

Efficacy and Safety of Anti-Interleukin-5 Therapies in Chronic Rhinosinusitis with Nasal Polyps: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Keywords

Nasal polyps · Anti-interleukin-5 monoclonal antibody · Benralizumab · Mepolizumab · Reslizumab · Meta-analysis

Abstract

Introduction: The efficacy and safety of benralizumab in patients with chronic rhinosinusitis with nasal polyps (CRSwNP) remain unresolved, and relevant meta-analyses are lacking. Additionally, mepolizumab has been evaluated in far fewer patients, and the evidence is unclear. We conducted a meta-analysis to identify evidence gaps that will guide future investigation of therapies targeting interleukin (IL)-5 signaling (anti-IL-5Rα or anti-IL-5) for CRSwNP. **Methods:** We performed a systematic review and meta-analysis that were registered with PROSPERO (No. CRD42021276867). A comprehensive search was performed in PubMed, Embase, Web of Science, and the Cochrane Library on September 2, 2021. Only randomized controlled trials (RCTs) assessing anti-IL-5 treatments (anti-IL-5Rα or anti-IL-5) in adult patients for CRSwNP were included. **Results:** Seven RCTs with 799 patients evaluating the efficacy and safety of treatments targeting IL-5 pathway (benralizumab [anti-IL-5Rα], mepoli-

zumab, and reslizumab [anti-IL-5]) were included. The overall pooled meta-analysis showed that anti-IL-5 treatments were associated with a significantly better nasal polyp score (weighted mean difference [WMD]: -0.71 ; 95% confidence interval [CI]: $[-0.87, -0.55]$; $p < 0.00001$). Anti-IL-5 treatments were associated with a significantly better nasal congestion score (WMD: -1.73 ; 95% CI: $[-2.29, -1.16]$; $p < 0.00001$). Anti-IL-5 treatments were associated with a significantly better Sino-Nasal Outcome Test (SNOT-22) score (WMD: -11.30 ; 95% CI: $[-14.77, -7.83]$; $p < 0.00001$). The overall pooled meta-analysis showed that anti-IL-5 treatments were associated with a significantly better University of Pennsylvania Smell Identification Test (UPSIT) score (WMD: 2.09 ; 95% CI: $[0.42, 3.77]$; $p = 0.01$). Anti-IL-5 treatments significantly reduced the loss of smell score in the overall pooled meta-analysis (WMD: -1.38 ; 95% CI: $[-1.97, -0.79]$; $p < 0.00001$). In the overall pooled meta-analysis, anti-IL-5 treatments showed no difference with the placebo in the risk of adverse events (AEs; risk ratio [RR]: 1.01 ; 95% CI: $[-0.93, 1.09]$; $p = 0.83$) and serious AEs (SAEs; RR: 0.73 ; 95% CI: $[0.40, 1.34]$; $p = 0.32$). **Conclusion:**

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This systematic review and meta-analysis identified that anti-IL-5 treatments significantly improved the size of nasal polyps, health-related quality of life, and sense of smell in moderate to severe CRSwNP, and they were safe and well tolerated.

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Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a common inflammatory disease affecting up to 4% of the population [1]. Patients with CRSwNP often have a high symptom burden (increased nasal congestion, a reduction/loss of smell, and facial pain/pressure), and poor health-related quality of life (HRQL) [2].

CRSwNP is a complex inflammatory disorder and is often resistant to medical and surgical management, leading to the recent study of biologic medications. Based on the presence of type 1, type 2, or type 3 inflammation, CRSwNP can be classified into three endotypes [3]. Most Western hemisphere patients with CRSwNP show a type 2 inflammatory signature [4], characterized by upregulation of the type 2 cytokines interleukin (IL)-4, IL-13, and IL-5, a high concentration of tissue immunoglobulin (Ig) E, and increased serum IgE [5].

Dupilumab (anti-IL-4 receptor alpha monoclonal antibody [mAb]) and omalizumab (anti-IgE mAb) have already entered the market for patients with CRSwNP, with approvals from the European Medicines Agency (EMA) [6] and Food and Drug Administration (FDA) [7]. Dupilumab improves the disease-specific HRQL and reduces disease severity [8]. Omalizumab significantly improves endoscopic, clinical, and patient-reported outcomes in moderate to severe CRSwNP and is safe and well tolerated [9].

CRSwNP associated with type 2 inflammation has a strong connection with tissue eosinophilia, suggesting that eosinophils may play an important role in the pathogenesis of CRSwNP. Benralizumab is directed against IL-5R α , primarily expressed by human eosinophils and basophils, blocking IL-5 signaling, and resulting in depletion of blood eosinophils and reduction of basophils. In addition, IL-5 plays a key pathogenic role in CRSwNP with type 2 inflammation. Mepolizumab and reslizumab are humanized monoclonal antibodies that selectively bind to and inactivate IL-5, thereby inhibiting eosinophilic inflammation.

Therapies targeting the IL-5 pathway (anti-IL-5 treatments, anti-IL-5R α , or anti-IL-5) have been evaluated in

some randomized controlled trials (RCTs), such as benralizumab (anti-IL-5 receptor alpha mAb) [10, 11], mepolizumab (anti-IL-5 mAb) [12, 13], and reslizumab (anti-IL-5 mAb). To date, the efficacy and safety of benralizumab remain unresolved, and relevant meta-analyses are lacking. The effect of mepolizumab has been evaluated in far fewer patients, and evidence is unclear [8]. Currently, a well-designed RCT concerning mepolizumab for CRSwNP has been published [14] and may provide supporting evidence. Therefore, we conducted a meta-analysis to evaluate the efficacy and safety of anti-IL-5 treatments (anti-IL-5R α or anti-IL-5) versus placebo in adult patients with CRSwNP and identify evidence gaps that will guide future investigation of anti-IL-5 therapies for CRSwNP.

Materials and Methods

We performed a systematic review and meta-analysis based on a priori protocol that was registered with PROSPERO (no. CRD42021276867) [15]. This review was reported according to the PRISMA extension statement [16].

Search Strategy

We searched PubMed, Embase, Web of Science, and the Cochrane Library on September 2, 2021, to identify potentially relevant studies. The search terms included the following combined text and MeSH terms: “nasal polyps,” “sinusitis,” “anti-IL-5 mAb,” “benralizumab,” “mepolizumab,” and “reslizumab.” The search strategies for major databases are provided in online supplementary Table (see www.karger.com/doi/10.1159/000521859 for all online suppl. material). We also evaluated the reference lists of the relevant studies to identify additional studies.

Studies were included if they met the following criteria: (1) population: adult patients (≥ 18 years old and of both sexes) with CRSwNP; (2) intervention and comparison: studies comparing anti-IL-5 treatments with a placebo, followed up for at least 24 weeks; (3) study design: RCTs; (4) studies written and published in the English language; and (5) studies reported at least one of the following outcomes: nasal polyp score (NPS), nasal congestion score (NCS), Sino-Nasal Outcome Test (SNOT-22) score, University of Pennsylvania Smell Identification Test (UPSIT) score, loss of smell score (LSS), Lund-Mackay score (LMS), adverse events (AEs), and serious AEs (SAEs).

Selection Process and Data Extraction

The titles and abstracts of the retrieved articles were screened for their potential relevance by 2 reviewers (Qiong Wang and Qun Sun). The full-text articles were then obtained and assessed by the same reviewers to determine whether they met the inclusion criteria for this meta-analysis. Any differences were resolved by discussion with a third author (Qingwu Wu).

Two reviewers (Qiguo Chen and Hao Li) read the full-text articles and extracted data using a predefined extraction form. The following data were extracted: first author, year of publication, patient characteristics, study methods, and outcome data.

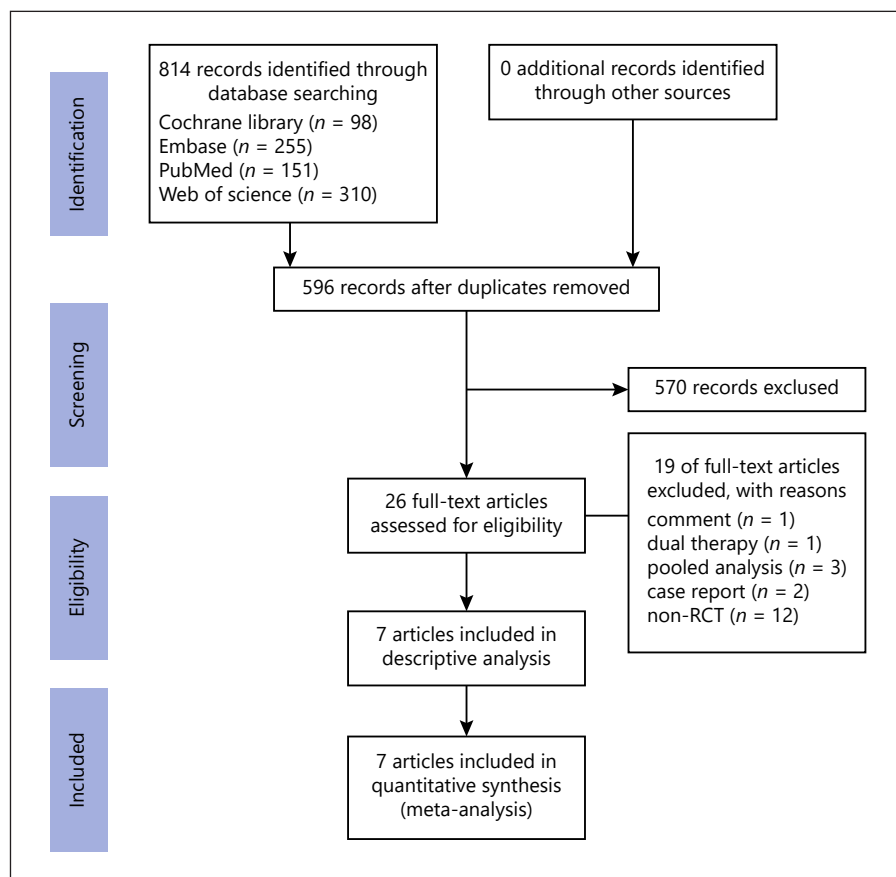


Fig. 1. PRISMA flow diagram of the literature search.

Assessment of the Risk of Bias

In the present meta-analysis, the qualities of RCTs were assessed using the original version of the Cochrane “risk of bias” tool. The risk of bias was assessed as “low,” “high,” or “unclear” for each of six domains, including sequence generation, allocation concealment, the blinding of participants, personnel and outcome assessment, incomplete outcome data, selective reporting, and other sources of bias (if required).

Statistical Analysis

We used Review Manager (version 5.3) for the meta-analysis. The study characteristics are shown in tables and described narratively. For dichotomous data, we planned to analyze treatment differences as a risk ratio (RR) calculated using the Mantel-Haenszel method. For continuous outcomes, if all the data were from the same scale, we pooled mean values obtained at follow-up with change outcomes and reported this as a mean difference. Statistical heterogeneity was assessed by the χ^2 test (with a significance level set at $p < 0.10$) and the I^2 statistic ($I^2 \geq 50\%$ indicates substantial heterogeneity). The possibility of publication bias was assessed by constructing a funnel plot if sufficient studies (>10) were available for an outcome.

Results

Study Selection and Characteristics

We identified 814 studies, among which seven (with data for 799 participants) were included in our meta-analysis (Fig. 1). The basic characteristics of the seven RCTs are summarized in Table 1. The sample size of the included RCTs ranged between 24 and 407 participants: three RCTs on benralizumab versus placebo (Canonica et al. [10], Takabayashi et al. [11], and Tversky et al. [17]), three RCTs on mepolizumab versus placebo (Bachert et al. [12], Gavaert et al. [13], and Han et al. [14]), and one RCT on reslizumab versus placebo (Gevaert et al. [18]). Two RCTs (Takabayashi et al. [11] and Gevaert et al. [18]) had three arms, and the others had two arms.

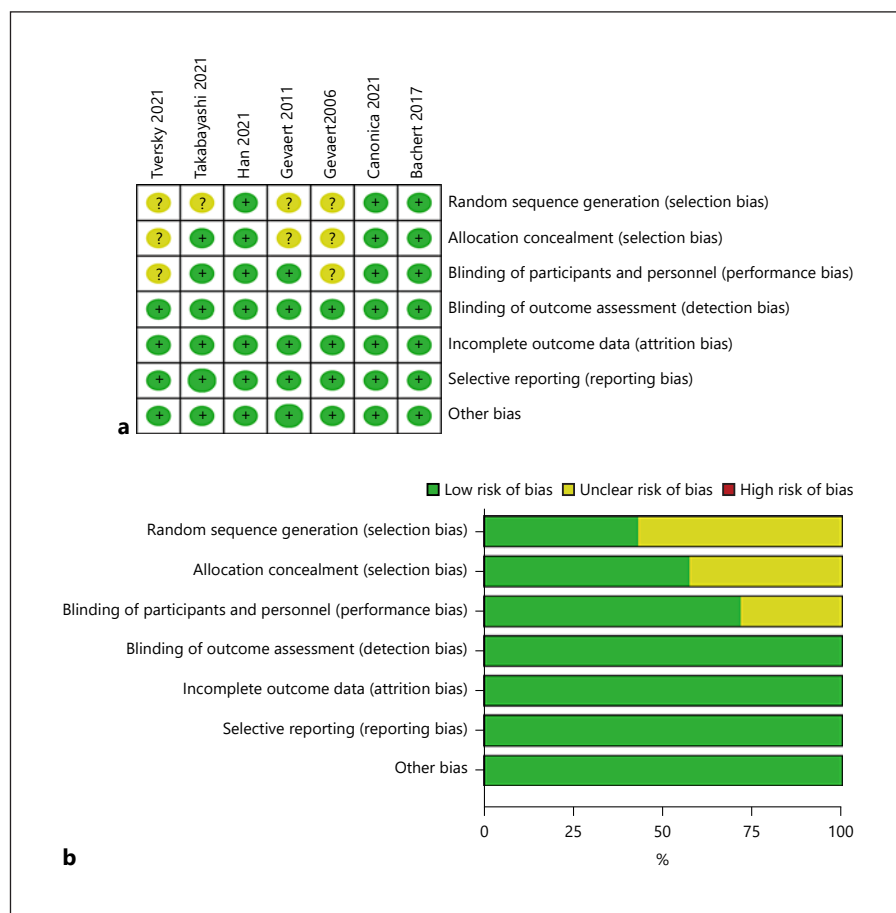
Risk of Bias Assessment

The quality of the included RCTs is shown in Figure 2. Three RCTs (Bachert et al. [12], Canonica et al. [10], and Han et al. [14]) had a low risk of bias. Two RCTs (Gevaert et al. [18] and Tversky et al. [17]) had unclear risks of bias

Table 1. Summary of the characteristics of the included studies

Study, year	Population	Comorbidity	Intervention	Placebo	Treatment length	Follow-up length	Age, mean (SD), years		Male, <i>n</i> (%)	
							intervention	placebo	intervention	placebo
Canonica et al. [10] (<i>n</i> = 153)	CRSwNP	Asthma (100%)	Benralizumab 30 mg every 8 weeks (first 3 doses q4w) subcutaneously	Subcutaneously, same dose and frequency	24 weeks	24 weeks	53.1 (12.3)	52.6 (11.1)	53 (55.2)	24 (42.1)
Takabayashi et al. [11] (<i>n</i> = 56)	CRSwNP	Asthma (81.8% [18/22] in the benralizumab 30 mg single group, 82.6% [19/23] in the benralizumab 30 mg q4w group, and 90.9% [10/11] in the placebo group)	1. Benralizumab 30 mg single subcutaneously (benralizumab administered on day 1 and the placebo administered on week 4 and week 8)	Subcutaneously, same dose and frequency	Day 1	24 weeks	54 (10.8)	53.3 (14.8)	11 (50)	7 (63.6)
			2. Benralizumab 30 mg q4w subcutaneously		8 weeks	53 (12.3)		12 (52.2)		
Tversky et al. [17] (<i>n</i> = 24)	CRSwNP	Asthma (83% [10/12] in the benralizumab group and 100% [12/16] in the placebo group)	Benralizumab 30 mg subcutaneously (first 3 doses q4w, last 1 dose q8w)	Subcutaneously, same dose and frequency	16 weeks	24 weeks	49.8 (12.1)	50.8 (13.1)	7 (58)	7 (58)
Bachert et al. [12] (<i>n</i> = 105)	CRSwNP	Asthma (81% [44/54] in the mepolizumab group and 75% [38/51] in the placebo group)	Mepolizumab 750 mg intravenously q4w	Intravenously, same dose and frequency	21 weeks	25 weeks	51 (11)	50 (10)	41 (76)	34 (67)
Gavaert et al. [13] (<i>n</i> = 30)	CRSwNP	Asthma (50% [10/20] in the mepolizumab group and 30% [3/10] in the placebo group)	Mepolizumab 750 mg intravenously q4w	Intravenously, same dose and frequency	8 weeks	48 weeks	50.1 (8.86)	45.9 (11.4)	14 (70)	8 (80)
Han et al. [14] (<i>n</i> = 407)	CRSwNP	Asthma (68% [140/206] in the mepolizumab group and 74% [149/201] in the placebo group)	Mepolizumab 100 mg subcutaneously q4w	Subcutaneously, same dose and frequency	52 weeks	76 weeks	48.6 (13.6)	48.9 (12.5)	139 (67)	125 (62)
Gevaert et al. [18] (<i>n</i> = 24)	CRSwNP	Asthma (87.5% [7/8] in the reslizumab 1 mg/kg group, 62.5% [5/8] in the reslizumab 1 mg/kg group, and 75% [6/8] in the placebo group)	1. Reslizumab 1 mg/kg intravenously	Intravenously, same dose and frequency	Day 1	36 weeks	43.6 (22–63)*	48 (21–59)*	6 (75)	6 (75)
			2. Reslizumab 3 mg/kg intravenously			48.5 (18–57)*		4 (50)		
SD, standard deviation. * Mean (interquartile range)										

Fig. 2. a “Risk of bias” summary: a review of the authors’ judgments concerning each risk of bias item for each included study. **b** “Risk of bias” graph: a review of the authors’ judgments concerning each risk of bias item presented as percentages across all included studies.



in random sequence generation, allocation concealment, and blinding of participants and personnel. One RCT (Gevaert et al. [13]) had an unclear risk of bias in random sequence generation and allocation concealment, and one RCT (Takabayashi et al. [11]) had an unclear risk of bias in random sequence generation.

Evidence of Efficacy

Figures 3 and 4 and Table 2 show the efficacy and the certainty of the evidence of anti-IL-5 treatments.

Nasal Polyp Score

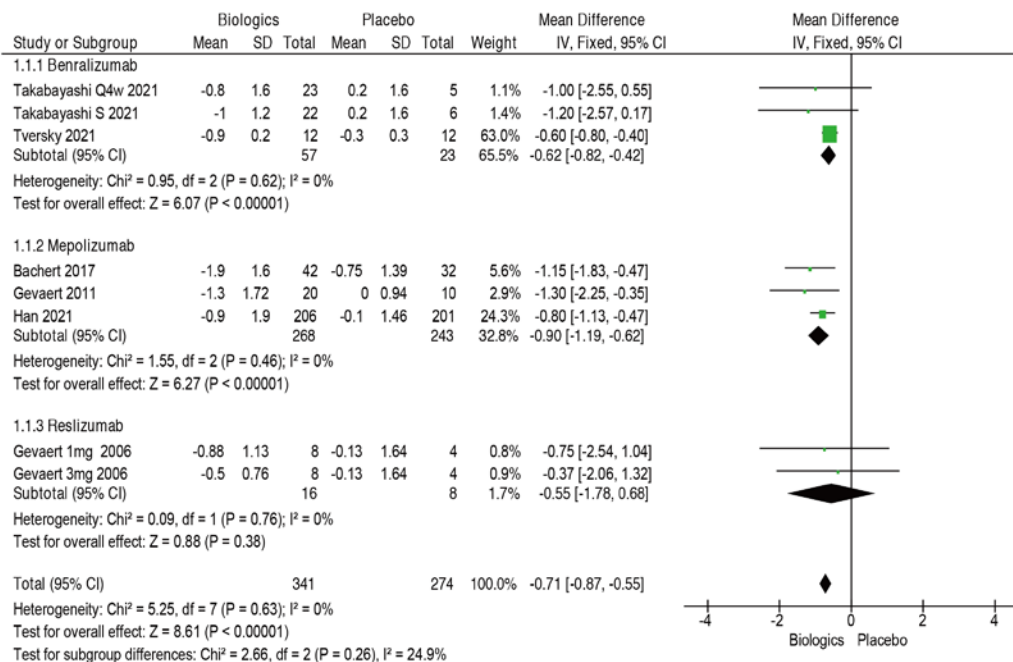
The total NPS (0–8) is the sum value from each nostril. In the meta-analysis, benralizumab and mepolizumab were superior (better) to the placebo in terms of the NPS (benralizumab: weighted mean difference [WMD]: -0.62 , 95% confidence interval [CI]: $[-0.82, -0.42]$, $p < 0.00001$; mepolizumab: WMD: -0.90 , 95% CI: $[-1.19, -0.62]$, $p < 0.00001$). No significant difference was found in reslizumab versus placebo ($p = 0.38$). The overall pooled me-

ta-analysis showed that anti-IL-5 treatments were associated with a significantly better NPS (WMD: -0.71 ; 95% CI: $[-0.87, -0.55]$; $p < 0.00001$; 6 RCTs; 651 participants; Fig. 3a). Canonica et al. [10] did not assess the NPS so that it was excluded in the meta-analysis.

Nasal Congestion Score

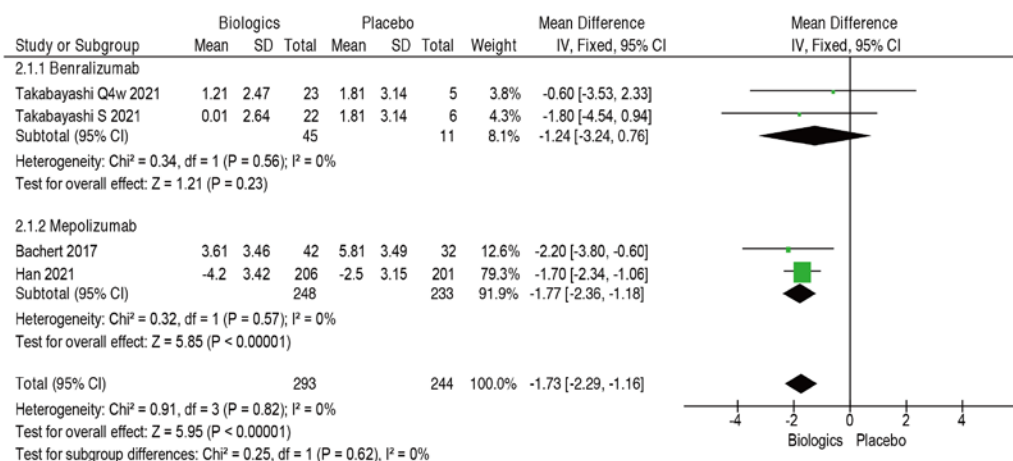
NCS was assessed using a visual analog scale (VAS, 0–10 cm). Mepolizumab reduced the NCS (WMD: -1.77 ; 95% CI: $[-2.36, -1.18]$; $p < 0.00001$), but no significant difference was exhibited in benralizumab versus placebo ($p = 0.23$). Anti-IL-5 treatments were associated with significantly better improvement of the NCS (WMD: -1.73 ; 95% CI: $[-2.29, -1.16]$; $p < 0.00001$; 3 RCTs; 537 participants; Fig. 3b). In the meta-analysis, the NCS was assessed by 0–5 score in Tversky et al. [17] and by 0–3 score in Gevaert et al. [13], and the NCS was not reported in Canonica et al. [10] and Gevaert et al. [18], so they were excluded.

NPS



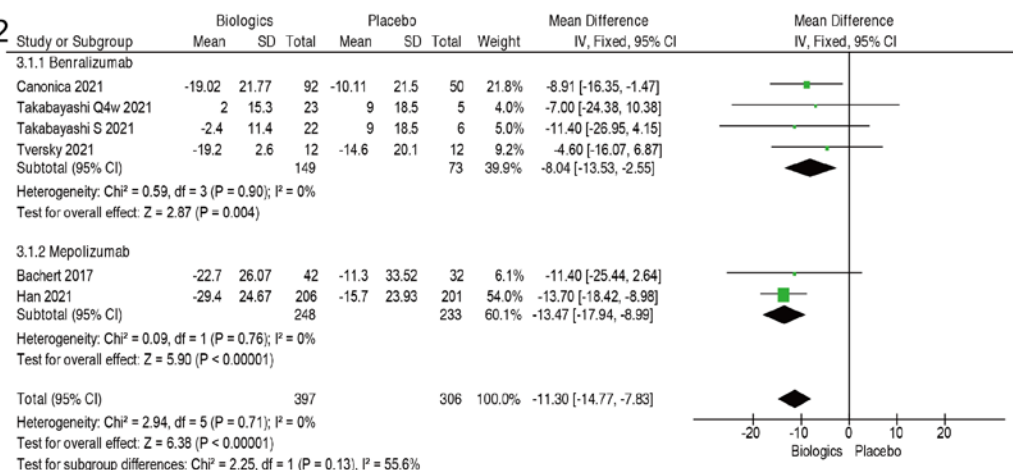
a

NCS



b

SNOT-22



c

(For legend see next page.)

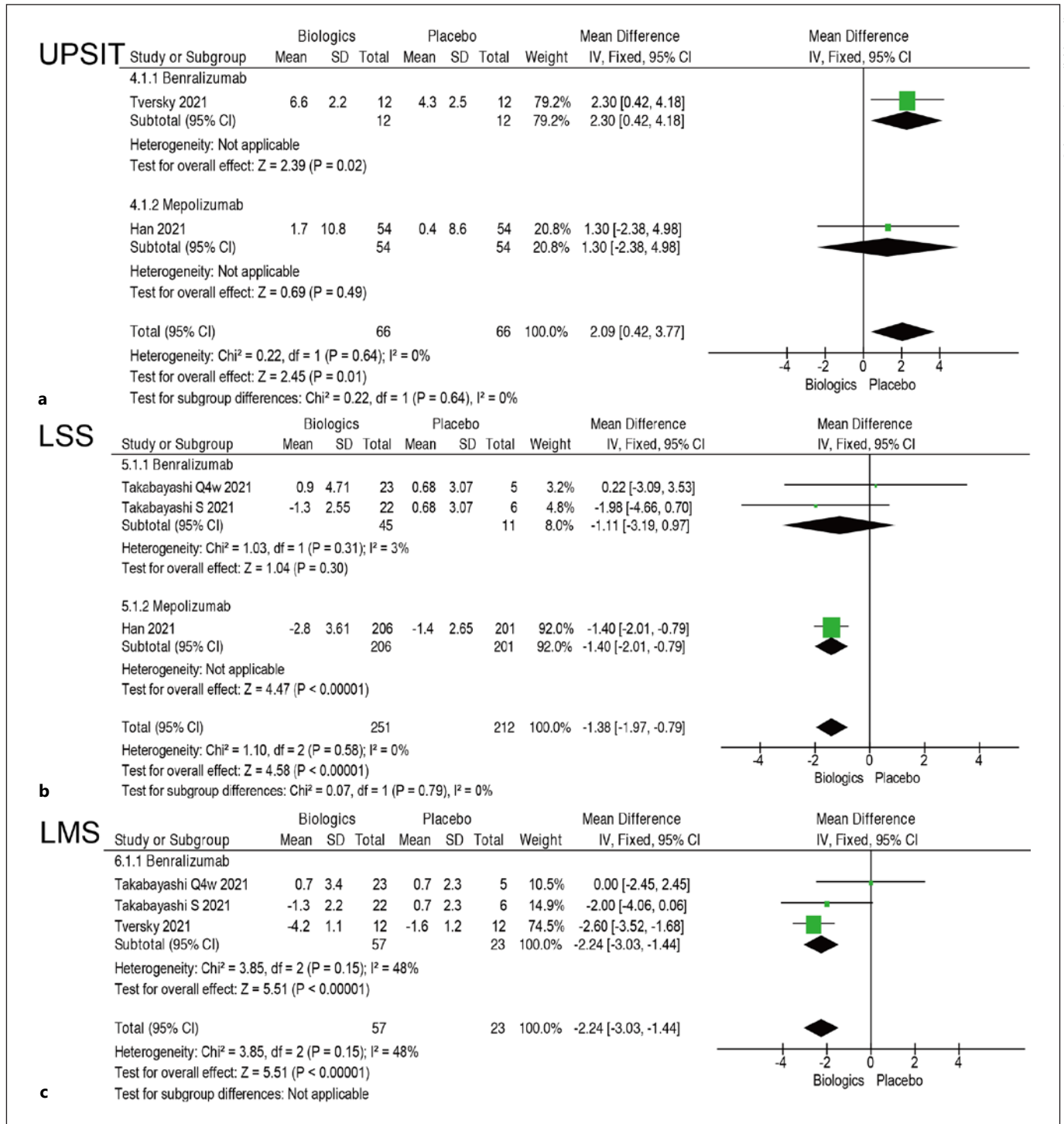


Fig. 4. Meta-analysis of anti-IL-15 therapies versus placebo, comparing efficacy. UPSIT score (a); LSS (b); LMS (c). Weight, the weight of each study; IV, inverse variance; Fixed, fixed-effects model.

Fig. 3. Meta-analysis of anti-IL-15 therapies versus placebo, comparing efficacy. NPS (a); NCS (b); SNOT-22 score (c). Weight, the weight of each study; IV, inverse variance; Fixed, fixed-effects model.

Table 2. Summary of outcomes and the certainty of the evidence

Outcomes	Participants (studies), (n)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	Certainty of the evidence (GRADE)
NPS	651 (6 RCTs)	—*	MD: −0.71 (−0.87, −0.55)	High
NCS	537 (3 RCTs)	—	MD: −1.73 (−2.29, −1.16)	High
SNOT-22	703 (5 RCTs)	—	MD: −11.30 (−14.77, −7.83)	High
UPSIT	132 (2 RCTs)	—	MD: 2.09 (0.42, 3.77)	Moderate
LSS	463 (2 RCTs)	—	MD: −1.38 (−1.97, −0.79)	Moderate
LMS	80 (2 RCTs)	—	MD: −2.24 (−3.03, −1.44)	Moderate
AEs	799 (7 RCTs)	RR: 1.01 (−0.93, 1.09)	—	High
SAEs	695 (4 RCTs)	RR: 0.73 (0.40, 1.34)	—	High

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect; moderate certainty: we are moderately confident in the effect estimate; and low certainty: Our confidence in the effect estimate is limited. MD, mean difference; GRADE, Grading of Recommendations Assessment, Development and Evaluation. * Not available.

Sino-Nasal Outcome Test

SNOT-22 is a disease-specific measure of HRQL (0–100). Benralizumab and mepolizumab were superior (better) to the placebo regarding the SNOT-22 score (benralizumab: WMD: −8.04, 95% CI: [−13.53, −2.55], $p = 0.004$; mepolizumab: WMD: −13.47, 95% CI: [−17.94, −8.99], $p < 0.00001$). An improvement was observed of at least the minimal clinically important difference (≥ 8.9 points) [19]. In the overall pooled meta-analysis, anti-IL-5 treatments were associated with a significantly better SNOT-22 score (WMD: −11.30; 95% CI: [−14.77, −7.83]; $p < 0.00001$; 5 RCTs; 703 participants; Fig. 3c). SNOT-22 scores were not reported in Gevaert et al. [13] and Gevaert et al. [18], so they were excluded in the meta-analysis.

University of Pennsylvania Smell Identification Test

The UPSIT includes 40 common smells embedded on individual scratch and sniff testing cards. Benralizumab improved the UPSIT score (WMD: 2.30; 95% CI: [0.42, 4.18]; $p = 0.02$) but not mepolizumab (WMD: 1.30; 95% CI: [−2.38, 4.98]; $p = 0.49$). The overall pooled meta-analysis showed that anti-IL-5 treatments were associated with a significantly better UPSIT score (WMD: 2.09; 95% CI [0.42, 3.77]; $p = 0.01$; 2 RCTs; 132 participants; Fig. 4a). UPSIT scores were not reported in Canonica et al. [10], Takabayashi et al. [11], Gevaert et al. [13], and Gevaert et al. [18]. In addition, the smell was assessed by the Sniffin' Sticks Screening-12 test and not the UPSIT in Bachert et al. [12]. Therefore, these RCTs were excluded.

Loss of Smell Score

The LSS was assessed using the VAS (0–10 cm). Mepolizumab reduced the LSS (WMD: −1.40; 95% CI: [−2.01, −0.79]; $p < 0.00001$) but not benralizumab (WMD: −1.1; 95% CI: [−3.19, 0.97]; $p = 0.30$). Anti-IL-5 treatments significantly reduced the LSS in the overall pooled meta-analysis (WMD: −1.38; 95% CI: [−1.97, −0.79]; $p < 0.00001$; 2 RCTs; 463 participants; Fig. 4b). The LSS was assessed only in 2 RCTs (Takabayashi et al. [11] and Han et al. [14]); other RCTs were excluded in the meta-analysis.

Lund-Mackay Score

The LMS determines the degree of sinus obstruction on a scale of 0–12 (bilateral score 0–24) [20]. In the overall pooled meta-analysis, benralizumab significantly reduced the LMS (WMD: −2.24; 95% CI: [−3.03, −1.44]; $p < 0.00001$; 2 RCTs; 80 participants; Fig. 4c). The LMS was assessed only in 2 RCTs (Takabayashi et al. [11] and Tversky et al. [17]); other RCTs were excluded in the meta-analysis.

Evidence of Safety

Figure 5 and Table 2 show the safety and the certainty of the evidence of the anti-IL-5 treatments.

Adverse Events

Compared with the placebo, no significant differences were exhibited in benralizumab, mepolizumab, or reslizumab in the risk of AEs. In the overall pooled meta-analysis, anti-IL-5 treatments showed no difference from the placebo in the risk of AEs (RR: 1.01; 95% CI [−0.93, 1.09]; $p = 0.83$; 7 RCTs; 799 participants; Fig. 5a). Most common

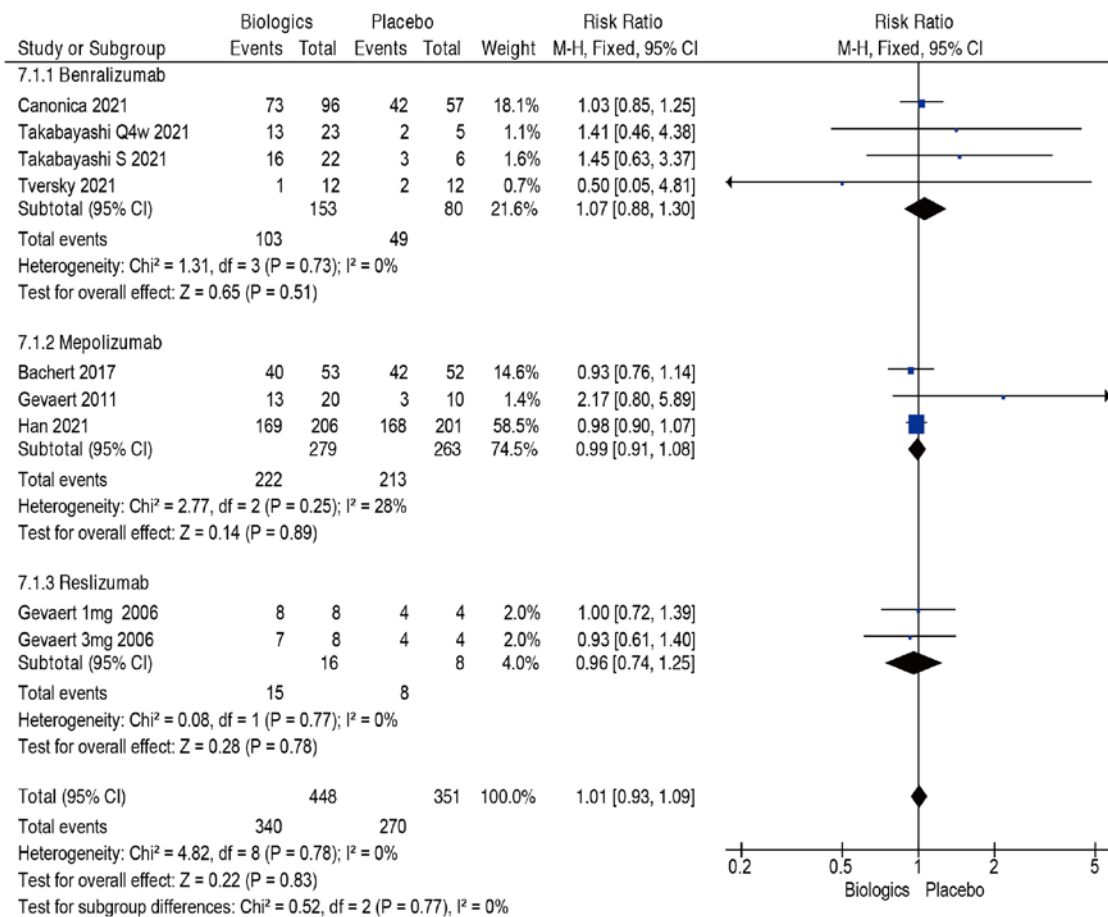
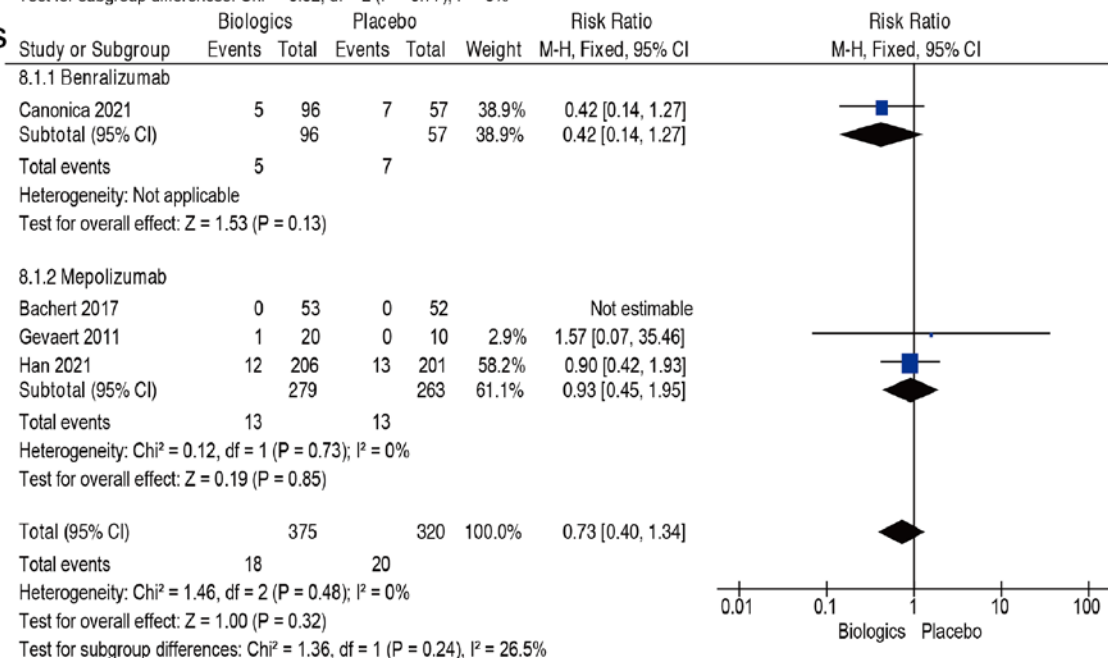
AEs**a****SAEs****b**

Fig. 5. Meta-analysis of anti-IL-15 therapies versus placebo, comparing safety. AEs (**a**); SAEs (**b**). Weight, the weight of each study; M-H, Mantel-Haenszel method; Fixed, fixed-effects model.

AEs (frequency $\geq 5\%$) reported at a greater frequency in benralizumab versus placebo included headache, sinusitis, pyrexia, and influenza [10]. The most frequently reported AEs in mepolizumab versus placebo were nasopharyngitis, headache, epistaxis, and sinusitis [14].

Serious AEs

No significant differences were exhibited in benralizumab and mepolizumab regarding SAEs. No SAEs were reported for reslizumab. In the overall pooled meta-analysis, anti-IL-5 treatments showed no difference from the placebo in the risk of SAEs in the overall pooled meta-analysis (RR: 0.73; 95% CI [0.40, 1.34]; $p = 0.32$; 4 RCTs; 695 participants; Fig. 5b). None of SAEs were considered related to treatment in those receiving mepolizumab [13, 14].

Sensitivity Analysis

The exclusion of one RCT decreased the degree of heterogeneity in some analyses, but the aggregated results did not change substantially.

Discussion

Principal Findings

This systematic review and meta-analysis identified seven RCTs with 799 participants evaluating the efficacy and safety of therapies targeting IL-5 signaling (anti-IL-5 treatments; benralizumab [anti-IL-5R α], mepolizumab, and reslizumab [anti-IL-5]) in CRSwNP. Anti-IL-5 treatments were more efficacious than the placebo and were safe in patients with CRSwNP. In the subgroup analysis, benralizumab improved the size of nasal polyps (measured by NPS and LMS), HRQL (measured by SNOT-22), and sense of smell (measured by UPSIT and LSS) but not NCS. Mepolizumab significantly improved the size of nasal polyps (NPS), symptoms (NCS), and HRQL (SNOT-22) and reduced the LSS but not the UPSIT score. Compared with the placebo, reslizumab showed no significant difference in improvement of the size of nasal polyps (NPS). Additionally, no difference was found for benralizumab, mepolizumab, and reslizumab in the risk of AEs and no difference for benralizumab and mepolizumab in the risk of SAEs. Overall the risk of bias was low, and the certainty of the evidence was high for most domains.

Comparison with Other Studies

To our best knowledge, this meta-analysis was the first on benralizumab in patients with CRSwNP. In Chong et

al.'s [8], Wu et al.'s [21], and Agache et al.'s [22] meta-analyses, 2 studies with 132 participants (Gavaert et al. [13] and Bachert et al. [12]) evaluated mepolizumab. Their results showed that mepolizumab might reduce the SNOT-22 score, and uncertainties existed concerning the effect of mepolizumab on disease severity (measured by the VAS) and SAEs. In our meta-analysis, we included a large sample study (Han et al. [14]) with 407 participants evaluating mepolizumab. Mepolizumab significantly improved the SNOT-22 score, NPS, and NCS and reduced the LSS, and no difference was found in the risk of SAEs.

Implication for Future Research and Clinical Practice

Seven RCTs were included in this systematic review and NMA, which recruited 799 patients with moderate to severe CRSwNP. The patients in the anti-IL-5 treatments group showed significant improvements in efficacy (NPS, NCS, SNOT-22, UPSIT, LSS, and LMS), with no increased risk of AEs and SAEs.

To date, whether the anti-IL-5 treatments is effective in patients with less severe CRSwNP and is safe in the long term are uncertain. Thus, further studies are required to evaluate their efficacy and safety in patients with less severe diseases (such as patients without asthma or NPS = 1 for each nostril or unilateral nostril) with a long follow-up. Additionally, a cost-effectiveness analysis for biologics therapies in CRSwNP is warranted [23], and head-to-head RCTs should be conducted to compare anti-IL-5 treatments to identify the best biologics for patients with CRSwNP.

Limitations of the Study

Despite the strict methodology of this meta-analysis using PRISMA guidelines, some limitations should be considered. First, the studies recruited participants with moderate to severe CRSwNP; more than half of the participants also had asthma as a comorbidity and were undergoing inhaled asthma therapy. Thus, no evidence exists regarding whether patients with less severe disease (such as patients without asthma or NPS = 1 for each nostril or unilateral nostril) would benefit. Second, a lack of a head-to-head study exists comparing anti-IL-5 treatments; thus, it remains unknown which anti-IL-5 treatment is the best biologic for patients with CRSwNP. Third, because only 7 studies for anti-IL-5 treatments were included, funnel plots could not be constructed [24]. Finally, dual therapy with benralizumab and dupilumab may be effective and well tolerated [25]. However, all the included studies evaluated a single biological agent; therefore, information on their combination could not be provided.

Conclusions

This meta-analysis identified that anti-IL-5 treatments significantly improved the size of nasal polyps, HRQL, and the sense of smell in moderate to severe CRSwNP, and they were safe and well tolerated. Studies are required to evaluate their effectiveness in patients with less severe diseases and their cost in treatment. A head-to-head comparison between anti-IL-5 treatments in patients with CRSwNP is also needed in future studies.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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Author Contributions

All the authors conceived and designed the study project. Q. Wang and Q. Sun performed the literature search and assessed the study details. Q. Chen and H.L. evaluated the study quality. L. Ding and Q. Wu performed the statistical analyses. With the support of Q. Wu, Q. Wang wrote the first draft of the manuscript, which was critically revised by all the other authors. All the authors gave final approval of the version to be submitted and agreed to be accountable for the whole manuscript.

Data Availability Statement

All the data are available in the manuscript and online supplementary file.

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Online supplementary table. Search strategies

Cochrane Library
1. MeSH descriptor: [Nasal Polyps] explode all trees 2. (nasi papilloma):ti,ab,kw OR (nose polyp*):ti,ab,kw OR (nasal polyp*):ti,ab,kw OR (nasal papilloma):ti,ab,kw OR (nasi polyposis):ti,ab,kw (Word variations have been searched) 3. #1 OR #2 4. MeSH descriptor: [Sinusitis] explode all trees 5. (CRSwNP):ti,ab,kw OR (chronic rhinosinusitis):ti,ab,kw OR (rhinopolyp*):ti,ab,kw OR (sinus Infection*):ti,ab,kw OR (pansinusitis):ti,ab,kw (Word variations have been searched) 6. #4 OR #5 7. #3 OR #6 8. (benralizumab):ti,ab,kw OR (Anti-IL-5Rα mAb):ti,ab,kw OR (Anti-IL-5 monoclonal antibody):ti,ab,kw OR (Fasenra):ti,ab,kw (Word variations have been searched) 9. (mepolizumab):ti,ab,kw OR (Bosatria):ti,ab,kw OR (Nucala):ti,ab,kw OR (Anti-IL-5 mAb):ti,ab,kw OR (Anti-IL-5 monoclonal antibody):ti,ab,kw (Word variations have been searched) 10. (reslizumab):ti,ab,kw OR (Cinqaero):ti,ab,kw OR (Cinqair):ti,ab,kw (Word variations have been searched) 11. #8 OR #9 OR #10 12. #7 AND #11
Embase
1. 'nose polyp'/exp 2. 'nasi papilloma':ab,ti OR 'nose polyp*':ab,ti OR 'nasal polyp*':ab,ti OR 'nasal papilloma':ab,ti OR 'nasi polyposis':ab,ti 3. #1 OR #2 4. 'sinusitis'/exp 5. crswnp:ab,ti OR 'chronic rhinosinusitis':ab,ti OR rhinopolyp*:ab,ti OR 'sinus infection*':ab,ti OR pansinusitis:ab,ti 6. #4 OR #5 7. 'benralizumab'/exp 8. benralizumab:ab,ti OR 'anti-il-5rα mab':ab,ti OR 'anti-il-5 monoclonal antibody':ab,ti OR fasenra:ab,ti 9. #7 OR #8 10. 'mepolizumab'/exp 11. mepolizumab:ab,ti OR bosatria:ab,ti OR nucala:ab,ti OR 'anti-il-5 mab':ab,ti 12. #10 OR #11 13. 'reslizumab'/exp 14. reslizumab:ab,ti OR cinqaero:ab,ti OR cinqair:ab,ti 15. #13 OR #14

16. #3 OR #6 17. #9 OR #12 OR #15 18. #16 AND #17 19. #18 AND [medline]/lim 20. #18 NOT #19
PubMed
1. nasal polyps[MeSH Terms] 2. (((((nasi papilloma[Title/Abstract]) OR (nose polyp*[Title/Abstract])) OR (nasal polyp*[Title/Abstract])) OR (nasi polyposis[Title/Abstract])) OR (nasal papilloma[Title/Abstract]) 3. #1 OR #2 4. sinusitis[MeSH Terms] 5. (((CRSwNP[Title/Abstract]) OR (chronic rhinosinusitis[Title/Abstract])) OR (rhinopolyp*[Title/Abstract])) OR (sinus Infection*[Title/Abstract]) 6. #4 OR #5 7. #3 OR #6 8. benralizumab[Supplementary Concept] 9. (((benralizumab[Title/Abstract]) OR (Anti-IL-5R α mAb[Title/Abstract])) OR (Anti-IL-5 monoclonal antibody[Title/Abstract])) OR (Fasenra[Title/Abstract]) 10. #8 OR #9 11. mepolizumab[Supplementary Concept] 12. (((((mepolizumab[Title/Abstract]) OR (Bosatria[Title/Abstract])) OR (Nucala[Title/Abstract])) OR (Anti-IL-5 mAb[Title/Abstract])) OR (Anti-IL-5 monoclonal antibody[Title/Abstract]) 13. #11 OR #12 14. reslizumab[Supplementary Concept] 15. ((reslizumab[Title/Abstract]) OR (Cinqaero[Title/Abstract])) OR (Cinqair[Title/Abstract]) 16. #14 OR #15 17. #10 OR #13 OR #16 18. #7 AND #17
Web of Science
1. nasal polyps (Topic) or nasi papilloma (Topic) or nose polyp* (Topic) or nasal polyp* (Topic) or nasal papilloma (Topic) or nasi polyposis (Topic) 2. (((((TS=(sinusitis)) OR TS=(CRSwNP)) OR TS=(chronic rhinosinusitis)) OR TS=(rhinopolyp*)) OR TS=(sinus Infection*)) OR TS=(pansinusitis) 3. #1 OR #2 4. (((TS=(benralizumab)) OR TS=(Anti-IL-5R α mAb)) OR TS=(Anti-IL-5 monoclonal antibody)) OR TS=(Fasenra) 5. (((((TS=(mepolizumab)) OR TS=(Bosatria)) OR TS=(Nucala)) OR TS=(Anti-IL-5 mAb)) OR TS=(Anti-IL-5 monoclonal antibody) 6. ((TS=(reslizumab)) OR TS=(Cinqaero)) OR TS=(Cinqair)

7. #4 OR #5 OR #6

8. #3 AND #7



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9, Figure 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-12 Figure 3-5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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PRISMA 2009 Checklist

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