endpoint by leave-one-out method: as-needed intranasal corticosteroid spray vs. regular intranasal corticosteroid spray.

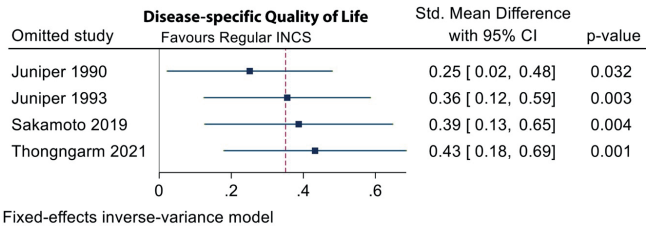


Figure S9. Sensitivity analysis for the comparison of improvement on disease-specific quality of life at endpoint by leave-one-out method: as-needed intranasal corticosteroid spray vs. regular intranasal corticosteroid spray.

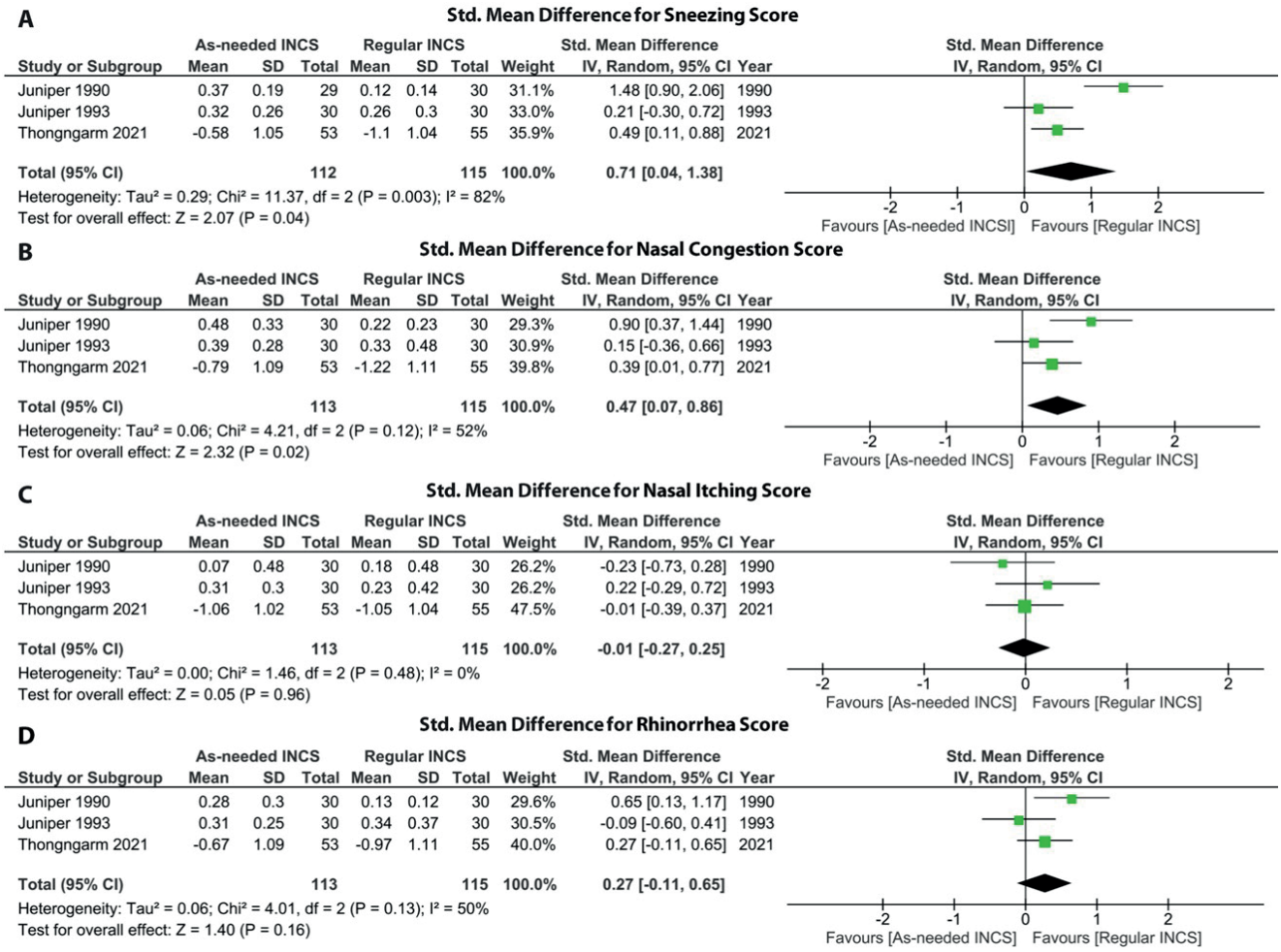


Figure S10. Improvement on individual nasal symptom scores at endpoint: as-needed intranasal corticosteroid spray vs. regular intranasal corticosteroid spray.

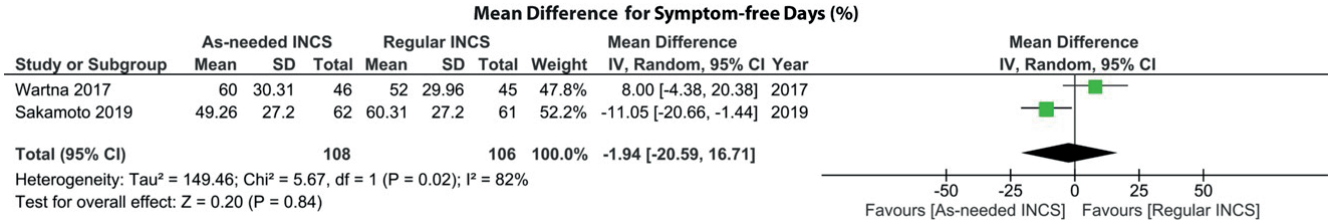


Figure S11. Improvement on symptom free days (%) at endpoint: as-needed intranasal corticosteroid spray vs. regular intranasal corticosteroid spray.

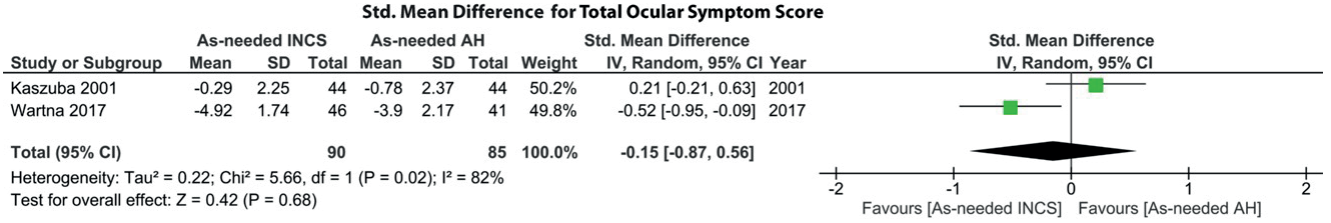


Figure S12. Improvement on total ocular symptom score at endpoint: as-needed intranasal corticosteroid spray vs. as-needed antihistamine.

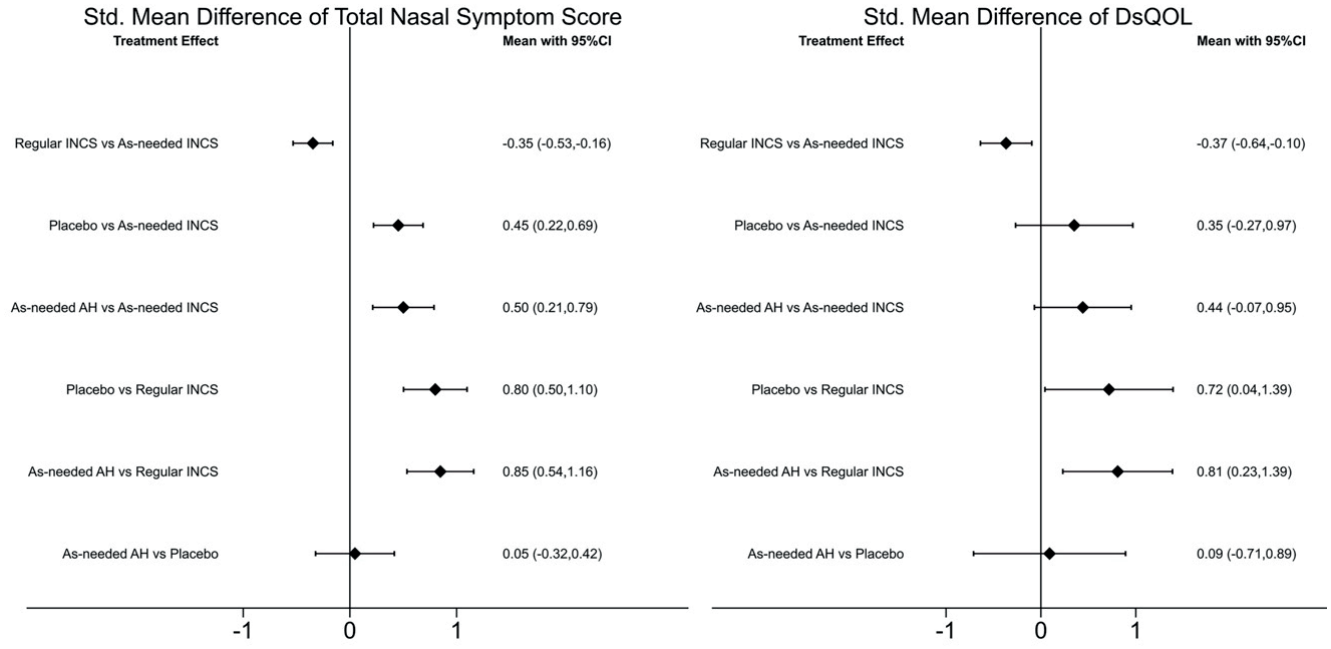
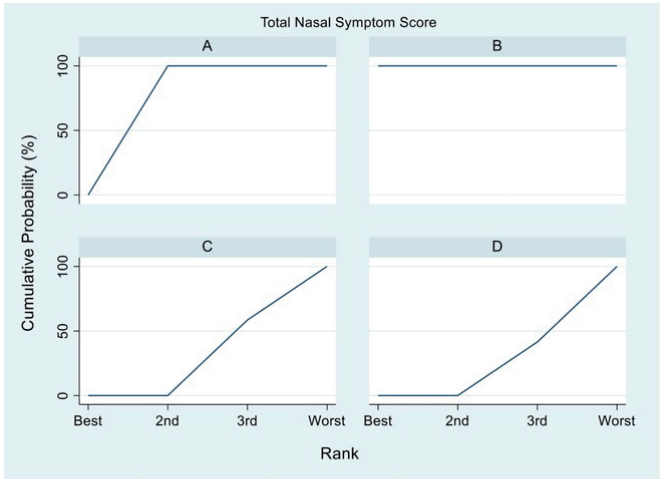
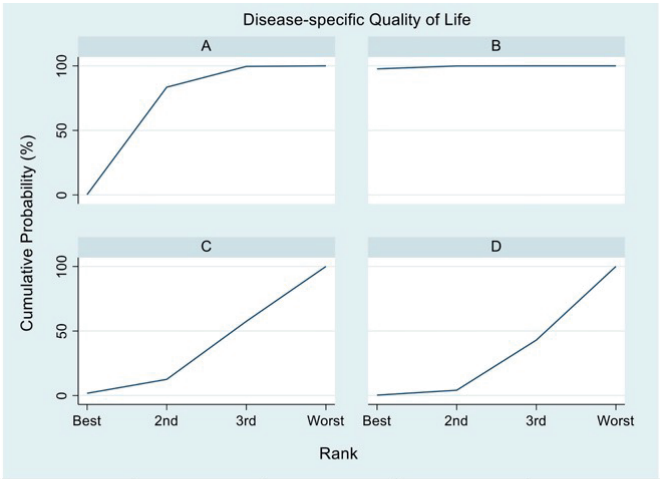


Figure S13. Interval plot of standardized mean difference of total nasal symptom score and disease-specific quality of life among direct and indirect comparisons of treatments.



	As-needed INCS	Regular INCS	Placebo	As-needed AH
Best	0	100	0	0
2nd	100	0	0	0
3rd	0	0	58.5	41.5
Worst	0	0	41.5	58.5
MEAN RANK	2	1	3.4	3.6
SUCRA	0.7	1	3.4	3.6



	As-needed INCS	Regular INCS	Placebo	As-needed AH
Best	0.3	97.7	1.7	0.3
2nd	83.2	2.2	10.8	3.8
3rd	16.1	0.1	45.0	38.8
Worst	0.4	0.0	42.5	57.1
MEAN RANK	2.2	1.0	3.3	3.5
SUCRA	0.6	1.0	0.2	0.2

Figure S14. Results of network rank test.

A, As-needed INCS; B, Regular INCS; C, Placebo; D, As-needed AH; SUCRA, surface under the cumulative ranking.