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Efficacy and safety of omalizumab in chronic rhinosinusitis with nasal polyps: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Objectives

To assess the efficacy and safety of omalizumab for chronic rhinosinusitis with nasal polyps (CRSwNP) and to identify evidence gaps that will guide future research on omalizumab for CRSwNP.

Design

Systematic review and meta-analysis.

Methods

A comprehensive search was performed in Pubmed, Embase, Web of Science, and the Cochrane Library on 13 October 2020. Two independent authors screened search results, extracted data and appraised studies using the Cochrane risk of bias tool. Only randomized controlled trials (RCTs) assessing omalizumab in adult patients for CRSwNP were included.

Results

A total of 4 RCTs involving 303 participants were identified. When comparing omalizumab to placebo, there was a significant difference in nasal polyps score (mean difference (MD) = -1.11; 95% confidence interval (CI), -2.09 to -0.13), nasal congestion score (MD = -0.78; 95% CI, -1.25 to -0.30), Sino-Nasal Outcome Test-22 (MD = -15.62; 95% CI, -19.79 to -11.45), Total Nasal Symptom Score (MD = -1.84; 95% CI, -2.43 to -1.25), and reduced need for surgery (risk ratio (RR) = 5.61; 95% CI, 1.99 to 15.81). Furthermore, there was no difference in the risk of serious adverse

events ((RR = 1.40; 95% CI, 0.29 to 6.80), adverse events (RR = 0.83; 95% CI, 0.60 to 1.15) and rescue systemic corticosteroid (RR = 0.52; 95% CI, 0.17 to 1.61).

Conclusions

This was the first meta-analysis that identified omalizumab significantly improved endoscopic, clinical, and patient-reported outcomes in adults with moderate to severe CRSwNP and it was safe and well-tolerated.

PROSPERO registration number

CRD42020207639.

Keywords: omalizumab; anti-IgE antibody; chronic rhinosinusitis; nasal polyps; systematic review; meta-analysis

Strengths and limitation of this study

1. Omalizumab, an anti-IgE antibody, is a novel treatment for CRSwNP. However, its efficacy and safety are not well known.

2. In this systematic review and meta-analysis, we identified that omalizumab improved health-related quality of life and reduced the extent of the disease and the need for surgery in adults with moderate to severe CRSwNP and it was safe.

3. Studies are required to evaluate their effectiveness in patients with less severe diseases and their cost in the treatment.

Introduction

Chronic rhinosinusitis (CRS) is common and affects up to 5-12% of the general population[1]. It is defined as inflammation of the nose and the paranasal sinuses characterized by nasal congestion, nasal discharge, facial pressure, and loss of smell. CRS with nasal polyps (CRSwNP) is a severe form of CRS and accounts for 18% of patients with CRS[2]. CRSwNP is associated with adult-onset asthma, decreased health-related quality of life (HRQoL)[3, 4], and substantial economic burden[5]. Many patients with CRSwNP often fail to achieve sufficient benefit from intranasal corticosteroids (INCS) or systemic corticosteroids (SCS) and/ or functional endoscopic sinus surgery (FESS)[6]. Although FESS may be successful initially, relapse occurs in 20% of patients after 12 months[7], in 40% after 18 months[8], and in 80% after 12 years despite ongoing INCS therapy[9]. Therefore, novel treatments such as biologics are needed for CRSwNP.

Omalizumab (anti-IgE antibody) is one of the biologics and may help patients with severe CRSwNP. It was reported that omalizumab made their symptom better and shrank their polyps in small-size randomized controlled trials (RCTs)[10, 11]. But some of its effectiveness and safety are not well known. Thus, some systematic reviews were conducted to assess the effectiveness and safety of it. But they found very little information or insufficient evidence about the use of omalizumab and cannot determine whether it was effective or not[12, 13]. Currently, some well-designed RCTs about omalizumab for CRSwNP were published[14], which may provide us with some evidence. Therefore, this systematic review was conducted to evaluate the efficacy and safety of

omalizumab versus placebo in adult patients with CRSwNP, and identify evidence gaps that will guide future research on omalizumab for CRSwNP.

Methods

We performed a systematic review based on a priori protocol that was registered with PROSPERO (No. CRD42020207639)[15]. This review was reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement[16] (Additional file 1).

Eligibility criteria

(a) Population: adult patients (>18) with CRSwNP; (b) Intervention and comparison: studies comparing omalizumab with placebo, given for at least 16 weeks; (c) Study design: randomized controlled trials (RCTs); (d) Studies written and published in the English language were included.

Search strategy and selection process

A comprehensive search was performed in Pubmed, Embase, Web of Science, and the Cochrane Library on 13 October 2020. We used the following combined text and MeSH terms: “nasal polyps”, “sinusitis” and “omalizumab”. Search strategies for major databases are provided in Appendix 1.

Titles and abstracts of the retrieved articles were then screened for their potential relevance by two reviewers (Q.W Wu and L.X Yuan). The full-text articles were obtained and assessed by the same reviewers to determine whether they met the inclusion criteria for this review. We resolved any differences by a discussion with a

third author (Q.T Yang).

Data extraction

Two reviewers (H.J Qiu and X.Y Wang) read full-text articles and extracted data using a pre-defined extraction form. Data were extracted on the following: first author, year of publication, patient characteristics, study methods, and outcome data.

Assessment of risk of bias

In this review, the original version of the Cochrane 'Risk of bias' tool was used to assess the risk of bias in included studies. The risk of bias was assessed as 'low', 'high' or 'unclear' for each of the following six domains: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessment; incomplete outcome data; selective reporting; other sources of bias (if required).

Statistical analysis

Study characteristics were shown in tables and described narratively. All meta-analyses were conducted by Review Manager (version 5.3). For dichotomous data, we planned to analyze treatment differences as a risk ratio (RR) calculated using the Mantel-Haenszel methods. For continuous outcomes, we planned to express treatment effects as a mean difference (MD) with standard deviation (SD) or as a standardized mean difference (SMD) if different scales had been used to measure the same outcome. Statistical heterogeneity was assessed by the Chi^2 test (with a significance level set at P value < 0.10) and the I^2 statistic. A random-effects model was used in the analysis if it was likely 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

We identified 1966 articles, of which 3 (with data for 302 participants) were included in our analysis (Figure 1). The 3 articles (Pinto 2010[10], Gevaert 2013[11], and Gavaert 2020[14]) were published between 2010 and 2020, of which Gavaert 2020 reported 2 RCTs (POLYP1 2020 and POLYP2 2020).

Study characteristics

A summary of key participant characteristics, interventions, and comparison pairs was shown in Table 1. Except for 2 participants in Pinto 2010, all the participants were adults with CRSwNP. All the studies were double-blind RCTs and used a placebo. Study duration ranged from 20 weeks to 26 weeks.

Risk of bias and quality of the clinical trials

There were 4 RCTs included in this review. Overall the risk of bias was low, except the random sequence generation of Pinto 2010 was unclear. Our judgments about each risk of bias item presented as percentages across all included studies were shown in Figure 2. Our judgments about each risk of bias item for each included study were shown in Figure 3.

Primary outcomes

The mean difference (MD) in the change of nasal polyps score (NPS) was -1.11 (95% confidence interval (CI), -2.09 to -0.13; 4 RCTs; 302 participants; I^2 = 90%; Figure

4A). We noted the high I^2 value and Pinto 2020 had no significant reduction in NPS. However, the removal of Pinto 2020 did not change the overall effect size in sensitivity analyses. Therefore, we considered the certainty of the evidence to be high despite the large I^2 value.

The pooled mean difference of nasal congestion score (NCS) is -0.78 favoring the groups receiving omalizumab (95% CI, -1.25 to -0.30; 3 RCTs; 288 participants; I^2 = 82%; Figure 4B). Although the heterogeneity was high in this analysis, all 3 RCTs showed a significant reduction in NCS with omalizumab.

The Sino-Nasal Outcome Test-22 (SNOT-22) score was 15.62 points lower in participants who received omalizumab (MD = -15.62; 95% CI, -19.79 to -11.45; 265 participants; I^2 = 0%; Figure 4C). Because the different measuring tools (Pinto 2010, SNOT-20; Gevaert 2013, Short-Form Health Questionnaire (SF-36)) and unavailable data , these 2 RCTs were excluded in this pooled analysis.

Secondary outcomes

The mean difference in the change of Total Nasal Symptom Score (TNSS) was 1.84 points lower in omalizumab group (MD = -1.84; 95% CI, -2.43 to -1.25; 3 RCTs; 279 participants; I^2 = 0%; Figure 4D).

No serious adverse events (SAEs) were reported in Gevaert 2013 and Pinto 2010. However, POLYP1 2020 reported 1 case in the placebo group with myocardial infarction and POLYP2 2020 reported 1 case of pneumonia in the placebo group and 3 cases in the omalizumab group (1 snake bite, 1 hand fracture, and 1 asthma

exacerbation). The pooled result indicated that there was no difference in the risk of SAEs (risk ratio (RR) = 1.40; 95% CI, 0.29 to 6.80; 4 RCTs; 302 participants; $I^2 = 28\%$; Figure 4E).

There was no difference in the risk of adverse events (AEs) (RR = 0.83; 95% CI, 0.60 to 1.15; 4 RCTs; 302 participants; $I^2 = 0\%$; Figure 4F). It was uncertain where or not there was a difference in the risk of rescue systemic corticosteroid (RSCS; RR = 0.52; 95% CI, 0.17 to 1.61; 3 RCTs; 279 participants; $I^2 = 0\%$; Figure 4G). POLYP1 2020 and POLYP2 2020 reported the number of reduced need for surgery (RNS). The proportion was higher in the group that received omalizumab (RR = 5.61; 95% CI, 1.99 to 15.81; 2 RCTs; 265 participants; $I^2 = 0\%$; Figure 4H).

Discussion

Principal findings

This systematic review and meta-analysis identified 4 RCTs with 302 participants evaluating the efficacy and safety of omalizumab in CRSwNP. It showed that omalizumab significantly improved the size of nasal polyps (measured by NPS), symptoms (measured by NCS and TNSS), and Health-related quality of life (HRQoL; measured by SNOT-22), and reduce the need for surgery (measured by RNS). What's more, there was no difference in the risk of SAEs, AEs, and RSCS.

Comparison with other studies

Hong included two studies (Gavaert 2013 and Pinto 2010) and made a narrative systematic review[12]. They concluded that there was insufficient evidence to determine

the effectiveness of omalizumab for CRS. In Chong's systematic review and meta-analysis, there were 3 small studies with 65 participants (Gavaert 2013, Pinto 2010, and NCT01066104) evaluated omalizumab[13]. Their results also showed that there were very uncertain about the effect of omalizumab on disease-specific HRQoL, severe adverse events, the extent of disease (CT scan scores), generic HRQoL, and adverse effects. NCT01066104[17] included in Chong's review was unpublished data, so it was excluded in our study according to our inclusion criteria.

Implication for future research and clinical practice

Patients with CRSwNP and comorbid asthma often have a high symptom burden, substantial impact on HRQoL, and a higher risk of RSCS and revision surgery[1]. There were 4 RCTs included in this systematic review, which recruited patients with moderate to severe CRSwNP. The patients in omalizumab group experienced significant improvements in HRQoL, and reduced disease severity and need for surgery. Furthermore, there was no increased risk of SAEs and AEs in patients treated with omalizumab. Thus, it was certain that omalizumab significantly improved endoscopic, clinical, and patient-reported outcomes in moderate to severe CRSwNP and it was well tolerated.

However, it is still unknown that omalizumab is effective in patients with less severe disease and more affordable compared to conventional treatment with topical and systemic corticosteroids and surgery. Therefore, studies are required to evaluate their effectiveness in patients with less severe diseases and their cost in the treatment. In

addition, long-term observational studies are also required to determine if omalizumab lose its effectiveness over time, or whether there are any late adverse events.

Limitations of the study

Despite the strict methodology of this systematic review and meta-analysis using PRIMSA guidelines, certain limitations should be considered. First, studies recruited participants with moderate to severe CRSwNP, as half of participants also had asthma as comorbidity or inhaled asthma therapy. Therefore, there is no evidence on whether or not patients with less severe disease (without asthma) would benefit. Secondly, 4 RCTs were all in adults and no available data for children. Thirdly, because the longest follow-up of 4 RCTs was only up to 26 weeks, there were too short to comprehensively and adequately assess the risks of side effect, RSCS, and RNS. Finally, there were only 4 RCTs (<10), so a possibility of publication bias was not assessed by constructing a funnel plot in this systematic review[18].

Conclusions

To the best of our knowledge, this was the first meta-analysis that identified omalizumab significantly improved endoscopic, clinical, and patient-reported outcomes in moderate to severe CRSwNP and it was safe and well-tolerated. Studies are required to evaluate their effectiveness in patients with less severe diseases and their cost in the treatment.

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N/A.

Contributors

Concept and design: R Zheng and Q.T Yang. Acquisition, analysis, or interpretation of data: Q.W Wu, L.X Yuan, Q.H Qiu, X.Y Wang, and X.K Huang. Drafting of the manuscript: QW Wu and L.X Yuan. Critical revision of the manuscript for important intellectual content: R Zheng and Q.T Yang. Statistical analysis: L.X Yuan. Supervision: R Zheng and Q.T Yang.

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Competing interests

No potential conflict of interest was reported by the authors.

Patient consent for publication

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information.

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Appendix 1. Search strategies

Pubmed
1. nasal polyps[MeSH Terms] 2. ((((nasal polyp*[Title/Abstract]) OR (nasal papilloma[Title/Abstract])) OR (nose polyp*[Title/Abstract])) OR (nasi papilloma[Title/Abstract])) OR (nasi polyposis[Title/Abstract]) 3. #1 OR #2 4. sinusitis[MeSH Terms] 5. ((((((chronic rhinosinusitis[Title/Abstract]) OR (rhinopolyp*[Title/Abstract])) OR (CRSwNP[Title/Abstract])) OR (sinus Infection*[Title/Abstract])) OR (rhinitis[Title/Abstract])) OR (pansinusitis[Title/Abstract])) OR (sphenoid* sinusitis[Title/Abstract]) 6. #4 OR #5 7. omalizumab[MeSH Terms] 8. (((Xolair[Title/Abstract]) OR (anti-IgE antibody[Title/Abstract])) OR (anti-IgE monoclonal antibody[Title/Abstract])) OR (anti-IgE mAb[Title/Abstract]) 9. #7 OR #8 10. #3 OR #6 11. #9 AND #10
Cochrane Library
1. MeSH descriptor: [Nasal Polyps] explode all trees 2. (nasal polyp*):ti,ab,kw OR (nasal papilloma):ti,ab,kw OR (nose polyp*):ti,ab,kw OR (nasi 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. (chronic rhinosinusitis):ti,ab,kw OR (rhinopolyp*):ti,ab,kw OR (CRSwNP):ti,ab,kw OR (sinus infection*):ti,ab,kw OR (rhinitis):ti,ab,kw (Word variations have been searched) 6. #4 OR #5 7. (pansinusitis):ti,ab,kw OR (sphenoid* sinusitis):ti,ab,kw (Word variations have been searched) 8. #6 OR #7 9. MeSH descriptor: [Omalizumab] explode all trees 10. (Xolair):ti,ab,kw OR (anti-IgE antibody):ti,ab,kw OR (anti-IgE monoclonal antibody):ti,ab,kw OR (anti-IgE mAb):ti,ab,kw (Word variations have been searched) 11. #9 OR #10 12. #3 OR #8 13. #11 AND #12
Embase

1. 'nose polyp'/exp 2. 'nasal polyp*' OR 'nasal papilloma'/exp OR 'nasal papilloma' OR 'nose polyp*' OR 'nasi papilloma' OR 'nasi polyposis':ab,ti 3. #1 OR #2 4. 'sinusitis'/exp 5. 'chronic rhinosinusitis rhinopolyp*' OR crswnp OR 'sinus infection*' OR rhinitis OR pansinusitis OR 'sphenoid* sinusitis':ab,ti 6. #4 OR #5 7. #3 OR #6 8. 'omalizumab'/exp 9. 'xolair' OR 'anti-ige antibody' OR 'anti-ige monoclonal antibody' OR 'anti-ige mab':ab,ti 10. #8 OR #9 11. #7 AND #10 12. #7 AND #10 AND [medline]/lim 13. #11 NOT #12
Web of Science
1. TOPIC: (nasal polyp*) OR TOPIC: (nasal papilloma) OR TOPIC: (nose polyp*) OR TOPIC: (nasi papilloma) OR TOPIC: (nasi polyposis) 2. TOPIC: (sinusitis) OR TOPIC: (chronic rhinosinusitis) OR TOPIC: (rhinopolyp*) OR TOPIC: (CRSwNP) OR TOPIC: (sinus Infection*) OR TOPIC: (rhinitis) OR TOPIC: (pansinusitis) OR TOPIC: (sphenoid* sinusitis) 3. #1 OR #2 4. TOPIC: (omalizumab) OR TOPIC: (Xolair) OR TOPIC: (anti-IgE antibody) OR TOPIC: (anti-IgE monoclonal antibody) OR TOPIC: (anti-IgE mAb) 5. #3 AND #4

Table 1. Summary of characteristics of included RCTs

Figure 1. PRISMA flow diagram of the literature search.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

Figure 4. Meta-analyses of omalizumab versus placebo, comparing efficacy and safety. Outcomes assessed are: (A) Nasal polyps score (NPS); (B) Nasal congestion score (NCS); (C) Sino-Nasal Outcome Test-22 (SNOT-22); (D) Total nasal symptom score (TNSS); (E) Serious adverse events (SAEs); (F) Adverse events (AEs); (G) Rescue systemic corticosteroid (RSCS) and (H) Reduced need for surgery (RNS).

Table 1. Summary of characteristics of included RCTs

Study, year	Population	Comorbidity	Omalizumab*	Placebo	Treatment length	Follow-up length	Age (y), mean (SD)		Male, no.(%)	
							Omalizumab	Placebo	Omalizumab	Placebo
Pinto 2010[10] (n = 14)	CRSwNP (all had undergone endoscopic sinus surgery)	inhaled asthma therapy (72% (5/7) in omalizumab group and 43% (3/7) in placebo group)	subcutaneously	injection, same dose and frequency	26 weeks	26 weeks	43.1 (9.8)	48.6 (9.1)	3 (43%)	7 (100%)
Gevaert[11] 2013 (n = 24)	CRSwNP	asthma (100%)	subcutaneously	injection, same dose and frequency	16 weeks	20 weeks	50 (44-56)[#]	45 (42-54)[#]	12 (80%)	4 (50%)
POLYP1[14] 2020 (n = 138)	CRSwNP	asthma (58.3% (42/72) in omalizumab group and 48.5% (32/66) in placebo group	subcutaneously	injection, same dose and frequency	24 weeks	24 weeks	50.0 (14.5)	52.2 (11.6)	47 (65.3)	41 (62.1)
POLYP2[14] 2020 (n = 127)	CRSwNP	asthma (61.3% (38/62) in omalizumab group and 60% (39/65) in placebo group)	subcutaneously	injection, same dose and frequency	24 weeks	24 weeks	49.0 (11.9)	51.0 (12.0)	39 (62.9)	44 (67.7)

*omalizumab subcutaneously (every 2 week or every month injections), based on total serum IgE levels and body weight, with a maximum dose of 375 mg; [#]mean (interquartile range, IQR); CRSwNP: chronic rhinosinusitis with nasal polyps; RCTs: randomized controlled trials; SD: standard deviation.

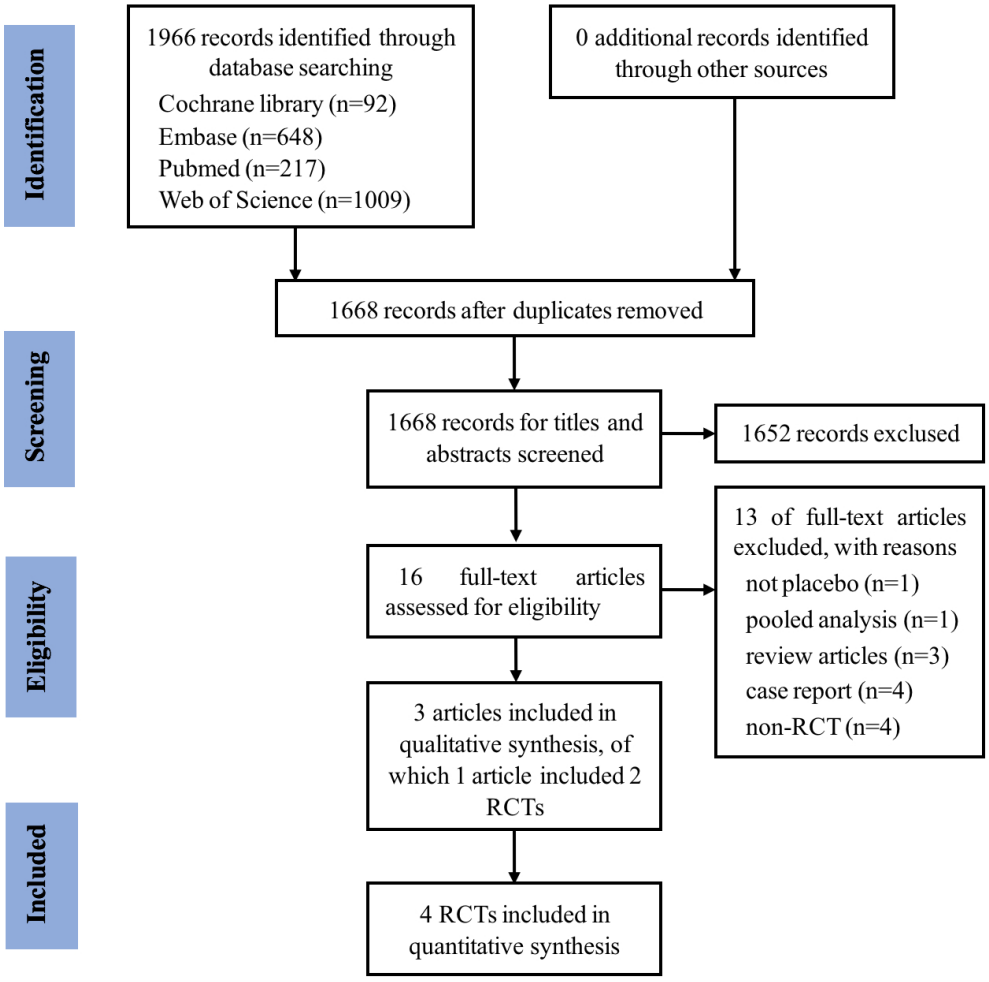

Figure 1. PRISMA flow diagram of the literature search.

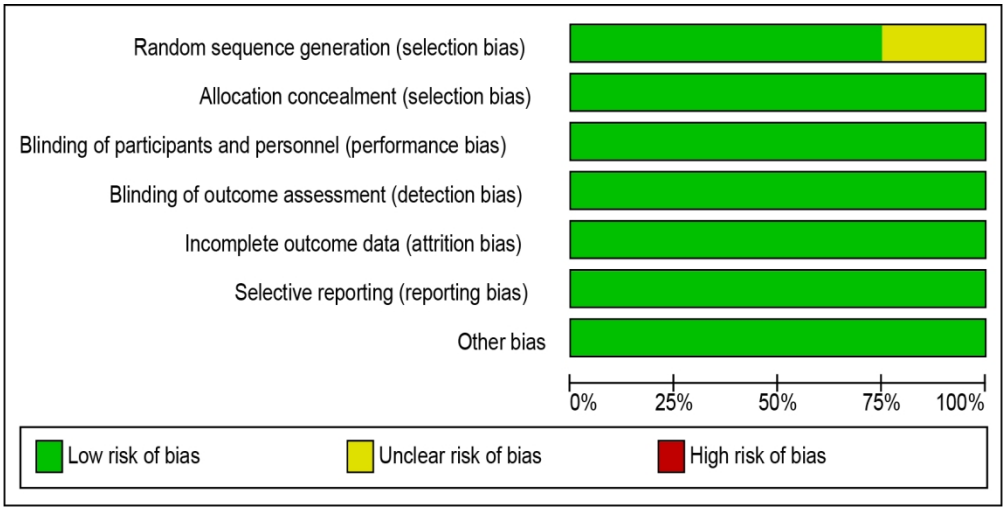

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

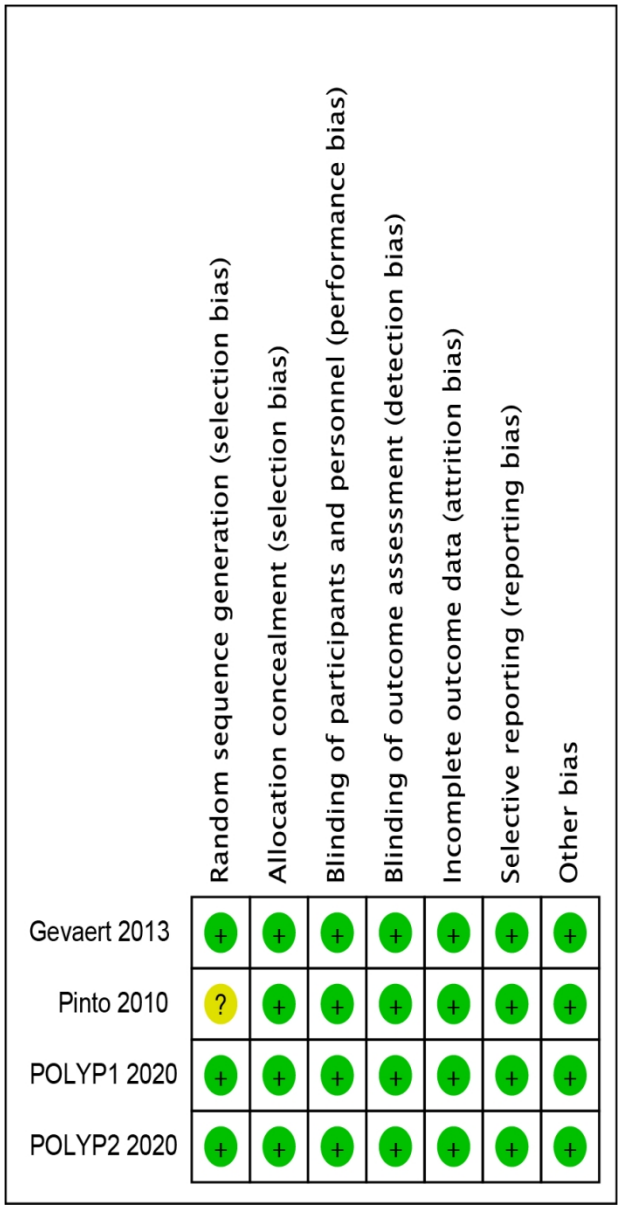

Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

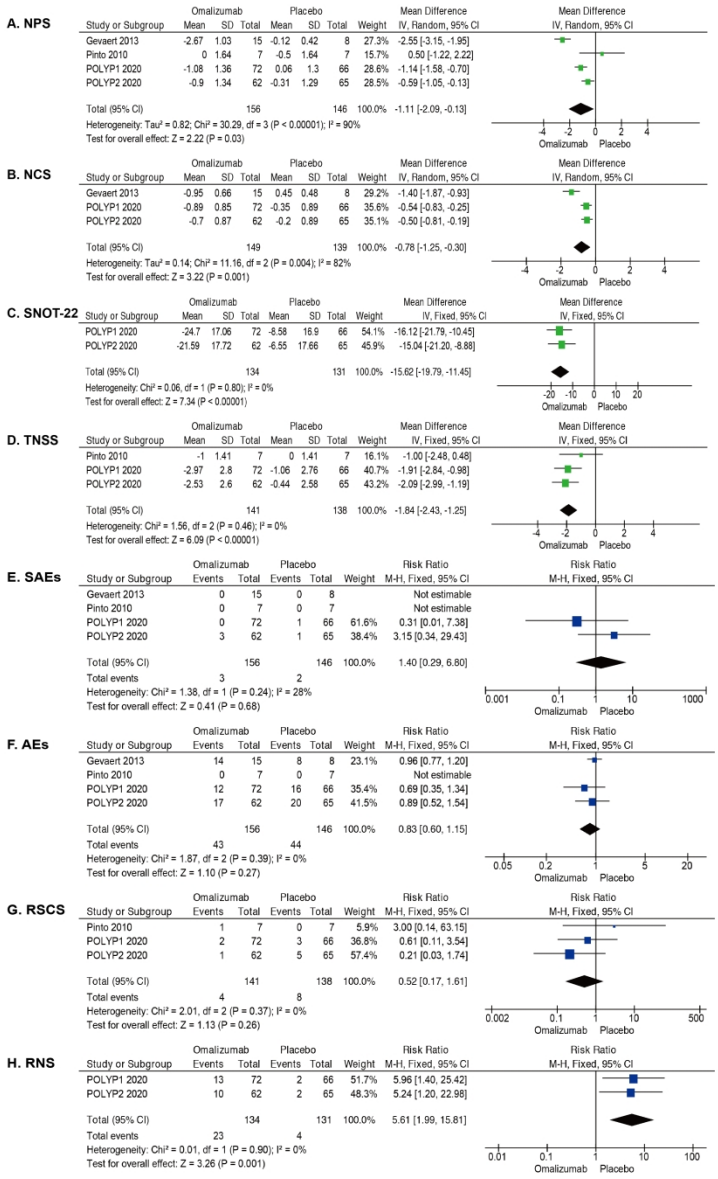

Figure 4. Meta-analyses of omalizumab versus placebo, comparing efficacy and safety. Outcomes assessed are: (A) Nasal polyps score (NPS); (B) Nasal congestion score (NCS); (C) Sino-Nasal Outcome Test-22 (SNOT-22); (D) Total nasal symptom score (TNSS); (E) Serious adverse events (SAEs); (F) Adverse events (AEs); (G) Rescue systemic corticosteroid (RSCS) and (H) Reduced need for surgery (RNS).

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
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
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.	5
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.	5
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.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
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).	5
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.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
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.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
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.	6

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.	7, 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.	7, 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).	7; Figure 2 and 3
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.	7-9; Figure 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-9; Figure 4
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]).	n/a
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).	9-10
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).	10-11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
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.	12

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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Efficacy and safety of omalizumab in chronic rhinosinusitis with nasal polyps: a systematic review and meta-analysis of randomized controlled trials

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Efficacy and safety of omalizumab in chronic rhinosinusitis with nasal polyps: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Objectives

To assess the efficacy and safety of omalizumab for chronic rhinosinusitis with nasal polyps (CRSwNP) and to identify evidence gaps that will guide future research on omalizumab for CRSwNP.

Design

Systematic review and meta-analysis.

Data Sources

A comprehensive search was performed in PubMed, Embase, Web of Science, and the Cochrane Library on 13 October 2020.

Eligibility Criteria

Randomized controlled trials (RCTs) comparing omalizumab with placebo, given for at least 16 weeks in adult patients with CRSwNP.

Data extraction and synthesis

Two independent authors screened search results, extracted data and assessed studies using the Cochrane risk of bias tool. Data were pooled using the inverse-variance method and expressed as mean differences (MDs) with 95% CIs. Heterogeneity was assessed by the Chi^2 test and the I^2 statistic.

Results

A total of 4 RCTs involving 303 participants were identified. When comparing omalizumab to placebo, there was a significant difference in nasal polyps score (mean

difference (MD) = -1.20; 95% confidence interval (CI), -1.48 to -0.92), nasal congestion score (MD = -0.67; 95% CI, -0.86 to -0.48), Sino-Nasal Outcome Test-22 (MD = -15.62; 95% CI, -19.79 to -11.45), total nasal symptom score (MD = -1.84; 95% CI, -2.43 to -1.25), and reduced need for surgery (risk ratio (RR) = 5.61; 95% CI, 1.99 to 15.81). Furthermore, there was no difference in the risk of serious adverse events ((RR = 1.40; 95% CI, 0.29 to 6.80), adverse events (RR = 0.83; 95% CI, 0.60 to 1.15) and rescue systemic corticosteroid (RR = 0.52; 95% CI, 0.17 to 1.61).

Conclusions

This was the first meta-analysis that identified omalizumab significantly improved endoscopic, clinical, and patient-reported outcomes in adults with moderate to severe CRSwNP and it was safe and well-tolerated.

PROSPERO registration number

CRD42020207639.

Keywords: omalizumab; anti-IgE antibody; chronic rhinosinusitis; nasal polyps; systematic review; meta-analysis

Strengths and limitation of this study

1. This systematic review and meta-analysis was based on a comprehensive search and included RCTs.
2. Studies were low risk of bias, which was assessed by the Cochrane risk of bias tool.
3. Because the longest follow-up of 4 RCTs was only up to 26 weeks, there were too short to comprehensively and adequately assess the risks of side effect.

Introduction

Chronic rhinosinusitis (CRS) is common and affects up to 5-12% of the general population[1]. It is defined as inflammation of the nose and the paranasal sinuses characterized by nasal congestion, nasal discharge, facial pressure, and loss of smell. CRS with nasal polyps (CRSwNP) is a severe form of CRS and accounts for 18% of patients with CRS[2]. CRSwNP is associated with adult-onset asthma, decreased health-related quality of life (HRQoL)[3, 4], and substantial economic burden[5]. Many patients with CRSwNP often fail to achieve sufficient benefit from intranasal corticosteroids (INCS) or systemic corticosteroids (SCS) and/ or functional endoscopic sinus surgery (FESS)[6]. Although FESS may be successful initially, relapse occurs in 20% of patients after 12 months[7], in 40% after 18 months[8], and in 80% after 12 years despite ongoing INCS therapy[9]. Therefore, novel treatments such as biologics are needed for CRSwNP.

Omalizumab (anti-IgE antibody) is one of the biologics and may help patients with severe CRSwNP. It was reported that omalizumab made their symptom better and shrank their polyps in small-size randomized controlled trials (RCTs)[10, 11]. But some of its effectiveness and safety are not well known. Thus, some systematic reviews were conducted to assess the effectiveness and safety of it. But they found very little information or insufficient evidence about the use of omalizumab and cannot determine whether it was effective or not[12, 13]. Currently, some well-designed RCTs about omalizumab for CRSwNP were published[14], which may provide us with some evidence. Therefore, this systematic review was conducted to evaluate the efficacy and safety of

omalizumab versus placebo in adult patients with CRSwNP, and identify evidence gaps that will guide future research on omalizumab for CRSwNP.

Methods

We performed a systematic review based on a priori protocol that was registered with PROSPERO (No. CRD42020207639)[15]. This review was reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement[16] (Additional file 1).

Eligibility criteria

(a) Population: adult patients (>18) with CRSwNP; (b) Intervention and comparison: studies comparing omalizumab with placebo, given for at least 16 weeks; (c) Primary outcomes: nasal polyps score, nasal congestion score, and Sino-Nasal Outcome Test-22 score; Secondary outcomes: total nasal symptom score, serious adverse events, adverse events, rescue systemic corticosteroid, and reduced need for surgery. (d) Study design: randomized controlled trials (RCTs); (e) Studies written and published in the English language were included.

Search strategy and selection process

A comprehensive search was performed in PubMed, Embase, Web of Science, and the Cochrane Library on 13 October 2020. We used the following combined text and MeSH terms: “nasal polyps”, “sinusitis” and “omalizumab”. Search strategies for major databases are provided in Appendix 1.

Titles and abstracts of the retrieved articles were then screened for their potential

relevance by two reviewers (Q.W Wu and L.X Yuan). The full-text articles were obtained and assessed by the same reviewers to determine whether they met the inclusion criteria for this review. We resolved any differences by a discussion with a third author (Q.T Yang).

Data extraction

Two reviewers (H.J Qiu and X.Y Wang) read full-text articles and extracted data using a pre-defined extraction form. Data were extracted on the following: first author, year of publication, patient characteristics, study methods, and outcome data.

Assessment of risk of bias

In this review, the original version of the Cochrane 'Risk of bias' tool was used to assess the risk of bias in included studies. The risk of bias was assessed as 'low', 'high' or 'unclear' for each of the following six domains: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessment; incomplete outcome data; selective reporting; other sources of bias (if required).

Statistical analysis

Study characteristics were 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 methods. For continuous outcomes, a generic inverse-variance method with fixed-effects models was used to calculate pooled mean differences and 95% confidence interval. Statistical heterogeneity was assessed by the Chi^2 test (with a significance level set at P value < 0.10) and the I^2 statistic ($I^2 \geqslant 50\%$ indicates

substantial heterogeneity). There are two large pharma-sponsored RCTs with most of the information and two smaller RCTs with effect sizes much larger and much smaller than the two main studies. A random-effects meta-analysis will exacerbate the effects of the bias. Therefore, we choose a fixed-effect analysis that will be affected less, although strictly it will also be inappropriate. Sensitivity analysis were performed, which included the removal of each single study from the meta-analysis one at a time and recalculation of the summary effect. The possibility of publication bias was assessed by constructing a funnel plot if sufficient studies (> 10) were available for an outcome. All meta-analysis were conducted by the Review Manager (version 5.3).

Results

Study selection

We identified 1966 studies, of which 3 (with data for 302 participants) were included in our analysis (Figure 1). The 3 studies (Pinto 2010[10], Gevaert 2013[11], and Gavaert 2020[14]) were published between 2010 and 2020, of which Gavaert 2020 reported 2 RCTs (POLYP1 2020 and POLYP2 2020).

Study characteristics

A summary of key participant characteristics, interventions, and comparison pairs was shown in Table 1. Except for 2 participants in Pinto 2010, all the participants were adults with CRSwNP. All the studies were double-blind RCTs and used a placebo. Study duration ranged from 20 weeks to 26 weeks.

146 **Table 1.** Summary of characteristics of included RCTs

Study, year	Population	Comorbidity	Omalizumab*	Placebo	Treatment length	Follow-up length	Age (y), mean (Range)		Male, no.(%)	
							Omalizumab	Placebo	Omalizumab	Placebo
Pinto 2010[10] (n = 14)	CRSwNP (all had undergone endoscopic sinus surgery)	inhaled asthma therapy (72% (5/7) in omalizumab group and 43% (3/7) in placebo group)	subcutaneously	injection, same dose and frequency	26 weeks	26 weeks	43.1 (18-75)	48.6 (18-75)	3 (43%)	7 (100%)
Gevaert[11] 2013 (n = 24)	CRSwNP	asthma (100%)	subcutaneously	injection, same dose and frequency	16 weeks	20 weeks	50 (≥18)	45 (≥18)	12 (80%)	4 (50%)
POLYP1[14] 2020 (n = 138)	CRSwNP	asthma (58.3% (42/72) in omalizumab group and 48.5% (32/66) in placebo group	subcutaneously	injection, same dose and frequency	24 weeks	24 weeks	50.0 (18-75)	52.2 (18-75)	47 (65.3)	41 (62.1)
POLYP2[14] 2020 (n = 127)	CRSwNP	asthma (61.3% (38/62) in omalizumab group and 60% (39/65) in placebo group)	subcutaneously	injection, same dose and frequency	24 weeks	24 weeks	49.0 (18-75)	51.0 (18-75)	39 (62.9)	44 (67.7)

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*omalizumab subcutaneously (every 2 week or every month injections), based on total serum IgE levels and body weight, with a maximum dose of 375 mg; CRSwNP: chronic rhinosinusitis with nasal polyps; RCTs: randomized controlled trials.

Risk of bias and quality of the clinical trials

There were 4 RCTs included in this review. Overall the risk of bias was low, except the random sequence generation of Pinto 2010 was unclear. Our judgments about each risk of bias item presented as percentages across all included studies were shown in Figure 2. Our judgments about each risk of bias item for each included study were shown in Figure 3.

Primary outcomes

Total nasal polyps score (NPS) ranges from 0 to 8 (sum of 0-4 for left and right nasal passage scores per participant), with a lower score indicating smaller-sized nasal polyps and the highest score indicating large polyps causing complete obstruction of the inferior nasal cavity.

The mean difference (MD) in the change of NPS was -1.20 (95% confidence interval (CI), -1.48 to -0.92; 4 RCTs; 302 participants; $I^2 = 90\%$; Figure 4A). We noted the high I^2 value and Pinto 2020 had no significant reduction in NPS. However, the removal of Pinto 2020 did not change the overall effect size in sensitivity analyses. Therefore, we considered the certainty of the evidence to be high despite the large I^2 value.

Nasal congestion score (NCS) was assessed daily by the participant via an electronic diary as the response to the following question: Is your nose blocked? The four available response options were scored from 0 (no symptoms) to 3 (severe symptoms). The pooled mean difference of NCS is -0.67 favoring the groups receiving omalizumab (95% CI, -0.86 to -0.48; 3 RCTs; 288 participants; $I^2 = 82\%$; Figure 4B). Although the

heterogeneity was high in this analysis, all 3 RCTs showed a significant reduction in NCS with omalizumab.

The mean difference in the change of Sino-Nasal Outcome Test-22 (SNOT-22) score was 15.62 points lower in participants who received omalizumab (MD = -15.62; 95% CI, -19.79 to -11.45; 265 participants; $I^2 = 0\%$; Figure 4C). There was an improvement of at least the minimal clinically important difference (MCID; ≥8.9 points).[17] Because the different measuring tools (Pinto 2010, SNOT-20; Gevaert 2013, Short-Form Health Questionnaire (SF-36)) and unavailable data , these 2 RCTs were excluded in this pooled analysis.

Secondary outcomes

Total nasal symptom score (TNSS) was defined as the sum of the scores for nasal congestion score, anterior rhinorrhea score, posterior rhinorrhea score, and sense of smell score, ranging from 0 (no symptoms) to 12 (most severe symptoms).

The mean difference in the change of TNSS was 1.84 points lower in omalizumab group (MD = -1.84; 95% CI, -2.43 to -1.25; 3 RCTs; 279 participants; $I^2 = 0\%$; Figure 4D).

No serious adverse events (SAEs) were reported in Gevaert 2013 and Pinto 2010. However, POLYP1 2020 reported 1 case in the placebo group with myocardial infarction and POLYP2 2020 reported 1 case of pneumonia in the placebo group and 3 cases in the omalizumab group (1 snake bite, 1 hand fracture, and 1 asthma exacerbation). The pooled result indicated that there was no difference in the risk of

SAEs (risk ratio (RR) = 1.40; 95% CI, 0.29 to 6.80; 4 RCTs; 302 participants; $I^2 = 28\%$; Figure 5A).

There was no difference in the risk of adverse events (AEs) (RR = 0.83; 95% CI, 0.60 to 1.15; 4 RCTs; 302 participants; $I^2 = 0\%$; Figure 5B). It was uncertain where or not there was a difference in the risk of rescue systemic corticosteroid (RSCS; RR = 0.52; 95% CI, 0.17 to 1.61; 3 RCTs; 279 participants; $I^2 = 0\%$; Figure 5C).

Reduced need for surgery (RNS) through week 24 was defined as achievement of NPS of 4 or lower (≤2 for each nostril). POLYP1 2020 and POLYP2 2020 reported the number of RNS. The proportion was higher in the group that received omalizumab (RR = 5.61; 95% CI, 1.99 to 15.81; 2 RCTs; 265 participants; $I^2 = 0\%$; Figure 5D).

Discussion

Principal findings

This systematic review and meta-analysis identified 4 RCTs with 302 participants evaluating the efficacy and safety of omalizumab in CRSwNP. It showed that omalizumab significantly improved the size of nasal polyps (measured by NPS), symptoms (measured by NCS and TNSS), and Health-related quality of life (HRQoL; measured by SNOT-22), and reduce the need for surgery (measured by RNS). What's more, there was no difference in the risk of SAEs, AEs, and RSCS.

Comparison with other studies

Hong included two studies (Gavaert 2013 and Pinto 2010) and made a narrative systematic review[12]. They concluded that there was insufficient evidence to determine the effectiveness of omalizumab for CRS. In Chong's systematic review and meta-analysis, there were 3 small studies with 65 participants (Gavaert 2013, Pinto 2010, and NCT01066104) evaluated omalizumab[13]. Their results also showed that there were very uncertain about the effect of omalizumab on disease-specific HRQoL, severe adverse events, the extent of disease (CT scan scores), generic HRQoL, and adverse effects. NCT01066104[18] included in Chong's review was unpublished data, so it was excluded in our study according to our inclusion criteria.

Implication for future research and clinical practice

Patients with CRSwNP and comorbid asthma often have a high symptom burden, substantial impact on HRQoL, a higher risk of RSCS and revision surgery[1]. Moreover,

patients with asthma are more likely to develop CRSwNP than are those without asthma, and they are more likely to receive more oral corticosteroid courses.[19] Therefore, the risk of RSCS may be due to asthma comorbidity.

There were 4 RCTs included in this systematic review, which recruited patients with moderate to severe CRSwNP. The patients in omalizumab group reduced disease severity and need for surgery, and experienced significant improvements in HRQoL (measured by SNOT-22). Placebo-corrected improvements of SNOT-22 was 15.6 points, which exceeded the commonly accepted MCID of 8.9 points.[17, 20] Furthermore, there was no increased risk of SAEs and AEs in patients treated with omalizumab. Thus, it was certain that omalizumab significantly improved endoscopic, clinical, and patient-reported outcomes in moderate to severe CRSwNP and it was well tolerated.

However, it is still unknown that omalizumab is effective in patients with less severe CRSwNP (such as serum IgE level <30 IU/mL and NPS=1 for each nostril or unilateral nostril) and more affordable compared to conventional treatment with topical and systemic corticosteroids and surgery. Therefore, studies are required to evaluate their effectiveness in patients with less severe diseases and their cost in the treatment. In addition, long-term observational studies are also required to determine if omalizumab lose its effectiveness over time, or whether there are any late adverse events.

Limitations of the study

Despite the strict methodology of this systematic review and meta-analysis using PRISMA guidelines, certain limitations should be considered. First, 4 RCTs were

recruited from the same group with moderate to severe CRSwNP. Therefore, there is no evidence on whether or not patients with less severe CRSwNP (serum IgE level <30 IU/mL and NPS=1 for each nostril or unilateral nostril) would benefit. Secondly, 4 RCTs were all in adults and no available data for children. Thirdly, because the longest follow-up of 4 RCTs was only up to 26 weeks, there were too short to comprehensively and adequately assess the risks of side effect, RSCS, and RNS. Finally, there were only 4 RCTs (<10), so a possibility of publication bias was not assessed by constructing a funnel plot in this systematic review[21].

Conclusions

To the best of our knowledge, this was the first meta-analysis that identified omalizumab significantly improved endoscopic, clinical, and patient-reported outcomes in moderate to severe CRSwNP and it was safe and well-tolerated. Studies are required to evaluate their effectiveness in patients with less severe diseases and their cost in the treatment.

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N/A.

Contributors

Concept and design: R Zheng and Q.T Yang. Acquisition, analysis, or interpretation of data: Q.W Wu, L.X Yuan, H.J Qiu, X.Y Wang, and X.K Huang. Drafting of the manuscript: Q.W Wu and L.X Yuan. Critical revision of the manuscript for important

intellectual content: R Zheng and Q.T Yang. Statistical analysis: L.X Yuan. Supervision: R Zheng and Q.T Yang.

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Competing interests

No potential conflict of interest was reported by the authors.

Patient consent for publication

Not required.

Patient and public involvement

No patients were involved in the development of the research question, selection of the outcome measures, design and implementation of the study, or interpretation of the results.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information.

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355 **Appendix 1.** Search strategies

PubMed
1. nasal polyps[MeSH Terms] 2. ((((nasal polyp*[Title/Abstract]) OR (nasal papilloma[Title/Abstract])) OR (nose polyp*[Title/Abstract])) OR (nasi papilloma[Title/Abstract])) OR (nasi polyposis[Title/Abstract]) 3. #1 OR #2 4. sinusitis[MeSH Terms] 5. ((((((chronic rhinosinusitis[Title/Abstract]) OR (rhinopolyp*[Title/Abstract])) OR (CRSwNP[Title/Abstract])) OR (sinus Infection*[Title/Abstract])) OR (rhinitis[Title/Abstract])) OR (pansinusitis[Title/Abstract])) OR (sphenoid* sinusitis[Title/Abstract]) 6. #4 OR #5 7. omalizumab[MeSH Terms] 8. (((Xolair[Title/Abstract]) OR (anti-IgE antibody[Title/Abstract])) OR (anti-IgE monoclonal antibody[Title/Abstract])) OR (anti-IgE mAb[Title/Abstract]) 9. #7 OR #8 10. #3 OR #6 11. #9 AND #10
Cochrane Library
1. MeSH descriptor: [Nasal Polyps] explode all trees 2. (nasal polyp*):ti,ab,kw OR (nasal papilloma):ti,ab,kw OR (nose polyp*):ti,ab,kw OR (nasi 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. (chronic rhinosinusitis):ti,ab,kw OR (rhinopolyp*):ti,ab,kw OR (CRSwNP):ti,ab,kw OR (sinus infection*):ti,ab,kw OR (rhinitis):ti,ab,kw (Word variations have been searched) 6. #4 OR #5 7. (pansinusitis):ti,ab,kw OR (sphenoid* sinusitis):ti,ab,kw (Word variations have been searched) 8. #6 OR #7 9. MeSH descriptor: [Omalizumab] explode all trees 10. (Xolair):ti,ab,kw OR (anti-IgE antibody):ti,ab,kw OR (anti-IgE monoclonal antibody):ti,ab,kw OR (anti-IgE mAb):ti,ab,kw (Word variations have been searched) 11. #9 OR #10 12. #3 OR #8 13. #11 AND #12
Embase

1. 'nose polyp'/exp 2. 'nasal polyp*' OR 'nasal papilloma'/exp OR 'nasal papilloma' OR 'nose polyp*' OR 'nasi papilloma' OR 'nasi polyposis':ab,ti 3. #1 OR #2 4. 'sinusitis'/exp 5. 'chronic rhinosinusitis rhinopolyp*' OR crswnp OR 'sinus infection*' OR rhinitis OR pansinusitis OR 'sphenoid* sinusitis':ab,ti 6. #4 OR #5 7. #3 OR #6 8. 'omalizumab'/exp 9. 'xolair' OR 'anti-ige antibody' OR 'anti-ige monoclonal antibody' OR 'anti-ige mab':ab,ti 10. #8 OR #9 11. #7 AND #10 12. #7 AND #10 AND [medline]/lim 13. #11 NOT #12
Web of Science
1. TOPIC: (nasal polyp*) OR TOPIC: (nasal papilloma) OR TOPIC: (nose polyp*) OR TOPIC: (nasi papilloma) OR TOPIC: (nasi polyposis) 2. TOPIC: (sinusitis) OR TOPIC: (chronic rhinosinusitis) OR TOPIC: (rhinopolyp*) OR TOPIC: (CRSwNP) OR TOPIC: (sinus Infection*) OR TOPIC: (rhinitis) OR TOPIC: (pansinusitis) OR TOPIC: (sphenoid* sinusitis) 3. #1 OR #2 4. TOPIC: (omalizumab) OR TOPIC: (Xolair) OR TOPIC: (anti-IgE antibody) OR TOPIC: (anti-IgE monoclonal antibody) OR TOPIC: (anti-IgE mAb) 5. #3 AND #4

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Figure 1. PRISMA flow diagram of the literature search.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

Figure 4. Meta-analyses of omalizumab versus placebo, comparing efficacy and safety. Outcomes assessed are: (A) Nasal polyps score (NPS), (B) Nasal congestion score (NCS), (C) Sino-Nasal Outcome Test-22 (SNOT-22), and (D) Total nasal symptom score (TNSS).

Figure 5. Meta-analyses of omalizumab versus placebo, comparing efficacy and safety. Outcomes assessed are: (A) Serious adverse events (SAEs), (B) Adverse events (AEs), (C) Rescue systemic corticosteroid (RSCS), and (D) Reduced need for surgery (RNS).

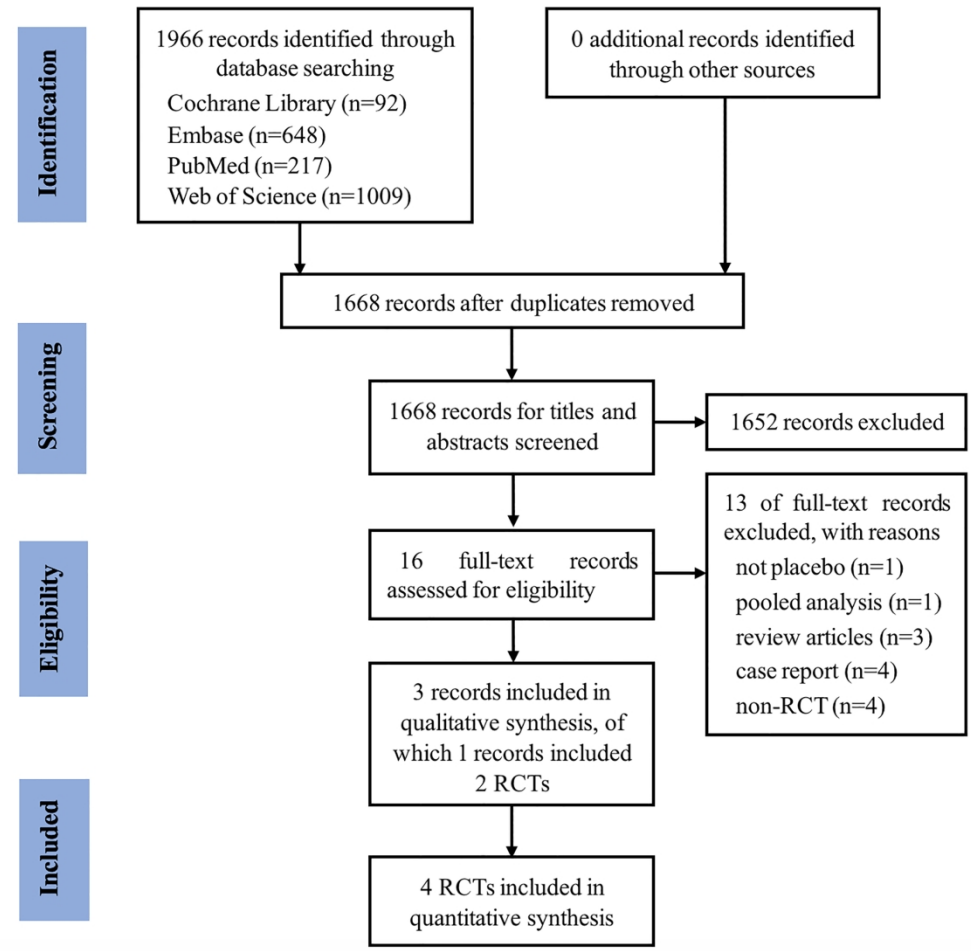

Figure 1. PRISMA flow diagram of the literature search.

231x220mm (300 x 300 DPI)

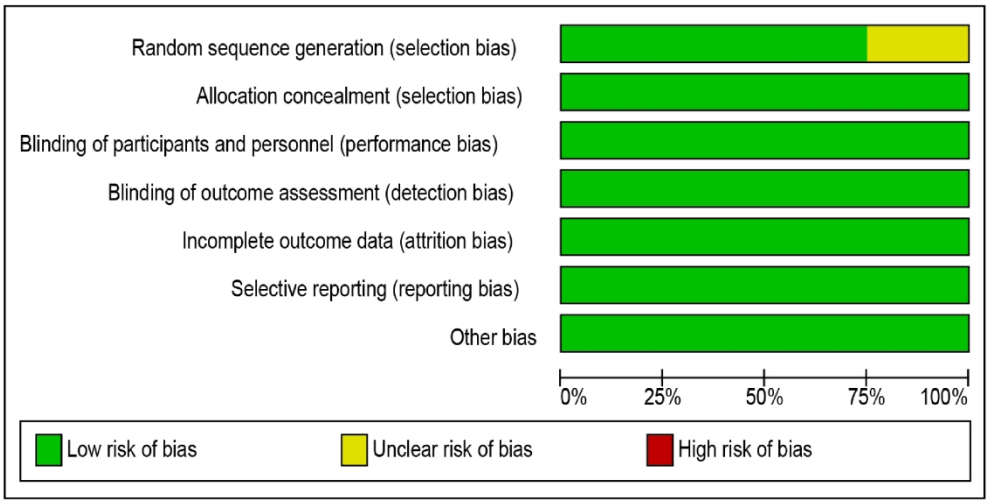

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

209x107mm (300 x 300 DPI)

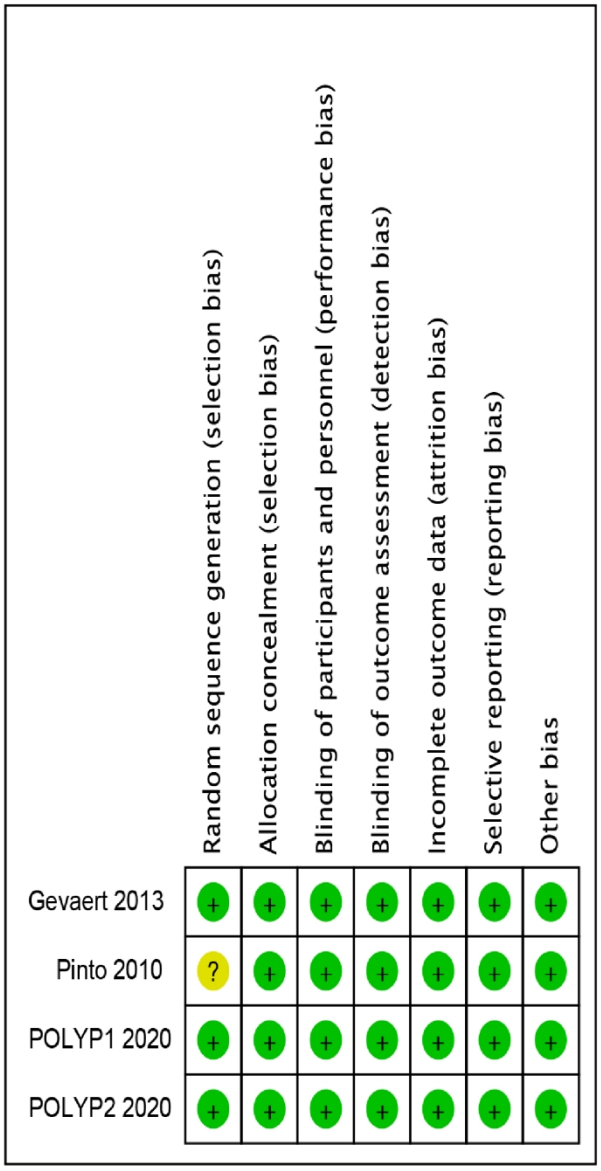

Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

107x204mm (300 x 300 DPI)

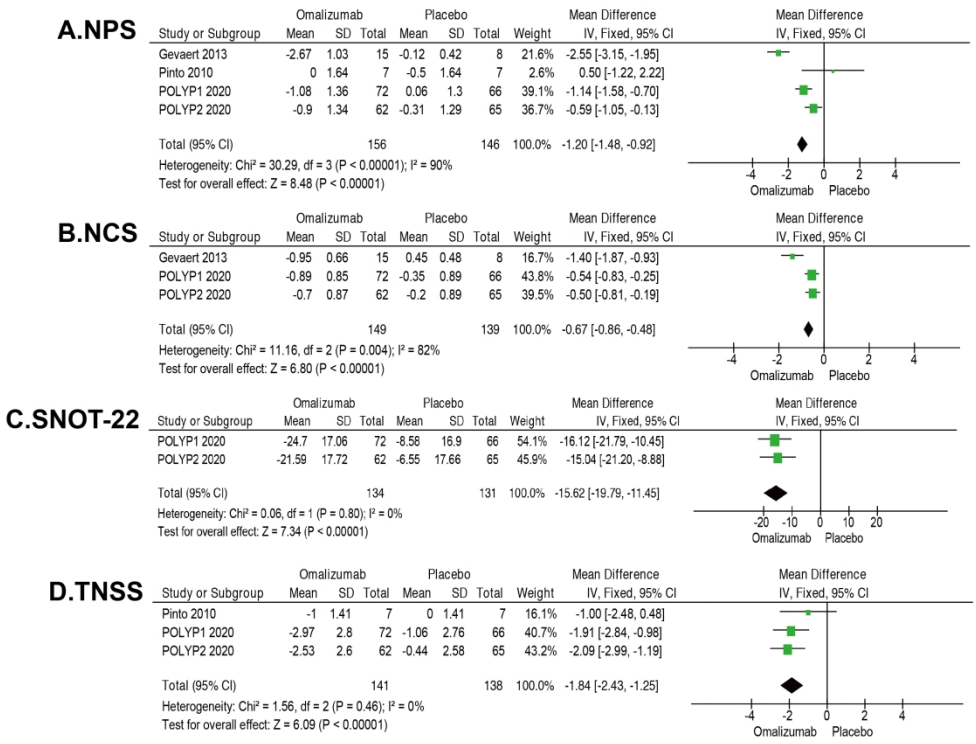

Figure 4. Meta-analyses of omalizumab versus placebo, comparing efficacy and safety. Outcomes assessed are: (A) Nasal polyps score (NPS), (B) Nasal congestion score (NCS), (C) Sino-Nasal Outcome Test-22 (SNOT-22), and (D) Total nasal symptom score (TNSS).

244x184mm (300 x 300 DPI)

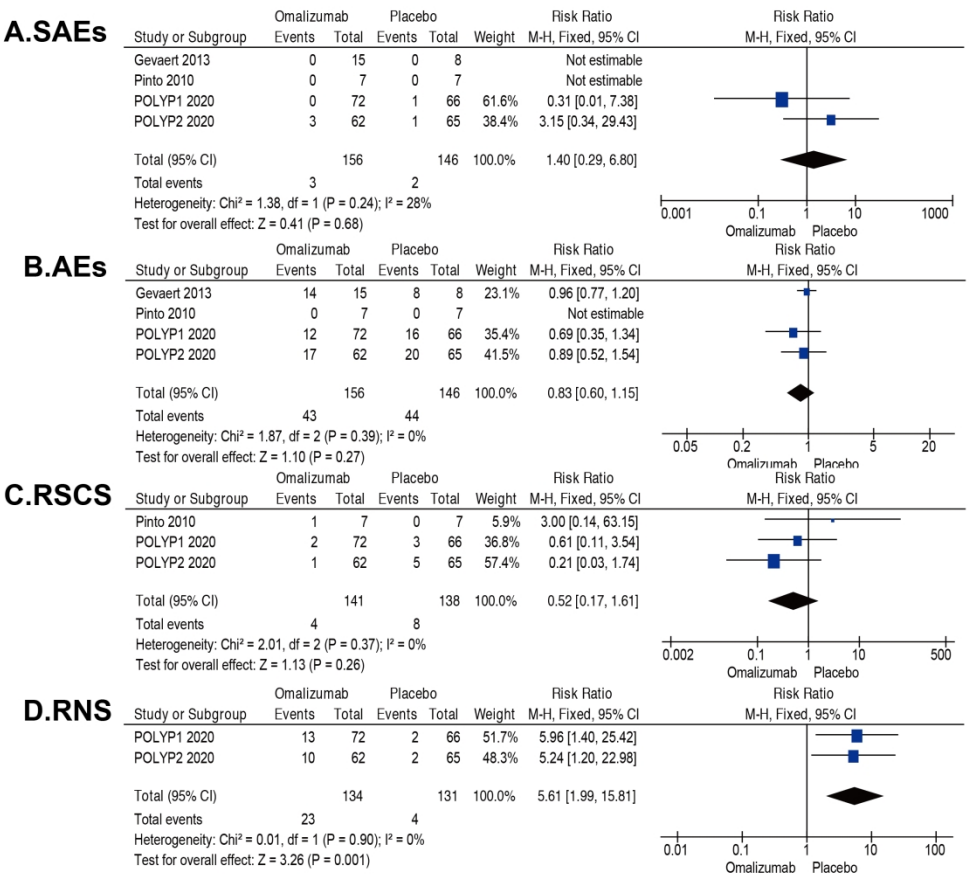

Figure 5. Meta-analyses of omalizumab versus placebo, comparing efficacy and safety. Outcomes assessed are: (A) Serious adverse events (SAEs), (B) Adverse events (AEs), (C) Rescue systemic corticosteroid (RSCS), and (D) Reduced need for surgery (RNS).

220x203mm (300 x 300 DPI)

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
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
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.	5
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.	5
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.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
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).	5
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.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
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.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
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.	6-7

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.	8, 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.	8, 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).	10; Figure 2 and 3
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.	11-12; Figure 4 and 5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-12; Figure 4 and 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]).	n/a
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			

PRISMA 2009 Checklist

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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BMJ Open

Efficacy and safety of omalizumab in chronic rhinosinusitis with nasal polyps: a systematic review and meta-analysis of randomized controlled trials

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Primary Subject Heading:	Ear, nose and throat/otolaryngology
Secondary Subject Heading:	Ear, nose and throat/otolaryngology
Keywords:	Adult otolaryngology < OTOLARYNGOLOGY, Endoscopic surgery < OTOLARYNGOLOGY, Adverse events < THERAPEUTICS, Clinical trials < THERAPEUTICS

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Efficacy and safety of omalizumab in chronic rhinosinusitis with nasal polyps: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Objectives

To assess the efficacy and safety of omalizumab for chronic rhinosinusitis with nasal polyps (CRSwNP) and to identify evidence gaps that will guide future research on omalizumab for CRSwNP.

Design

Systematic review and meta-analysis.

Data Sources

A comprehensive search was performed in PubMed, Embase, Web of Science, and the Cochrane Library on 13 October 2020.

Eligibility Criteria

Randomized controlled trials (RCTs) comparing omalizumab with placebo, given for at least 16 weeks in adult patients with CRSwNP.

Data extraction and synthesis

Two independent authors screened search results, extracted data and assessed studies using the Cochrane risk of bias tool. Data were pooled using the inverse-variance method and expressed as mean differences (MDs) with 95% CIs. Heterogeneity was assessed by the Chi^2 test and the I^2 statistic.

Results

A total of 4 RCTs involving 303 participants were identified. When comparing omalizumab to placebo, there was a significant difference in nasal polyps score (mean

difference (MD) = -1.20; 95% confidence interval (CI), -1.48 to -0.92), nasal congestion score (MD = -0.67; 95% CI, -0.86 to -0.48), Sino-Nasal Outcome Test-22 (MD = -15.62; 95% CI, -19.79 to -11.45), total nasal symptom score (MD = -1.84; 95% CI, -2.43 to -1.25), and reduced need for surgery (risk ratio (RR) = 5.61; 95% CI, 1.99 to 15.81). Furthermore, there was no difference in the risk of serious adverse events ((RR = 1.40; 95% CI, 0.29 to 6.80), adverse events (RR = 0.83; 95% CI, 0.60 to 1.15) and rescue systemic corticosteroid (RR = 0.52; 95% CI, 0.17 to 1.61).

Conclusions

This was the first meta-analysis that identified omalizumab significantly improved endoscopic, clinical, and patient-reported outcomes in adults with moderate to severe CRSwNP and it was safe and well-tolerated.

PROSPERO registration number

CRD42020207639.

Keywords: omalizumab; anti-IgE antibody; chronic rhinosinusitis; nasal polyps; systematic review; meta-analysis

Strengths and limitation of this study

1. This systematic review and meta-analysis was based on a comprehensive search and included RCTs.
2. Studies were low risk of bias, which was assessed by the Cochrane risk of bias tool.
3. Because the longest follow-up of 4 RCTs was only up to 26 weeks, there were too short to comprehensively and adequately assess the risks of side effect.

Introduction

Chronic rhinosinusitis (CRS) is common and affects up to 5-12% of the general population[1]. It is defined as inflammation of the nose and the paranasal sinuses characterized by nasal congestion, nasal discharge, facial pressure, and loss of smell. CRS with nasal polyps (CRSwNP) is a severe form of CRS and accounts for 18% of patients with CRS[2]. CRSwNP is associated with adult-onset asthma, decreased health-related quality of life (HRQoL)[3, 4], and substantial economic burden[5]. Many patients with CRSwNP often fail to achieve sufficient benefit from intranasal corticosteroids (INCS) or systemic corticosteroids (SCS) and/ or functional endoscopic sinus surgery (FESS)[6]. Although FESS may be successful initially, relapse occurs in 20% of patients after 12 months[7], in 40% after 18 months[8], and in 80% after 12 years despite ongoing INCS therapy[9]. Therefore, novel treatments such as biologics are needed for CRSwNP.

Omalizumab (anti-IgE antibody) is one of the biologics and may help patients with severe CRSwNP. It was reported that omalizumab made their symptom better and shrank their polyps in small-size randomized controlled trials (RCTs)[10, 11]. But some of its effectiveness and safety are not well known. Thus, some systematic reviews were conducted to assess the effectiveness and safety of it. But they found very little information or insufficient evidence about the use of omalizumab and cannot determine whether it was effective or not[12, 13]. Currently, some well-designed RCTs about omalizumab for CRSwNP were published[14], which may provide us with some evidence. Therefore, this systematic review was conducted to evaluate the efficacy and safety of

omalizumab versus placebo in adult patients with CRSwNP, and identify evidence gaps that will guide future research on omalizumab for CRSwNP.

Methods

We performed a systematic review based on a priori protocol that was registered with PROSPERO (No. CRD42020207639)[15]. This review was reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement[16] (Additional file 1).

Eligibility criteria

(a) Population: adult patients (>18) with CRSwNP; (b) Intervention and comparison: studies comparing omalizumab with placebo, given for at least 16 weeks; (c) Primary outcomes: nasal polyps score, nasal congestion score, and Sino-Nasal Outcome Test-22 score; Secondary outcomes: total nasal symptom score, serious adverse events, adverse events, rescue systemic corticosteroid, and reduced need for surgery. (d) Study design: randomized controlled trials (RCTs); (e) Studies written and published in the English language were included.

Search strategy and selection process

A comprehensive search was performed in PubMed, Embase, Web of Science, and the Cochrane Library on 13 October 2020. We used the following combined text and MeSH terms: “nasal polyps”, “sinusitis” and “omalizumab”. Search strategies for major databases are provided in Appendix 1.

Titles and abstracts of the retrieved articles were then screened for their potential

relevance by two reviewers (Q.W Wu and L.X Yuan). The full-text articles were obtained and assessed by the same reviewers to determine whether they met the inclusion criteria for this review. We resolved any differences by a discussion with a third author (Q.T Yang).

Data extraction

Two reviewers (H.J Qiu and X.Y Wang) read full-text articles and extracted data using a pre-defined extraction form. Data were extracted on the following: first author, year of publication, patient characteristics, study methods, and outcome data.

Assessment of risk of bias

In this review, the original version of the Cochrane 'Risk of bias' tool was used to assess the risk of bias in included studies. The risk of bias was assessed as 'low', 'high' or 'unclear' for each of the following six domains: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessment; incomplete outcome data; selective reporting; other sources of bias (if required).

Statistical analysis

Study characteristics were 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 methods. For continuous outcomes, a generic inverse-variance method with fixed-effects models was used to calculate pooled mean differences and 95% confidence interval. Statistical heterogeneity was assessed by the Chi^2 test (with a significance level set at P value <0.10) and the I^2 statistic ($I^2 \geqslant 50\%$ indicates

substantial heterogeneity). There are two large pharma-sponsored RCTs with most of the information and two smaller RCTs with effect sizes much larger and much smaller than the two main studies. A random-effects meta-analysis may exacerbate the effects of the bias and a fixed-effect analysis will be affected less, although strictly fixed-effect analysis will also be inappropriate.[17] Therefore, we choose a fixed-effect analysis in this study. Sensitivity analysis were performed, which included the removal of each single study from the meta-analysis one at a time and recalculation of the summary effect. The possibility of publication bias was assessed by constructing a funnel plot if sufficient studies (>10) were available for an outcome. All meta-analysis were conducted by the Review Manager (version 5.3).

Results

Study selection

We identified 1966 studies, of which 3 (with data for 302 participants) were included in our analysis (Figure 1). The 3 studies (Pinto 2010[10], Gevaert 2013[11], and Gavaert 2020[14]) were published between 2010 and 2020, of which Gavaert 2020 reported 2 RCTs (POLYP1 2020 and POLYP2 2020).

Study characteristics

A summary of key participant characteristics, interventions, and comparison pairs was shown in Table 1. Except for 2 participants in Pinto 2010, all the participants were adults with CRSwNP. All the studies were double-blind RCTs and used a placebo. Study duration ranged from 20 weeks to 26 weeks.

147 **Table 1.** Summary of characteristics of included RCTs

Study, year	Population	Comorbidity	Omalizumab*	Placebo	Treatment length	Follow-up length	Age (y), mean (Range)		Male, no.(%)	
							Omalizumab	Placebo	Omalizumab	Placebo
Pinto 2010[10] (n = 14)	CRSwNP (all had undergone endoscopic sinus surgery)	inhaled asthma therapy (72% (5/7) in omalizumab group and 43% (3/7) in placebo group)	subcutaneously	injection, same dose and frequency	26 weeks	26 weeks	43.1 (18-75)	48.6 (18-75)	3 (43%)	7 (100%)
Gevaert[11] 2013 (n = 24)	CRSwNP	asthma (100%)	subcutaneously	injection, same dose and frequency	16 weeks	20 weeks	50 (≥18)	45 (≥18)	12 (80%)	4 (50%)
POLYP1[14] 2020 (n = 138)	CRSwNP	asthma (58.3% (42/72) in omalizumab group and 48.5% (32/66) in placebo group	subcutaneously	injection, same dose and frequency	24 weeks	24 weeks	50.0 (18-75)	52.2 (18-75)	47 (65.3)	41 (62.1)
POLYP2[14] 2020 (n = 127)	CRSwNP	asthma (61.3% (38/62) in omalizumab group and 60% (39/65) in placebo group)	subcutaneously	injection, same dose and frequency	24 weeks	24 weeks	49.0 (18-75)	51.0 (18-75)	39 (62.9)	44 (67.7)

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*omalizumab subcutaneously (every 2 week or every month injections), based on total serum IgE levels and body weight, with a maximum dose of 375 mg; CRSwNP: chronic rhinosinusitis with nasal polyps; RCTs: randomized controlled trials.

Risk of bias and quality of the clinical trials

There were 4 RCTs included in this review. Overall the risk of bias was low, except the random sequence generation of Pinto 2010 was unclear. Our judgments about each risk of bias item presented as percentages across all included studies were shown in Figure 2. Our judgments about each risk of bias item for each included study were shown in Figure 3.

Primary outcomes

Total nasal polyps score (NPS) ranges from 0 to 8 (sum of 0-4 for left and right nasal passage scores per participant), with a lower score indicating smaller-sized nasal polyps and the highest score indicating large polyps causing complete obstruction of the inferior nasal cavity.

The mean difference (MD) in the change of NPS was -1.20 (95% confidence interval (CI), -1.48 to -0.92; 4 RCTs; 302 participants; $I^2 = 90\%$; Figure 4A). We noted the high I^2 value and Pinto 2020 had no significant reduction in NPS. However, the removal of Pinto 2020 did not change the overall effect size in sensitivity analyses. Therefore, we considered the certainty of the evidence to be high despite the large I^2 value.

Nasal congestion score (NCS) was assessed daily by the participant via an electronic diary as the response to the following question: Is your nose blocked? The four available response options were scored from 0 (no symptoms) to 3 (severe symptoms). The pooled mean difference of NCS is -0.67 favoring the groups receiving omalizumab (95% CI, -0.86 to -0.48; 3 RCTs; 288 participants; $I^2 = 82\%$; Figure 4B). Although the

heterogeneity was high in this analysis, all 3 RCTs showed a significant reduction in NCS with omalizumab.

The mean difference in the change of Sino-Nasal Outcome Test-22 (SNOT-22) score was 15.62 points lower in participants who received omalizumab (MD = -15.62; 95% CI, -19.79 to -11.45; 265 participants; $I^2 = 0\%$; Figure 4C). There was an improvement of at least the minimal clinically important difference (MCID; ≥8.9 points).[18] Because the different measuring tools (Pinto 2010, SNOT-20; Gevaert 2013, Short-Form Health Questionnaire (SF-36)) and unavailable data , these 2 RCTs were excluded in this pooled analysis.

Secondary outcomes

Total nasal symptom score (TNSS) was defined as the sum of the scores for nasal congestion score, anterior rhinorrhea score, posterior rhinorrhea score, and sense of smell score, ranging from 0 (no symptoms) to 12 (most severe symptoms).

The mean difference in the change of TNSS was 1.84 points lower in omalizumab group (MD = -1.84; 95% CI, -2.43 to -1.25; 3 RCTs; 279 participants; $I^2 = 0\%$; Figure 4D).

No serious adverse events (SAEs) were reported in Gevaert 2013 and Pinto 2010. However, POLYP1 2020 reported 1 case in the placebo group with myocardial infarction and POLYP2 2020 reported 1 case of pneumonia in the placebo group and 3 cases in the omalizumab group (1 snake bite, 1 hand fracture, and 1 asthma exacerbation). The pooled result indicated that there was no difference in the risk of

SAEs (risk ratio (RR) = 1.40; 95% CI, 0.29 to 6.80; 4 RCTs; 302 participants; $I^2 = 28\%$; Figure 5A).

There was no difference in the risk of adverse events (AEs) (RR = 0.83; 95% CI, 0.60 to 1.15; 4 RCTs; 302 participants; $I^2 = 0\%$; Figure 5B). It was uncertain where or not there was a difference in the risk of rescue systemic corticosteroid (RSCS; RR = 0.52; 95% CI, 0.17 to 1.61; 3 RCTs; 279 participants; $I^2 = 0\%$; Figure 5C).

Reduced need for surgery (RNS) through week 24 was defined as achievement of NPS of 4 or lower (≤2 for each nostril). POLYP1 2020 and POLYP2 2020 reported the number of RNS. The proportion was higher in the group that received omalizumab (RR = 5.61; 95% CI, 1.99 to 15.81; 2 RCTs; 265 participants; $I^2 = 0\%$; Figure 5D).

Discussion

Principal findings

This systematic review and meta-analysis identified 4 RCTs with 302 participants evaluating the efficacy and safety of omalizumab in CRSwNP. It showed that omalizumab significantly improved the size of nasal polyps (measured by NPS), symptoms (measured by NCS and TNSS), and Health-related quality of life (HRQoL; measured by SNOT-22), and reduce the need for surgery (measured by RNS). What's more, there was no difference in the risk of SAEs, AEs, and RSCS.

Comparison with other studies

Hong included two studies (Gavaert 2013 and Pinto 2010) and made a narrative systematic review[12]. They concluded that there was insufficient evidence to determine the effectiveness of omalizumab for CRS. In Chong's systematic review and meta-analysis, there were 3 small studies with 65 participants (Gavaert 2013, Pinto 2010, and NCT01066104) evaluated omalizumab[13]. Their results also showed that there were very uncertain about the effect of omalizumab on disease-specific HRQoL, severe adverse events, the extent of disease (CT scan scores), generic HRQoL, and adverse effects. NCT01066104[19] included in Chong's review was unpublished data, so it was excluded in our study according to our inclusion criteria.

Implication for future research and clinical practice

Patients with CRSwNP and comorbid asthma often have a high symptom burden, substantial impact on HRQoL, a higher risk of RSCS and revision surgery[1]. Moreover,

patients with asthma are more likely to develop CRSwNP than are those without asthma, and they are more likely to receive more oral corticosteroid courses.[20] Therefore, the risk of RSCS may be due to asthma comorbidity.

There were 4 RCTs included in this systematic review, which recruited patients with moderate to severe CRSwNP. The patients in omalizumab group reduced disease severity and need for surgery, and experienced significant improvements in HRQoL (measured by SNOT-22). Placebo-corrected improvements of SNOT-22 was 15.6 points, which exceeded the commonly accepted MCID of 8.9 points.[18, 21] Furthermore, there was no increased risk of SAEs and AEs in patients treated with omalizumab. Thus, it was certain that omalizumab significantly improved endoscopic, clinical, and patient-reported outcomes in moderate to severe CRSwNP and it was well tolerated.

However, it is still unknown that omalizumab is effective in patients with less severe CRSwNP (such as NPS=1 for each nostril or unilateral nostril) and more affordable compared to conventional treatment with topical and systemic corticosteroids and surgery. Therefore, studies are required to evaluate their effectiveness in patients with less severe diseases and their cost in the treatment. In addition, long-term observational studies are also required to determine if omalizumab lose its effectiveness over time, or whether there are any late adverse events.

Limitations of the study

Despite the strict methodology of this systematic review and meta-analysis using PRISMA guidelines, certain limitations should be considered. First, 4 RCTs were

recruited from the same group with moderate to severe CRSwNP. Therefore, there is no evidence on whether or not patients with less severe CRSwNP (NPS=1 for each nostril or unilateral nostril) would benefit. Secondly, 4 RCTs were all in adults and no available data for children. Thirdly, because the longest follow-up of 4 RCTs was only up to 26 weeks, there were too short to comprehensively and adequately assess the risks of side effect, RSCS, and RNS. Finally, there were only 4 RCTs (<10), so a possibility of publication bias was not assessed by constructing a funnel plot in this systematic review[17].

Conclusions

To the best of our knowledge, this was the first meta-analysis that identified omalizumab significantly improved endoscopic, clinical, and patient-reported outcomes in moderate to severe CRSwNP and it was safe and well-tolerated. Studies are required to evaluate their effectiveness in patients with less severe diseases and their cost in the treatment.

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N/A.

Contributors

Concept and design: R Zheng and Q.T Yang. Acquisition, analysis, or interpretation of data: Q.W Wu, L.X Yuan, H.J Qiu, X.Y Wang, and X.K Huang. Drafting of the manuscript: Q.W Wu and L.X Yuan. Critical revision of the manuscript for important

intellectual content: R Zheng and Q.T Yang. Statistical analysis: L.X Yuan. Supervision: R Zheng and Q.T Yang.

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Competing interests

No potential conflict of interest was reported by the authors.

Patient consent for publication

Not required.

Patient and public involvement

No patients were involved in the development of the research question, selection of the outcome measures, design and implementation of the study, or interpretation of the results.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information.

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Ethics approval

It was not required.

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Figure 1. PRISMA flow diagram of the literature search.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

Figure 4. Meta-analyses of omalizumab versus placebo, comparing efficacy and safety. Outcomes assessed are: (A) Nasal polyps score (NPS), (B) Nasal congestion score (NCS), (C) Sino-Nasal Outcome Test-22 (SNOT-22), and (D) Total nasal symptom score (TNSS).

Figure 5. Meta-analyses of omalizumab versus placebo, comparing efficacy and safety. Outcomes assessed are: (A) Serious adverse events (SAEs), (B) Adverse events (AEs), (C) Rescue systemic corticosteroid (RSCS), and (D) Reduced need for surgery (RNS).

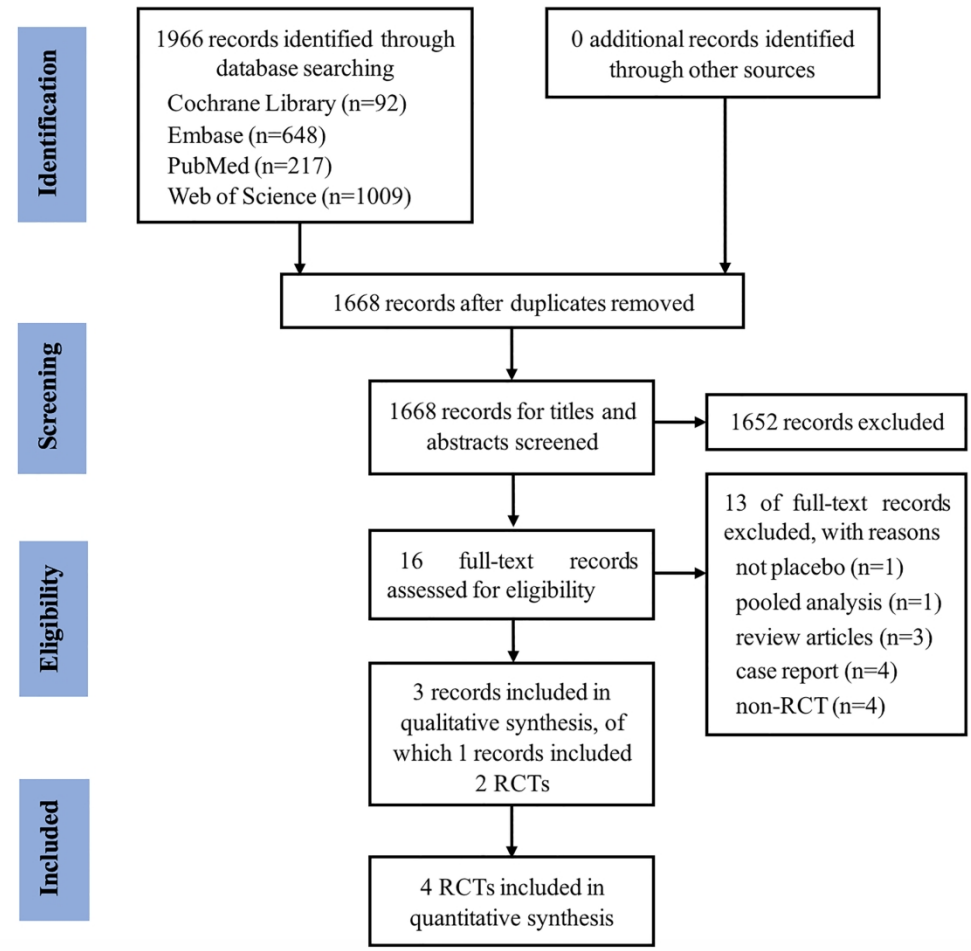

Figure 1. PRISMA flow diagram of the literature search.

231x220mm (300 x 300 DPI)

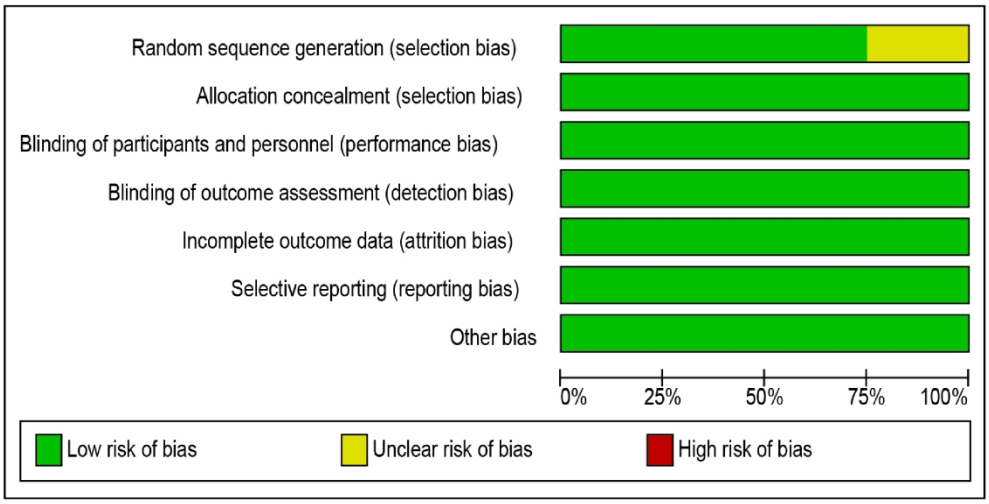

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

209x107mm (300 x 300 DPI)

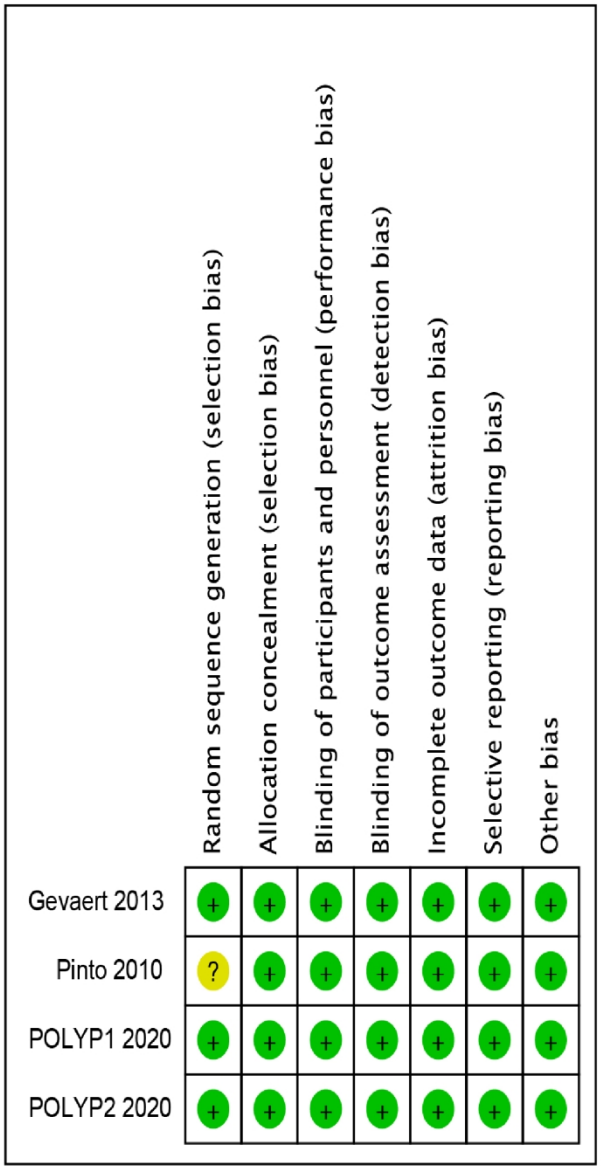

Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

107x204mm (300 x 300 DPI)

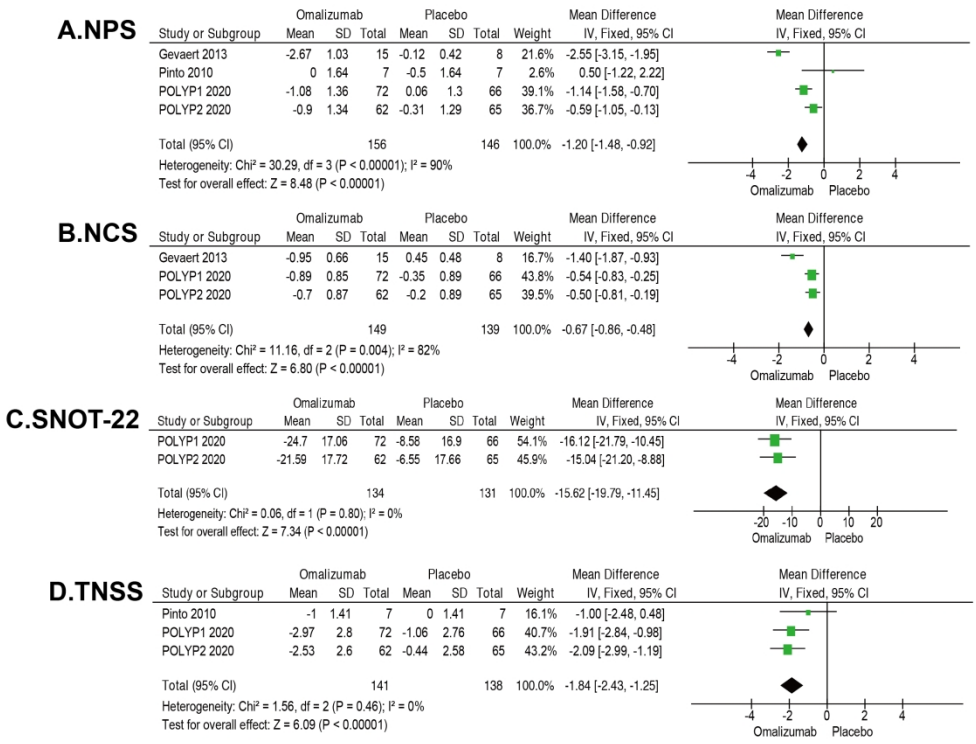

Figure 4. Meta-analyses of omalizumab versus placebo, comparing efficacy and safety. Outcomes assessed are: (A) Nasal polyps score (NPS), (B) Nasal congestion score (NCS), (C) Sino-Nasal Outcome Test-22 (SNOT-22), and (D) Total nasal symptom score (TNSS).

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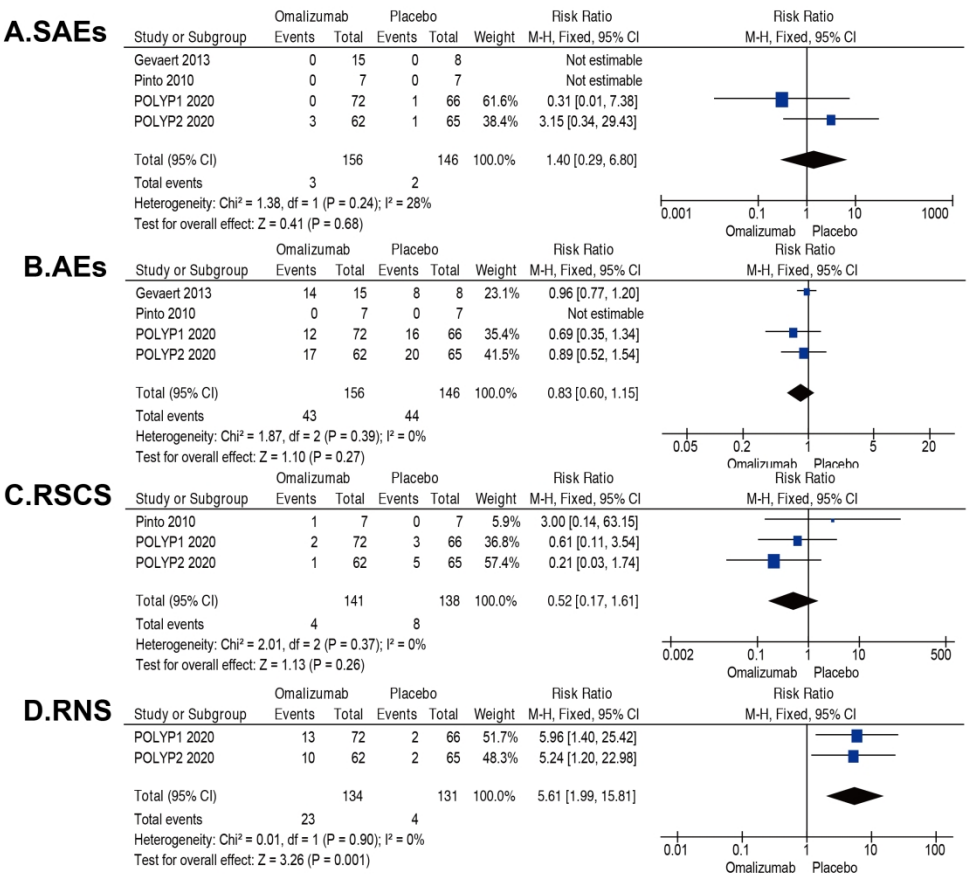

Figure 5. Meta-analyses of omalizumab versus placebo, comparing efficacy and safety. Outcomes assessed are: (A) Serious adverse events (SAEs), (B) Adverse events (AEs), (C) Rescue systemic corticosteroid (RSCS), and (D) Reduced need for surgery (RNS).

220x203mm (300 x 300 DPI)

Appendix. Search strategies

PubMed
1. nasal polyps[MeSH Terms] 2. ((((nasal polyp*[Title/Abstract]) OR (nasal papilloma[Title/Abstract])) OR (nose polyp*[Title/Abstract])) OR (nasi papilloma[Title/Abstract])) OR (nasi polyposis[Title/Abstract]) 3. #1 OR #2 4. sinusitis[MeSH Terms] 5. ((((((chronic rhinosinusitis[Title/Abstract]) OR (rhinopolyp*[Title/Abstract])) OR (CRSwNP[Title/Abstract])) OR (sinus Infection*[Title/Abstract])) OR (rhinitis[Title/Abstract])) OR (pansinusitis[Title/Abstract])) OR (sphenoid* sinusitis[Title/Abstract]) 6. #4 OR #5 7. omalizumab[MeSH Terms] 8. (((Xolair[Title/Abstract]) OR (anti-IgE antibody[Title/Abstract])) OR (anti-IgE monoclonal antibody[Title/Abstract])) OR (anti-IgE mAb[Title/Abstract]) 9. #7 OR #8 10. #3 OR #6 11. #9 AND #10
Cochrane Library
1. MeSH descriptor: [Nasal Polyps] explode all trees 2. (nasal polyp*):ti,ab,kw OR (nasal papilloma):ti,ab,kw OR (nose polyp*):ti,ab,kw OR (nasi 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. (chronic rhinosinusitis):ti,ab,kw OR (rhinopolyp*):ti,ab,kw OR (CRSwNP):ti,ab,kw OR (sinus infection*):ti,ab,kw OR (rhinitis):ti,ab,kw (Word variations have been searched) 6. #4 OR #5 7. (pansinusitis):ti,ab,kw OR (sphenoid* sinusitis):ti,ab,kw (Word variations have been searched) 8. #6 OR #7 9. MeSH descriptor: [Omalizumab] explode all trees 10. (Xolair):ti,ab,kw OR (anti-IgE antibody):ti,ab,kw OR (anti-IgE monoclonal antibody):ti,ab,kw OR (anti-IgE mAb):ti,ab,kw (Word variations have been searched) 11. #9 OR #10 12. #3 OR #8 13. #11 AND #12
Embase
1. 'nose polyp'/exp 2. 'nasal polyp*' OR 'nasal papilloma'/exp OR 'nasal papilloma' OR 'nose polyp*' OR

'nasi papilloma' OR 'nasi polyposis':ab,ti 3. #1 OR #2 4. 'sinusitis'/exp 5. 'chronic rhinosinusitis rhinopolyp*' OR crswnp OR 'sinus infection*' OR rhinitis OR pansinusitis OR 'sphenoid* sinusitis':ab,ti 6. #4 OR #5 7. #3 OR #6 8. 'omalizumab'/exp 9. 'xolair' OR 'anti-ige antibody' OR 'anti-ige monoclonal antibody' OR 'anti-ige mab':ab,ti 10. #8 OR #9 11. #7 AND #10 12. #7 AND #10 AND [medline]/lim 13. #11 NOT #12
Web of Science
1. TOPIC: (nasal polyp*) OR TOPIC: (nasal papilloma) OR TOPIC: (nose polyp*) OR TOPIC: (nasi papilloma) OR TOPIC: (nasi polyposis) 2. TOPIC: (sinusitis) OR TOPIC: (chronic rhinosinusitis) OR TOPIC: (rhinopolyp*) OR TOPIC: (CRSwNP) OR TOPIC: (sinus Infection*) OR TOPIC: (rhinitis) OR TOPIC: (pansinusitis) OR TOPIC: (sphenoid* sinusitis) 3. #1 OR #2 4. TOPIC: (omalizumab) OR TOPIC: (Xolair) OR TOPIC: (anti-IgE antibody) OR TOPIC: (anti-IgE monoclonal antibody) OR TOPIC: (anti-IgE mAb) 5. #3 AND #4

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
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
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.	5
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.	5
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.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
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).	5
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.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
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.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
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.	6-7

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.	8, 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.	8, 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).	10; Figure 2 and 3
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.	11-12; Figure 4 and 5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-12; Figure 4 and 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]).	n/a
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			

PRISMA 2009 Checklist

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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