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REVIEW ARTICLE

As-needed versus regular intranasal corticosteroid for allergic rhinitis: A systematic review and meta-analysis

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Abstract

Background: Daily intranasal corticosteroid (INCS) is recommended for treating allergic rhinitis (AR). Nevertheless, patients are generally not adherent and use it on-demand. The data on the efficacy of as-needed INCS was insufficient.

Objective: We conducted a systematic review and meta-analysis to assess the efficacy of as-needed INCS compared with regular use for AR.

Methods: We searched PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials for randomized controlled trials (RCTs) until May 2021. A pairwise meta-analysis used a random-effects model to estimate the pooled standardized mean difference (SMD). The primary outcome was the total nasal symptom score (TNSS) changes from baseline at 4 and 6 weeks. Secondary outcomes were the changes of individual nasal symptom score and quality-of-life (QoL) score.

Results: We identified five eligible RCTs with a total of 436 patients with AR. Only four studies had adequate data for quantitative synthesis. The TNSS changes of as-needed INCS were not significantly different from the regular use at both 4 (SMD 0.23 [95%CI: -0.14 to 0.60], p = 0.230) and 6 weeks (SMD 0.21 [95%CI: -0.02 to 0.44], p = 0.080). Most of the changes of individual nasal symptom scores and QoL scores were not significantly different between the two regimens. At 50% or more INCS dose of regular use, as-needed and regular INCS provided a similar efficacy. The treatment effect was, however, less sustained with as-needed INCS.

Conclusion: The efficacy of as-needed use of INCS at 50% of corticosteroid exposure was comparable to regular use in improving nasal symptoms and QoL.

Key words: allergic rhinitis, as-needed, efficacy, intranasal corticosteroid, on-demand, regular, self-adjusted

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Abbreviations:

AR	allergic rhinitis
ARIA	Allergic Rhinitis and its Impact on Asthma
BDP	beclomethasone dipropionate
FF	fluticasone furoate
FP	fluticasone propionate
INCS	intranasal corticosteroid
MF	mometasone furoate
PAR	perennial allergic rhinitis
QoL	quality of life
RCQ-36	Rhinoconjunctivitis Quality of Life-36 questionnaire
RCT	randomized controlled trial

Abbreviations (Continued):

RoB	risk of bias
RQLQ	Rhinitis Quality of Life Questionnaire
SAR	seasonal allergic rhinitis
SD	standard deviation
SMD	standardized mean difference
TNSS	total nasal symptom score

Introduction

Intranasal corticosteroid (INCS) is still the mainstay of treatment in patients with moderate-to-severe or persistent allergic rhinitis (AR), and regular use is recommended.[1,2] Nonetheless, real-world evidence shows that the vast majority of AR patients are not adherent to their medication.[3] They usually stop treatment when they feel better and increase their treatment when uncontrolled.[4] Patients sometimes feel relief despite the absence of INCS use due to the fluctuation of the amount of allergen in their environment. A few types of INCS are currently available over the counter in some countries. As a result, more patients have direct access to medication and usually use it on demand. This patient behavior was observed not only in the use of INCS but also in other AR medications.

Two randomized controlled trials (RCTs) have addressed the efficacy of as-needed use of INCS in treating seasonal AR (SAR).[5,6] They found that as-needed fluticasone propionate (FP) was more effective than placebo in improving nasal symptoms. The symptom score changes from baseline in the as-needed FP group from both studies were 1.5 and 2.02, respectively, exceeding the minimal clinically important difference (MCID) of 0.55.[7] As-needed use of INCS is, therefore, a statistically and clinically effective treatment regimen. Although the full treatment effect of INCS takes up to several days to be achieved, FP was analyzed using 22 RCTs, and it was found that the onset could occur as early as 12 hours after administration.[8] The mechanism of as-needed INCS may partially be explained by its effect on preventing the late phase allergic response and subsequent inflammatory cell infiltrates alongside repeated allergen exposures.[9]

There have been a few studies comparing as-needed and regular use of INCS. Integrated with patient behavior, this on-demand treatment strategy reflects real-life usage and is pragmatic to balance adequate symptom control that is satisfactory for the patient versus the long-term side effects and healthcare costs. However, the efficacy of as-needed INCS is not generally well accepted yet.[10] Thus, we performed a systematic review and meta-analysis aimed to assess the clinical efficacy of as-needed INCS compared with its regular use in treating patients with AR.

Methods

Protocol and registration

We performed a systematic review and pairwise meta-analysis of RCTs to compare the clinical efficacy between as-needed and regular use of INCS in treating patients with AR. The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[11] We registered the study protocol with PROSPERO (Registration Number CRD42021246525). Due to the nature of the study, it was considered exempt from ethics approval.

Data sources and strategy

We searched electronic medical and scientific databases, including PubMed/MEDLINE, Scopus, Web of Science, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL), to identify relevant literature from their inception dates to May 31, 2021. We used keywords to determine the appropriate controlled vocabulary terms (e.g., MeSH headings). Only studies written in English were included. The authors (C.W., M.S.) reviewed the lists of references from previously reported studies, systematic reviews, and/or meta-analyses. Relevant studies identified from these reference lists that were not included in the previously mentioned database searches were also included. Duplicate records were removed using a citation manager and manual review by the authors.

Study selection

Study selection was based on the presence of all of the following criteria:

1) an RCT study design
2) patients with AR of all ages
3) as-needed use of INCS as the primary intervention
4) regular use of INCS as the control intervention

Exclusion criteria were studies published in languages other than English. Trials with mixed populations of AR and non-AR were excluded unless it was possible to retrieve the required data for the outcomes of AR.

Outcome measures

The primary outcome was the clinical efficacy of INCS measured using total nasal symptom score (TNSS), including nasal congestion, nasal itching, sneezing, and rhinorrhea. The secondary outcomes were the improvement of individual nasal symptom score, quality-of-life (QoL) score, nasal peak inspiratory flow, adverse events, and loss to follow-up. We focused on the outcomes that were measured at 4 and 6 weeks after randomization. We calculated the changes in the measured parameters from baseline to be used in the analysis.

Screening

We searched the titles and abstracts of relevant literature from the pre-specified databases up to May 31, 2021. An open-source machine learning called ASReview was used for priority screening.[12] ASReview needs five relevant and five irrelevant inputs to learn and rearrange the records automatically. Studies by Juniper et al. (1990),[13] Juniper et al. (1993),[14] Khan et al. (2010),[15] Wartna et al. (2017),[16] and Thongngarm et al. (2021)[17] were used as relevant inputs. Two investigators (C.W. and T.T.) screened the rearranged records using ASReview. The screening was stopped after investigators had screened approximately 50% of the records.

Data collection and extraction

The following information was independently extracted from each article by two trained investigators (C.W. and T.T.): study authorship, year of publication, study period, country/location including environmental and pollution factors,

language, study design, inclusion and exclusion criteria, population type (i.e., children and/or adults), patient demographics, potential effect modifiers (e.g., cumulative dose of as-needed INCS and type of INCS), sample size, primary objective, and study conclusion. Summary tables of study characteristics were tabulated to be used for the assessment of study eligibility. We contacted the corresponding author of any study with incomplete outcome data via e-mail. If the authors did not provide any response within 2 weeks, we repeated the request. If no response was received after the second attempt, the data were reported as missing or were imputed as appropriate.

For the primary endpoint (i.e., the mean changes in TNSS) and other continuous endpoints, we extracted the exact mean change values and their standard deviations (SD) from each study if they were readily available. If a study did not directly report the mean change and the SD, we extracted the crude score (mean and SD) at baseline and the score at 4 and 6 weeks. According to the Cochrane Handbook for Systematic Reviews of Interventions,[18] we used the extracted figures to calculate the mean change and SD. If the study did not report the score measured at 4 or 6 weeks, the score within plus or minus a one-week interval from these 2 points (e.g., 3rd week or 5th week) was used if available. For studies that reported the trend of TNSS or other continuous scoring using graphs, we extracted the data from the figures using Digitizelt program (http://www.digitizeit.de/). For studies that did not report the SD or any measure of dispersion, the SD was imputed using the SD from the study with the most similar design and population.[19] For studies that only reported the median and interquartile range, we employed the methods proposed by Luo, et al.,[20] and Wan, et al.[21] to estimate the mean and SD of the samples.

Risk-of-bias assessment

Two authors (P.P. and T.T.) independently assessed the risk of bias of each included study. Any discrepancy in the quality assessment was discussed with the third author (M.S.). The methodological quality of each RCT was evaluated using Risk-of-Bias 2 (RoB2) assessment tools by the Cochrane collaboration.[22] The tool assesses domain-specific quality in 5 aspects: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Study quality was rated qualitatively as "low risk of bias", "high risk of bias", or "some concerns".

Statistical analysis

All analyses were performed using Stata 17 (StataCorp, Texas, USA). We used a traditional approach of pairwise meta-analysis for quantitative synthesis. Heterogeneity of the included studies was evaluated using the Cochrane's Q test and the I-squared statistics (I^2). As all included studies were expected to possess clinical and methodological heterogeneity, DerSimonian and Laird random-effects model was used to pool the estimates. Due to variation in the scoring components and the scaling of the TNSS, the individual nasal symptoms score, and the QoL score, we pooled the estimates from all studies as standardized mean difference (SMD). The interpretation of SMD in our study was based on the definition by Cohen.[23] Treatment effects with an SMD of 0.2, 0.5, and 0.8 were considered small, medium, and large effects, respectively. We also examined the temporal changes in the treatment effects using cumulative meta-analysis. A p-value < 0.05 was considered statistically significant.

Sensitivity and subgroup analysis

In the presence of unacceptably high heterogeneity, the sources of heterogeneity were identified and appropriately managed with subgroup analysis and meta-regression. Potential effect modifiers for subgroup analyses were the study location, the quality of study according to RoB2, age group of the patient, type of INCS (i.e., hydrophilic and lipophilic INCS), and cumulative dose of INCS. A leave-one-out sensitivity analysis was performed to examine the robustness of both the primary and the secondary endpoints. However, subgroup analysis and meta-regression were performed only on the primary outcome of interest.

Strength of evidence

We graded the strength of evidence for the synthesized meta-analytic results by considering the RoB of each study, inconsistency of results, indirectness of evidence, imprecision, and reporting bias following the Grading Quality of Evidence and Strength of Recommendations (GRADE).

Results

Search results and characteristics of included studies

A total of 5,079 records were identified from all databases. Of these records, 2,472 were duplicates and were removed. The remaining 2,607 records were imported into ASReview for machine learning-assisted priority screening. Altogether, two authors (C.W. and M.S.) screened a total of 1,557 records (59.7%) of the inputs. Fifteen records were identified as relevant from ASReview and were sought for retrieval. Three records were excluded as one was a registered protocol, and full-text articles were not retrievable for the other two. The remaining 12 studies were assessed for eligibility, and 5 studies with a total of 436 patients with AR were finally included in the analysis for this systematic review. However, only 4 studies with a total of 286 patients with AR had adequate data for quantitative synthesis. The PRISMA 2020 flow diagram is provided in **Figure 1**.

Characteristics of the included studies, including the study site, type of AR, intervention assigned, age, sex, duration of rhinitis, and baseline TNSS are presented in **Table 1**. The male-to-female proportion of all studies was 0.52:0.48. One study was conducted in children. Two studies were published before 2010 and used hydrophilic INCS, whereas three were published after 2010 and used lipophilic INCS. Only Thongngarm, et al. reported the exact value of cumulative INCS dose in each treatment arm, while Juniper, et al. reported the number of daily puffs in each treatment arm.

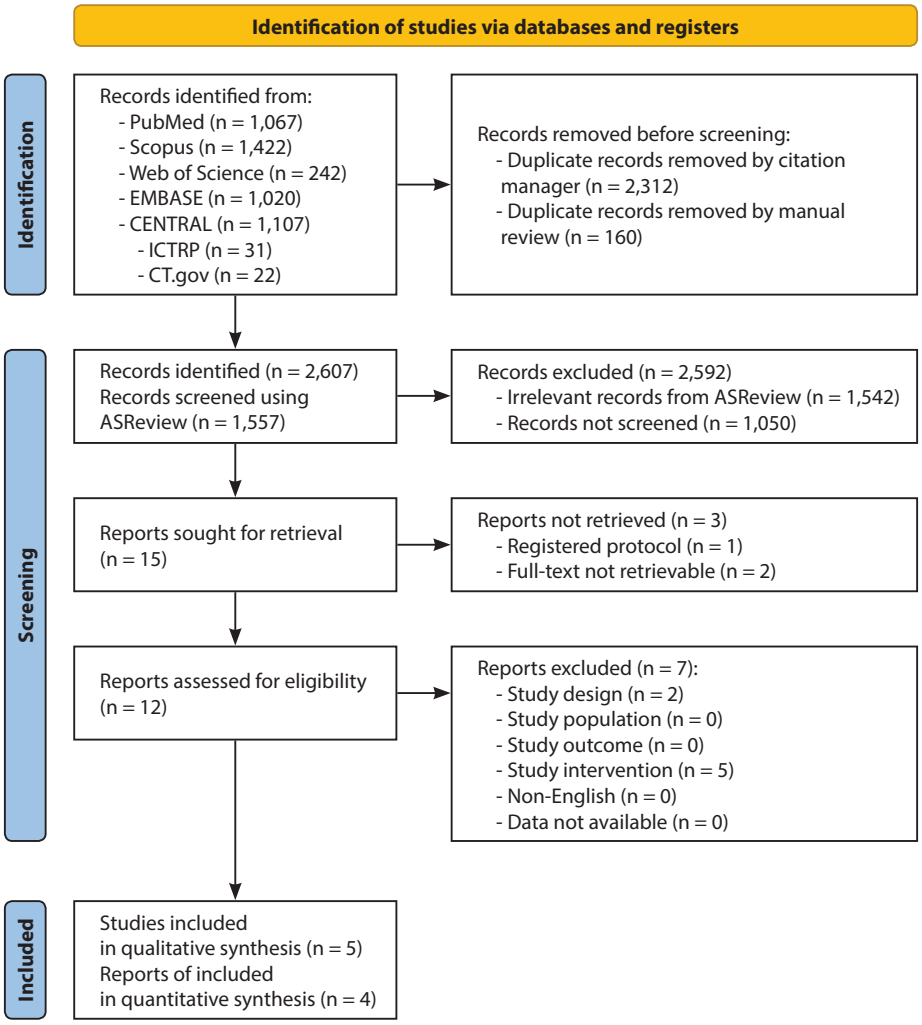

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram of included and excluded studies.

Table 1. Characteristics of the included studies.

Studies*	Site of study	Type/duration of RCTs	Type of AR	Study size (n)	Intervention (n)	Age (y)	Female (%)	Duration of rhinitis (y)	Baseline TNSS
Juniper (1990)	Canada	Double blinded/6 wk	SAR	60	As-needed BDP (30)	41.5 ± 13.2¶	45	NR	1.3 (estimated from figure)
					Regular BDP (30)	44.1 ± 12.8¶			
Juniper (1993)	Canada	Open/6 wk	SAR	60	As-needed BDP (30)	16-70¥	37	NR	1.6 (estimated from figure)
					Regular BDP (30)				
Khan (2010)	Saudi Arabia	NR/6 wk	NR	58	As-needed MF (29)	37.3¶	38	2.8¶	6#
					Regular MF (29)	35.7¶		2.9¶	
Wartna (2017)	Netherlands	Single-blinded/12 wk	SAR	150	As-needed FP (52)	11.6¶	48	NR	6.4 ± 2.2¶
					Regular FP (50)				
					As-needed levocetirizine (48)				
Thongngarm (2021)	Thailand	Single-blinded/6 wk	PAR	108	As-needed FF (53)	30 ± 8.4¶	74	15#	8.2 ± 1.6¶
					Regular FF (55)				

Notes: *All studies were performed as single-centered studies; #median; ¶mean or mean ± SD; ¥range; AR, allergic rhinitis; BDP, beclomethasone dipropionate; FF, fluticasone furoate; FP, fluticasone propionate; MF, mometasone furoate; mo, month; n, number; NR, not reported; PAR; perennial allergic rhinitis; SAR; seasonal allergic rhinitis; TNSS, total nasal symptom score; wk, weeks; y, years

Risk-of-bias assessment

Based on the Cochrane RoB2, one study was rated with a high risk of bias, while the other four studies were rated as some concerns. The study rated as high RoB was due to suspicion of selective reporting of results. The rest of the studies were rated as some concerns of RoB in this domain as no studies had published pre-specified statistical analytic protocol. All studies were rated low RoB for missing data on the endpoints. Only one study was rated as low RoB for the randomization process.

Changes in TNSS from baseline

The clinical efficacy of as-needed use of INCS compared to regular use in TNSS changes among the 4 included studies involving 286 patients with AR is illustrated in **Figure 2**. The treatment effect of as-needed use of INCS was not significantly different from regular use in TNSS changes from baseline at both 4 weeks (SMD 0.23 [95%CI: -0.14 to 0.60]; p = 0.230) and 6 weeks (SMD 0.21 [95%CI: -0.02 to 0.44]; p = 0.080). However, the trend of changes in TNSS somewhat favored regular use, especially at 6 weeks after randomization. There was a moderate amount of heterogeneity in pooling the TNSS at 4 weeks. The difference in the treatment effect between as-needed use of INCS and regular use seemed to decrease as more evidence accumulated over time, especially for TNSS changes at 4 weeks.

Changes in individual nasal symptom score from baseline

Three studies involving 228 patients with AR were assessed for clinical efficacy of as-needed use of INCS in improving individual nasal symptom score, including nasal congestion, nasal itching, sneezing, and rhinorrhea. For nasal congestion score changes from baseline, the treatment effect of as-needed use of INCS was not significantly different from regular use at 4 weeks (SMD 0.20 [95%CI: -0.06 to 0.47]; p = 0.120). However, the treatment effect at 6 weeks was significantly different in favor of regular INCS (SMD 0.28 [95%CI 0.02, 0.54]; p = 0.040) as shown in **Figure 3**. Overall, the treatment effect of as-needed use of INCS was not significantly different from regular use in nasal itching and rhinorrhea scores at both 4 and 6 weeks. The results on the sneezing score were consistent with the findings of the nasal congestion score.

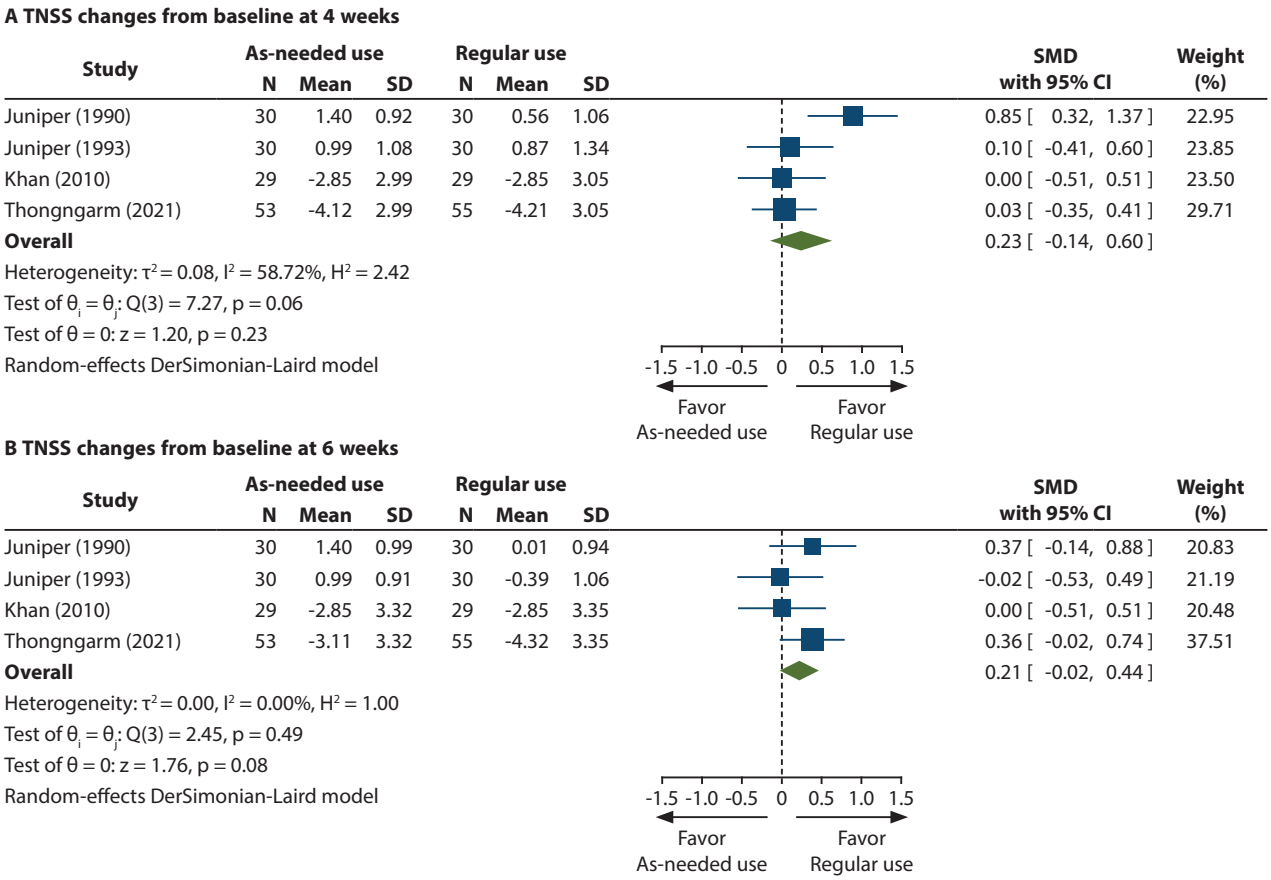

Figure 2. Forest plot showing results of pairwise meta-analysis of randomized controlled trials examining the comparative efficacy of as-needed versus regular intranasal corticosteroid: A, total nasal symptom score changes from baseline at 4 weeks and B, total nasal symptom score changes from baseline at 6 weeks.

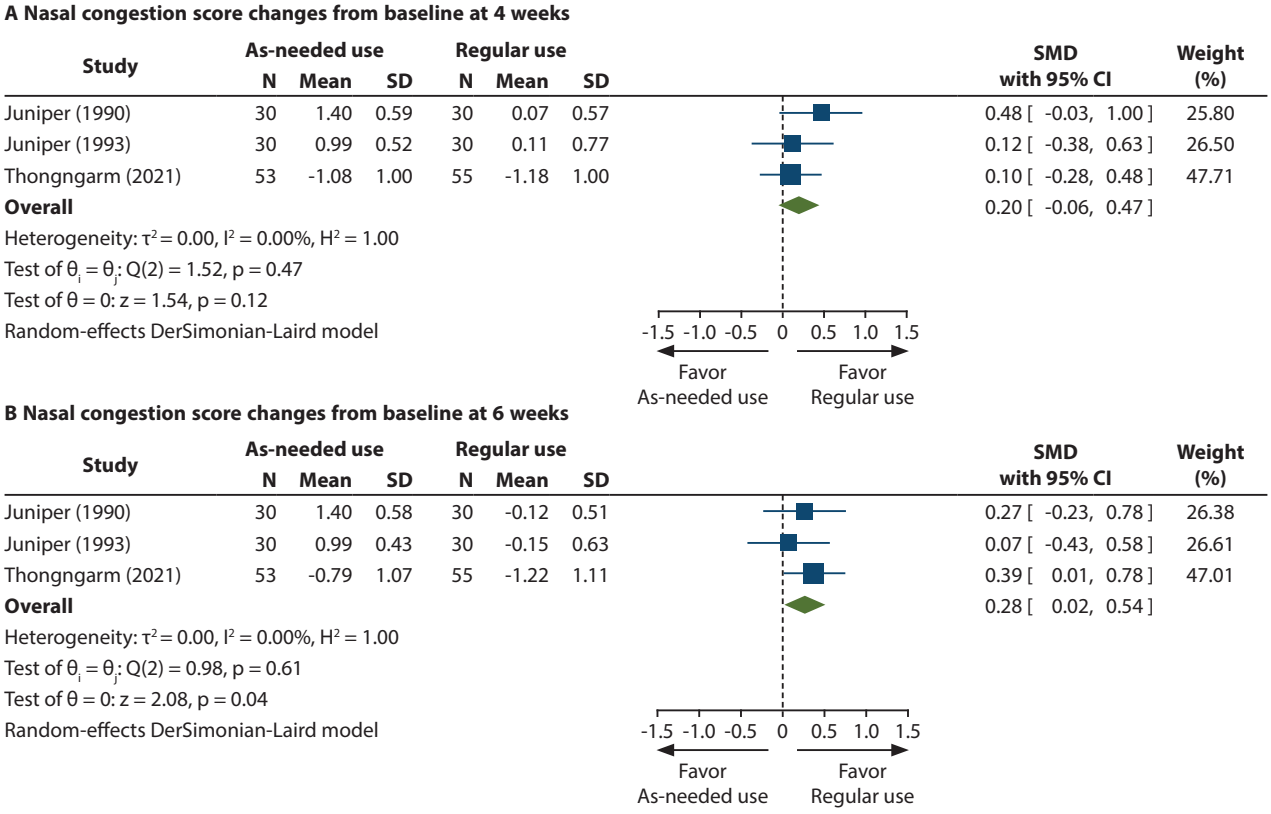

Figure 3. Forest plot showing the pairwise meta-analysis of randomized controlled trials examining the comparative efficacy of as-needed versus regular intranasal corticosteroid: A, nasal congestion score changes from baseline at 4 weeks and B, nasal congestion score changes from baseline at 6 weeks.

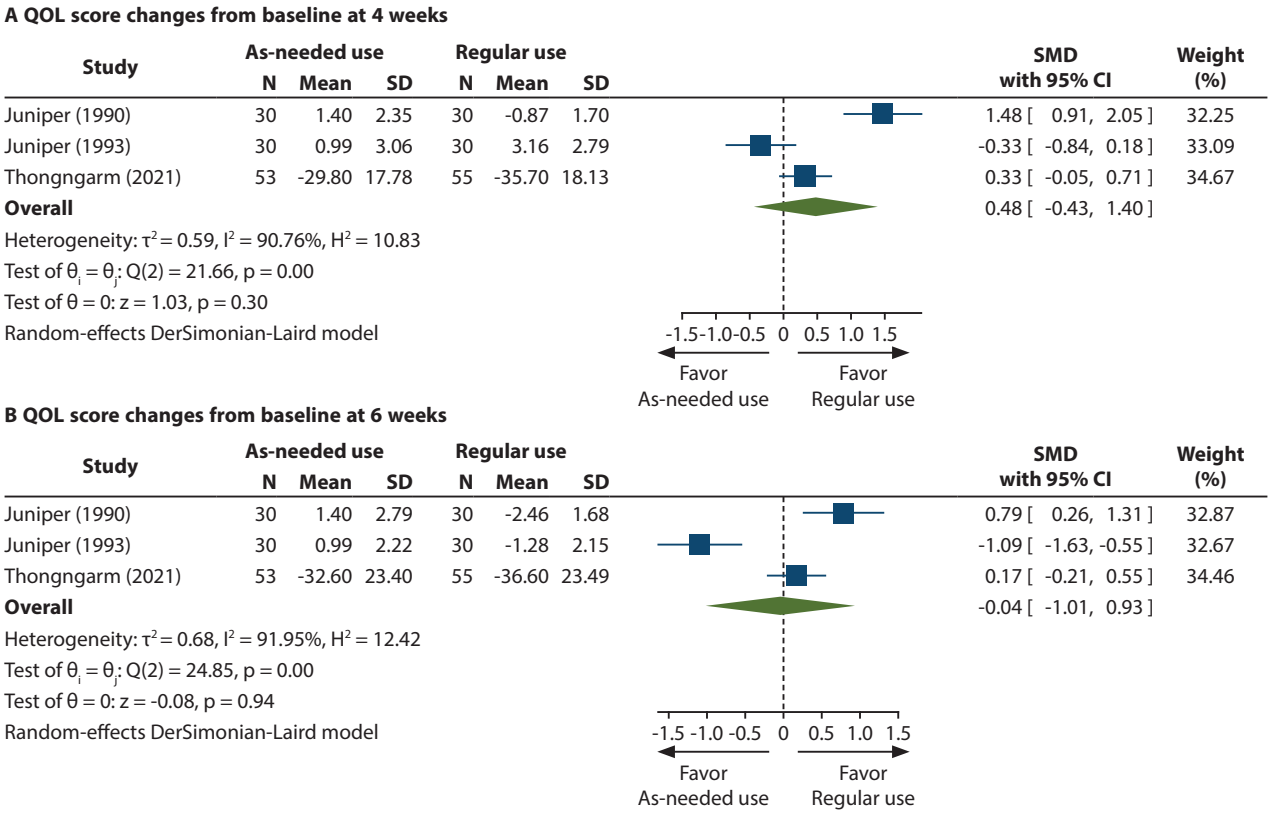

Figure 4. Forest plot showing results of pairwise meta-analysis of randomized controlled trials examining the comparative efficacy of as-needed versus regular intranasal corticosteroid: A, quality-of-life score changes from baseline at 4 weeks and B, quality-of-life score changes from baseline at 6 weeks.

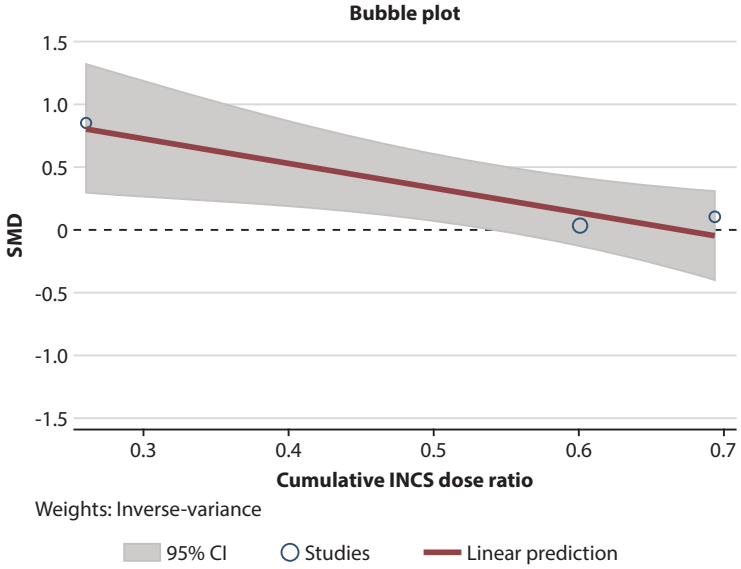

Figure 5. Bubble plot with fitted linear prediction line of the association between the ratio of cumulative intranasal corticosteroid dose and the standardized mean difference of total nasal symptom score changes from baseline at 4 weeks between as-needed intranasal corticosteroid and regular intranasal corticosteroid. Circle markers are sized according to the weights of each study.

Changes in QoL score from baseline

We used the data from three studies to assess the efficacy of as-needed use of INCS compared to the regular use in improving the overall QoL. The two studies by Juniper, et al. used Rhinitis Quality of Life Questionnaire (RQLQ) as measures for QoL whereas Thongngarm, et al. used Rhinoconjunctivitis Quality of Life-36 questionnaire (RCQ-36). The pooled treatment effect of as-needed use of INCS was not significantly different from the regular use in QoL score changes at both 4 weeks (SMD 0.48 [95%CI: -0.43 to 1.40], p = 0.300) and 6 weeks (SMD - 0.04 [95%CI: -1.01 to 0.47], p = 0.930) as shown in **Figure 4**. However, there was highly significant heterogeneity for both syntheses.

Subgroup and sensitivity analyses

Heterogeneity was observed in the pooling of primary endpoint, and we then performed subgroup analyses to identify the sources of heterogeneity. Based on the available data, we were able to address only three out of six pre-specified effect modifiers, which were studies published before/after 2010, type of INCS, and cumulative dose of INCS. As two studies using hydrophilic INCS were published before 2010, and the other two using lipophilic INCS were published after 2010, only one subgroup analysis was performed. The treatment effect of as-needed use of INCS was not significantly different from the regular use in both subgroups, p = 0.270 and 0.850 at 4 weeks and 6 weeks, respectively. The difference in treatment effect between the two treatment arms at 4 weeks seemed to be minimal when lipophilic INCS was used.

We examined the effect of cumulative INCS dose ratio on the SMD of TNSS changes from baseline at 4 weeks through an exploratory meta-regression. We found a significant association between the cumulative INCS dose ratio and the difference in treatment effect between as-needed use of INCS and regular use (p = 0.015). In other words, the greater the difference in cumulative INCS dose between as-needed use and regular use was, the larger the treatment effect was in favor of regular use. A bubble plot visualizing the trend of association is presented in **Figure 5**.

A leave-one-out sensitivity analysis was performed to examine the robustness of our primary results. No study substantially influenced the overall treatment effect for TNSS changes from baseline at 4 and 6 weeks. However, when either the study by Juniper, et al. (1993) or Khan, et al. (2010) was excluded, the conclusion on the difference of treatment effect at 6 weeks changed. Most of the sensitivity analysis results were consistent with the overall results except for nasal congestion score and sneezing score changes from baseline at 6 weeks. We did not formally evaluate publication bias as the number of studies included was too few.

Discussion

This systematic review and meta-analysis revealed that as-needed INCS did not result in significantly different treatment outcomes and QoL compared to regular use in patients with AR. Thus, as-needed use has the potential to decrease the cumulative dose of INCS during treatment substantially. However, there was a trend favoring regular use of INCS in improving nasal symptoms at week 6, suggesting a more sustained effect.

Five RCTs addressed the efficacy of as-needed INCS compared with regular use. One study was conducted in children, while the rest were performed in adults. Three studies involved patients with SAR, one involved those with PAR, and one did not report the type of AR. Studies before 2010 yielded high heterogeneity. After that, the others were quite consistent; as a result, the overall heterogeneity did exist. Besides Juniper, et al.'s study in 1990,[13] the rest of recruited studies showed that as-needed INCS is as effective as regular use in improving TNSS.[14-17] The result discrepancy

could be explained by a few reasons. First, patients in the as-needed group in Thongngarm, et al.'s and Khan, et al.'s studies were assigned to use regular INCS during the first week, followed by as-needed use for the rest of the study duration. This one-week INCS use was probably crucial to ensure the treatment effect as previous evidence showed that even a 48-hour pretreatment with INCS was able to inhibit allergen-induced nasal hyperreactivity.[9] Nevertheless, in Wartna, et al.'s and Juniper, et al.'s study in 1993, although subjects were initially assigned to use INCS as-needed, their symptom improvement remained comparable to regular use. The results suggest that INCS used as-needed right after symptoms occur had some treatment effect.[9] Second, the types of INCS are different among studies. Beclomethasone dipropionate (BDP) was used in both of Juniper, et al.'s studies, while fluticasone furoate (FF), FP, and mometasone furoate (MF) were used in Thongngarm, et al.'s, Wartna, et al.'s, and Khan, et al.'s studies, respectively. Due to the better pharmacological profiles, the newer lipophilic INCS, including FF, FP, and MF, may be more efficacious than BDP even when used as-needed.[24] This speculative reason needs more studies to compare the efficacy among different INCS when used as-needed since no evidence supports the greater effectiveness of one agent over another.[25] Although most studies yielded comparable efficacy of both INCS-used regimens, there was a trend towards regular use having a more sustained effect.[14,15,17] Of note, improvement in QoL alongside TNSS was not significantly different between the two regimens.[14,17]

Another factor potentially affecting the efficacy of INCS when used as-needed is its cumulative dose. The amount of INCS to represent as-needed use has never been studied except for the cumulative dose of 75% or less as a cut-off established by Dykewicz, et al.[6] The average cumulative dose of as-needed INCS in Thongngarm, et al.'s, Wartna, et al.'s, and Juniper, et al.'s study in 1993 were 51%, 28%, and 39%, respectively, with efficacy comparable in both regimens while Juniper, et al.'s study in 1990 was 13% with results favoring regular use.[13,14,16,17] As expected, the amount of INCS positively correlated with the improvement of TNSS.[26] Based on our exploratory meta-regression, we found that as-needed use at the 50% or more cumulative INCS dose of regular use may result in comparable efficacy to the regular regimen supporting the findings from Thongngarm's study. Of note, the protocols in most of the RCTs for INCS use in the regular group did not allow for lowering of the dose when symptoms were well controlled, so the regular group may have done well with a lower dose while the apparent proportion of INCS use compared to regular use was thus likely overestimated. We suggest that comparing as-needed to regular use may reveal an even lower apparent proportion of INCS use in real-life clinical practice that would reflect that as-needed use is even more practical and effective in the real-life use, in which the patient is allowed to lower their dose.

Given its sustained treatment effect, the regular use of INCS should be encouraged for at least 2-4 weeks[27] until symptoms are well controlled to ensure maximum efficacy and minimize imperceptible residual inflammation,[28] thereby reducing the risk of a flare-up. In patients who are well controlled with regular INCS, the next generation Allergic Rhinitis and its Impact on Asthma (ARIA) guideline recommends step-down treatment to an antihistamine.[1] However, the MASK study[29] demonstrated that the treatment adherence in AR patients was low, so some patients using as-needed antihistamines may experience a symptom flare-up. Interestingly, Kaszuba, et al.[30] reported that as-needed INCS was more effective than as-needed oral antihistamine. Therefore, carefully stepping-down treatment from regular to as-needed INCS could bridge the gap between the INCS and antihistamine treatment steps. Additional advantages of as-needed INCS for AR comprise 1) considerably less corticosteroid exposure that reduces long-term adverse effects[31] and 2) titrating the treatment regimen to the patient's preferred behavior, possibly enhancing their adherence to and acceptability of the treatment. The only concern would be the risk of breakthrough symptoms in some patients. However, choosing an INCS with a relatively rapid onset of action, establishing a written action plan, coaching patients to use INCS right after symptoms occur, and following-up regularly should minimize this drawback. Taking the present study's findings and those of the MASK study[29] together, developing an on-demand treatment concept is a fundamental patient-centered approach to balance acceptable symptom control, long-term side effects, and the cost. This approach is similar to as-needed inhaled budesonide-formoterol in patients with asthma in step 1-2 GINA guidelines.[32] Taking the concept of using as-needed budesonide-formoterol for mild asthma to the ARIA guideline,[1] using as-needed combined INCS/intranasal antihistamine (INAH) in a single bottle for treating allergic rhinitis becomes of interest as its efficacy may be similar to regular INCS. Further studies comparing the efficacy among treatment regimens, including as-needed INCS, as-needed INCS/INAH and regular INCS, to prove our hypothesis are essential. Studies on biomarkers to guide the dose adjustment with the as-needed use of intranasal medication to minimize subtle inflammation are also required.

The strength of this study is in the use of data sources from RCTs specifically designed to answer the research question regarding the comparative efficacy of as-needed and regular use of INCS. This minimized the magnitude of selection bias and strengthened the internal validity of the pooled estimates. Most of the pooled results were consistent and medically plausible. The likelihood of missing out on eligible studies was low through an extensive searching strategy and priority searching with machine learning. Furthermore, this systematic review and meta-analysis is the first to evaluate the clinical efficacy of as-needed use of INCS compared with regular use in patients with AR to date. However, this study also has several limitations. First, the total number of studies included for evidence synthesis was small. Second, there was substantial clinical and methodological heterogeneity among the five included studies, for instance, the types and severity of AR. The AR severity usually varies considerably among individuals and fluctuates over time, potentially affecting the treatment response. To address this issue, a random-effects model was used for pooling the outcomes. Moreover, pre-specified subgroup analysis

and meta-regression were also performed. Third, the meta-regression result reported in this study should be perceived as exploratory as the number of the included studies was less than 10, which was inadequate according to the latest Cochrane Handbook.[18] However, there was still contradicting evidence that a lower number of observations per included covariates might be sufficient.[33] Fourth, most of the data used for quantitative synthesis were not readily available and needed to be extracted from graphs, which might be a threat to the internal validity of the present study. For this reason, we strictly followed the standard guidelines for data extraction and imputation of missing values. Fifth, all continuous outcomes, including TNSS, were pooled as SMD, which might not be simple to interpret.[34] Moreover, the SMD was heavily influenced by the size of the SD of the outcomes in each study. Thus, the pooled SMD could be over- or underestimated easily. However, based on the results of a leave-one-out meta-analysis, our pooled estimates were not substantially influenced by any single study for both the primary and the secondary endpoints at 4 weeks. Finally, all included studies had RoB issues. Most were rated as some concern, and one was rated as high risk. The quality of the pooled evidence can only be as good as the quality of data used for syntheses. Leave-one-out sensitivity analysis by excluding studies with high risk of bias (Juniper, et al., 1993) still showed consistent results for all endpoints at 4 weeks.

In conclusion, as-needed INCS with substantially less corticosteroid exposure was similar to the regular use in improving nasal symptoms and QoL in patients with AR. However, there may be an unpredictable minority who experience breakthrough symptoms due to less sustained treatment effects. Therefore, regular use of INCS should be encouraged until patients are well controlled, and then as-needed INCS could be an alternative step-down option.

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Conflict of interests

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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Author contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

Ethics approval

Ethics approval was considered exempt due to the nature of systematic review and meta-analysis.

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