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Which Is the Best Biologic for Nasal Polyps: Dupilumab, Omalizumab, or Mepolizumab? A Network Meta-Analysis

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Keywords
Nasal polyps · Dupilumab · Omalizumab · Mepolizumab · Network meta-analysis

Abstract
Introduction: Compared with the placebo, biologics are beneficial in reducing nasal polyp mass and safe in patients with chronic rhinosinusitis with nasal polyps (CRSwNP). However, there lacks a head-to-head randomized trial comparing biologics. We aimed to determine the best biologic for CRSwNP. ***Methods:*** We performed a systematic review and network meta-analysis (NMA), which was registered with PROSPERO (No. CRD42021226766). A comprehensive search was performed in PubMed, Embase, Web of Science, and the Cochrane Library on December 29, 2020. Only randomized controlled trials (RCTs) assessing biologics in adult patients for CRSwNP were included. ***Results:*** Nine RCTs with 1,190 patients comparing 3 different biologics (dupilumab, omalizumab, and mepolizumab) and the placebo were included. Dupilumab had the best efficacy in terms of nasal polyp score (NPS), Sino-Nasal Outcome Test-22 (SNOT-22) score, University of Pennsylvania Smell Identification Test (UPSIT) score, and nasal congestion score (NCS) for surface under the cumulative ranking curve (SUCRA) values of 0.900, 0.916, 1.000, and 0.807, respectively. Omalizumab ranked second in efficacy in terms of SNOT-22, UPSIT, and NCS for SUCRA values of 0.606, 0.500, and 0.693, respectively. Mepolizumab ranked second in efficacy in terms of NPS for SUCRA values of 0.563 and had the highest risk of adverse events (AEs) for SUCRA values of 0.746. ***Conclusion:*** This is the first NMA that compared different biologics in patients with CRSwNP. Based on the efficacy (NPS) and safety (AEs), dupilumab is the best choice and omalizumab is the second best option for CRSwNP. Although mepolizumab ranked second in efficacy, it had the highest risk of AEs.

Introduction

Chronic rhinosinusitis (CRS) is a common inflammatory condition affecting more than 8–11% of the population in Asia [1, 2], 10% of the population in Western countries [3]. Eighteen percent of all patients with CRS have the added burden of nasal polyposis [4].

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Knowledge of the inflammatory mechanisms of chronic rhinosinusitis with nasal polyps (CRSwNP) continues to grow [5]. Although there are a variety of pathophysiologic pathways that may result in nasal polyps, a unifying mechanism has not been determined. The large majority of subjects in Europe and North America demonstrate nasal mucosal inflammation characterized by eosinophils and type 2 cytokines [6]. Type 2 CRSwNP is characterized by tissue eosinophilia, upregulation of type 2 cytokines, increased tissue IgE concentrations, and increased serum IgE. Type 2 cytokines comprise IL-4, IL-13, and IL-5, which regulate T- and B-cell activation and IgE synthesis, eosinophil recruitment, survival and activation, epithelial cell activation and mucus production, and macrophage activation and remodeling [7]. It is well known that the percentage of type 2 immune reactions is different all over the world, ranging from 15% to 85% of CRSwNP, for example, in parts of China to Western Europe [8].

The biologics most studied for the treatment of CRSwNP target the typical type 2 cytokines IL-4 and IL-13 via blocking the IL-4 receptor alpha (dupilumab), IL-5 (mepolizumab), and IgE (omalizumab) [9, 10]. Studies indicate that dupilumab [11, 12], mepolizumab [13, 14], and omalizumab [15–17] could be beneficial in reducing nasal polyp mass (nasal polyp score [NPS]) and safe in severe CRSwNP patients [18].

Because there lacks a head-to-head randomized trial comparing biologics, it is difficult for physicians to choose the best biologic for treatment of CRSwNP. Thus, a network meta-analysis (NMA) comparing biologics may help.Despite that NMA is limited by not providing a direct head-to-head comparison between treatments, it allows for indirect comparisons in the absence of trials involving a direct comparison of interventions, and it can provide useful evidence of the relative treatment effects between competing interventions. To compare the efficacy and safety of dupilumab, mepolizumab, and omalizumab in patients with CRSwNP, we used indirect evidence from randomized controlled trials (RCTs) and provided the objective rank of various interventions based on the corresponding surface under the cumulative ranking curve (SUCRA) in this NMA.

Materials and Methods

We performed a systematic review and NMA based on a priori protocol that was registered with PROSPERO (No. CRD42021226766) [19]. This review was reported according to the PRISMA extension statement [20].

Eligibility Criteria

Studies included fulfilled the following eligibility requirements: (a) population: adult patients (≥18 years old and of both sexes) with CRSwNP; (b) intervention and comparison: studies comparing biologics with placebo, given for at least 8 weeks and followed up for at least 16 weeks in double-blind treatment; (c) study design: RCTs; and (d) studies written and published in English.

Search Strategy and Selection Process

We performed a comprehensive search in PubMed, Embase, Web of Science, and the Cochrane Library on December 29, 2020. We used the text words "dupilumab" and "mepolizumab," and the following MeSH terms: "nasal polyps," "sinusitis," "antibodies, monoclonal," and "omalizumab." Search strategies for major databases were provided in online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000519228.

Titles and abstracts of the retrieved articles were screened for their potential relevance by 2 reviewers (Q. Wu and Y. Zhang). The full-text articles were then obtained and assessed by the same reviewers to determine whether they met the inclusion criteria for this systematic review. Any differences were resolved by a discussion with a third author (Q.Yang).

Data Extraction

Two competent reviewers (W. Kong and X. Wang) with more than 5 years of experience in Rhinology read full-text articles and extracted data using a pre-defined extraction form. The 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 systematic 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 6 domains, including sequence generation, allocation concealment, blinding of participants, personnel and outcome assessment, incomplete outcome data, selective reporting, and other sources of bias (if required). We assessed the certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation framework [21].

Outcomes

Our primary outcomes were efficacy (NPS) and safety (adverse events [AEs] measured by the number of subjects who had 1 or more AEs). Secondary outcomes were total Sino-Nasal Outcome Test-22 (SNOT-22) score, University of Pennsylvania Smell Identification Test (UPSIT) score, and nasal congestion score (NCS).

Statistical Analysis

Study characteristics are shown in tables and described narratively. Pair-wise meta-analysis was conducted by Review Manager (version 5.3), and NMA was done using the network and network graphs packages in Stata (version 15.1). For dichotomous data, we analyzed treatment differences as a risk ratio (RR) calculated using the Mantel-Haenszel method. For continuous outcomes, if all data were from the same scale, we pooled mean values obtained at follow-up with change outcomes and reported this as a mean difference (MD). However, if a standard MD (SMD) was used as an effect measure, change and endpoint data were not pooled. Statistical heterogeneity was assessed by the χ^2 test (with a significance

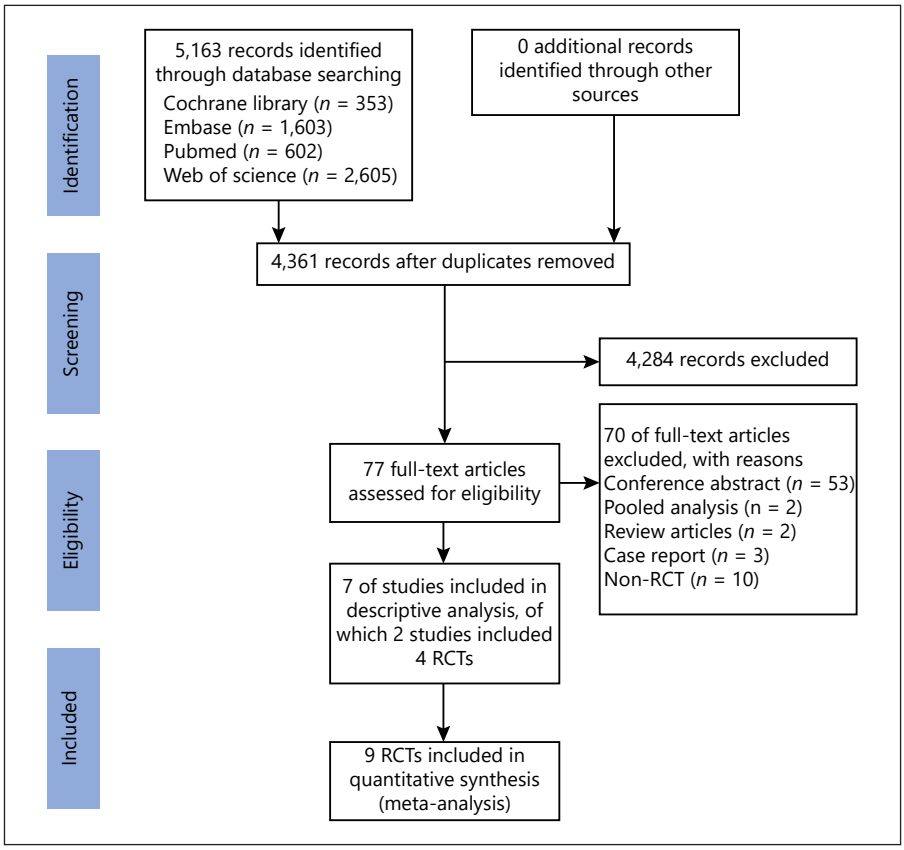

Fig. 1. PRISMA flow diagram of the literature search. RCT, randomized controlled trial.

level set at p value <0.10) and the I^2 statistic. There are large Phase 3 trials that have most of the information and small point-of-care trials with effect sizes much smaller than large Phase 3 trials. 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. To rank the treatments for each outcome, we used the surface under the cumulative ranking curve (SUCRA) and the mean ranks. 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

Figure 1 shows that the initial search identified 5,163 citations; 802 citations were identified as duplicates and removed. After screening the titles and abstracts, the full-texts of 77 potential articles were retrieved for review. Finally, 9 RCTs (7 studies; 1,190 patients) were included in our NMA.

The basic characteristics of the 9 RCTs are summarized in Table 1. All the RCTs included adult patients with CRSwNP, more than half of which had comorbid asthma. Demographics and clinical characteristics were similar between treatment groups and across the studies. The sample size of the included RCTs ranged between 14 and 448 patients. All the RCTs were two-arm. There were 4 RCTs (omalizumab vs. placebo), 3 RCTs (dupilumab vs. placebo), and 2 RCTs (mepolizumab vs. placebo). The available direct comparisons are shown in Figure 2. None of the studies compared the treatments as they all were placebo comparators.

Risk of Bias Assessment

The quality of the included RCTs is shown in online suppl. Figure. 1. Four RCTs were low risk of bias [11–13]. Four RCTs had an unclear risk of bias in random sequence generation and allocation concealment [14–16]. One RCT had an unclear risk of bias in random sequence generation, allocation concealment, and blinding of participants and personnel [17]. Online suppl. Table 2 shows the certainty of evidence assessed by Grading of Recommendations Assessment, Development and Evaluation. It is high for the direct comparisons involving omalizumab, dupilumab, mepolizumab, and placebo and moderate for the indirect comparison involving omalizumab, dupilumab, and mepolizumab.

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Table 1. Summary of characteristics of included RCTs

Study, year	Population	Comorbidity	Intervention	Placebo	Treatment length	Follow-up length	Age (mean, SD), years		Male, *n* (%)	
							inter-vention	placebo	inter-vention	placebo
Pinto 2010 [17] (*n* = 14)	CRSwNP (all had undergone endoscopic sinus surgery)	Inhaled asthma therapy (72% (5/7) in omalizumab group and 43% (3/7) in the placebo group)	Omalizumab Subcutaneously, once or twice monthly (dose dependent on participant weight and the serum IgE level)	Injection, same dose and frequency	26 weeks	26 weeks	43.1 (9.8)	48.6 (9.1)	3 (43)	7 (100)
Gevaert 2013 [15] (*n* = 24)	CRSwNP	Asthma (100%)	Omalizumab Subcutaneously (every 2 weeks/8 injections in total or every month/4 injections in total), based on total serum IgE levels and body weight	Injection, same dose and frequency	16 weeks	20 weeks	50 (44–56)#	45 (42–54)#	12 (80)	4 (50)
POLYP1 2020 [16] (*n* = 138)	CRSwNP	Asthma (58.3% (42/72) in omalizumab group and 48.5% (32/66) in the placebo group	Omalizumab 75–600 mg subcutaneously every 2 or 4 weeks, depended on total serum IgE levels and body weight	Injection, same dose and frequency	24 weeks	24 weeks	50.0 (14.5)	52.2 (11.6)	47 (65.3)	41 (62.1)
POLYP2 2020 [16] (*n* = 127)	CRSwNP	Asthma (61.3% (38/62) in omalizumab group and 60% (39/65) in the placebo group)	Omalizumab 75–600 mg subcutaneously every 2 or 4 weeks, depended on total serum IgE levels and body weight	Injection, same dose and frequency	24 weeks	24 weeks	49.0 (11.9)	51.0 (12.0)	39 (62.9)	44 (67.7)
Bachert 2016 [12] (*n* = 60)	CRSwNP	Asthma (53.3% (16/30) in dupilumab group and 63.3% (19/30) in the placebo group)	Dupilumab 600 mg loading dose subcutaneously, followed by 300 mg every week	Injection, same dose and frequency	15 weeks	16 weeks	47.4 (9.8)	49.3 (9.1)	18 (60.6)	16 (53.3)
SINUS24 2019 [11] (*n* = 276)	CRSwNP	Asthma (57% (82/143) in dupilumab group and 59% (79/133) in the placebo group)	Dupilumab 300 mg subcutaneously every 2 weeks	Injection, same dose and frequency	24 weeks	24 weeks	52 (39–61)#	50 (41–60)#	88 (62)	70 (5)
SINUS52 2019 [11] (*n* = 448)	CRSwNP	Asthma (60% (176/295) in dupilumab group and 59% (91/145) in the placebo group)	(a) Dupilumab 300 mg subcutaneously every 2 weeks for 52 weeks; (b) dupilumab 300 mg subcutaneously every 2 weeks for 24 weeks, followed by every 4 weeks until 52 weeks	Injection, same dose and frequency	52 weeks	24 weeks and 52 weeks	(a) 51 (42–61)#; (b) 53 (42–63)#	53 (44–61)#	(a) 97 (65%); (b) 87 (60)	95 (62)
Gavaert 2011 [14] (*n* = 30)	CRSwNP	Asthma (50% (10/20) in mepolizumab group and 30% (3/10) in the placebo group)	Mepolizumab 750 mg intravenously every 4 weeks	Intravenously, same dose and frequency	8 weeks	48 weeks	50.1 (8.86)	45.9 (11.4)	14 (70)	8 (80)
Bachert 2017 [13] (*n* = 105)	Severe recurrent bilateral nasal polyposis	Asthma (81% (44/54) in mepolizumab group and 75% (38/51) in the placebo group)	Mepolizumab 750 mg intravenously every 4 weeks	Intravenously, same dose and frequency	21 weeks	25 weeks	51 (11)	50 (10)	41 (76)	34 (67)

RCT, randomized controlled trial. * 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.

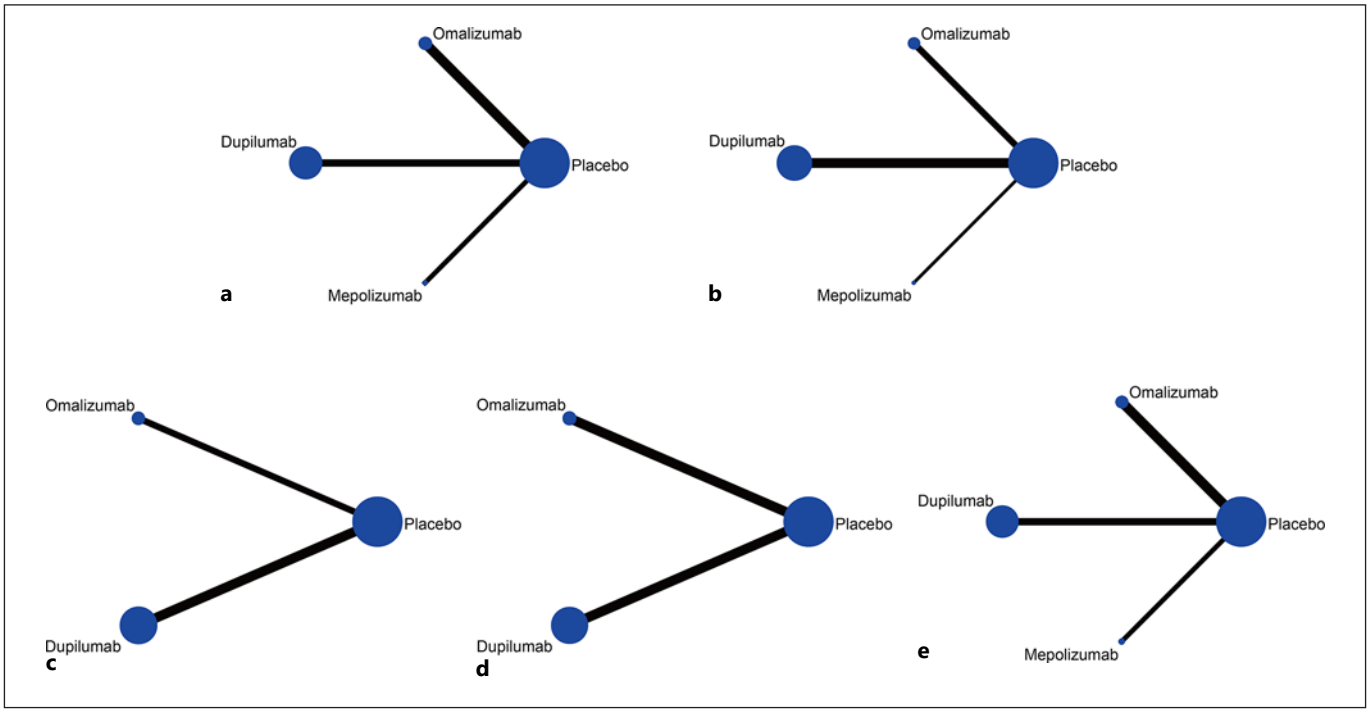


Fig. 2. Evidence network of eligible comparisons for an NMA: NPS (**a**); SNOT-22 (**b**); UPSIT (**c**); NCS (**d**); and AEs (**e**). The width of the lines is proportional to the number of RCTs comparing every pair of treatments, and the size of every node is proportional to the number of participants. NMA, network meta-analysis; NPS, nasal polyp score; SNOT-22, Sino-Nasal Outcome Test-22; UPSIT, University of Pennsylvania Smell Identification Test; NCS, nasal congestion score; AEs, adverse events; RCT, randomized controlled trial.

Pair-Wise Meta-Analysis

Table 2 and online suppl. Figure. 2 show the results of the pair-wise meta-analysis, represented by weighted MD (WMD) or RR with a 95% confidence interval (CI).

NPS: In the pair-wise meta-analysis, omalizumab, dupilumab, and mepolizumab were superior to placebo in terms of NPS (WMD: −1.25, 95% CI: [−1.52, −0.97], p < 0.00001; WMD: −1.89, 95% CI: [−2.15, −1.64], p < 0.00001; WMD: −1.20, 95% CI: [−1.76, −0.65], p < 0.0001, respectively). A greater proportion of omalizumab-versus placebo-treated and mepolizumab-versus placebo-treated patients achieved at least a 1-point (56.3% vs. 28.7% [16]; 50% vs. 27% [13]) improvement in NPS. The proportion of patients achieving at least a 2-point improvement in NPS was higher with dupilumab (46%) than with the placebo (3%) [11].

SNOT-22: Omalizumab and dupilumab were superior to placebo with regards to SNOT-22 in the pair-wise meta-analysis (WMD: −15.62, 95% CI: [−19.79, −11.45], p < 0.00001; WMD: −18.95, 95% CI: [−21.71, −16.19], p < 0.00001, respectively). No significant difference was exhibited in mepolizumab versus placebo (p = 0.11).

UPSIT: In the pair-wise meta-analysis, omalizumab and dupilumab were superior to placebo in terms of UPSIT (WMD: 3.84, 95% CI: [2.19, 5.50], p < 0.00001; WMD: 10.96, 95% CI: [9.72, 12.19], p < 0.00001, respectively). The proportion of patients with anosmia (UPSIT score of ≤18) in the dupilumab groups decreased from 74% to 24% [11]. Smell was assessed by Sniffin' Sticks Screening-12 test not UPSIT in mepolizumab [13] so that there were no data for the meta-analysis.

NCS: Omalizumab and dupilumab were superior to placebo in the terms of NCS in the pair-wise meta-analysis (WMD: −0.67, 95% CI: [−0.87, −0.48], p < 0.00001; WMD: −0.86, 95% CI: [−0.98, −0.73], p < 0.00001, respectively). A 1-point or greater improvement in NCS was observed in 44.4% omalizumab-treated patients and in 21.4% placebo-treated patients [16]. Nasal blockage was assessed by visual analog scale score not NCS in mepolizumab [13] so that there were no data for the meta-analysis.

AEs: No significant differences were exhibited in any pair-wise comparisons in the terms of AEs.

Table 2. Pair-wise meta-analysis comparing NPS, SNOT-22, UPSIT, NCS, and AEs

Comparison	Including RCTs, *n*	Pair-wise meta-analysis		I^2, %
		WMD or RR (95% CI)	*p* value	
NPS				
Omalizumab versus placebo	4	−1.25 (−1.52, −0.97)	<0.00001*	91
Dupilumab versus placebo	3	−1.89 (−2.15, −1.64)	<0.00001*	0
Mepolizumab versus placebo	2	−1.20 (−1.76, −0.65)	<0.0001*	0
SNOT-22				
Omalizumab versus placebo	2	−15.62 (−19.79, −11.45)	<0.00001*	0
Dupilumab versus placebo	3	−18.95 (−21.71, −16.19)	<0.00001*	0
Mepolizumab versus placebo	1	−11.40 (−25.44, 2.64)	0.11	–[#]
UPSIT[&]				
Omalizumab versus placebo	2	3.84 (2.19, 5.50)	<0.00001*	0
Dupilumab versus placebo	3	10.96 (9.72, 12.19)	<0.00001*	51
NCS[&]				
Omalizumab versus placebo	3	−0.67 (−0.87, −0.48)	<0.00001*	83
Dupilumab versus placebo	3	−0.86 (−0.98, −0.73)	<0.00001*	0
AEs				
Omalizumab versus placebo	4	0.88 (0.73, 1.07)	0.21	0
Dupilumab versus placebo	3	0.96 (0.90, 1.03)	0.23	71
Mepolizumab versus placebo	2	1.04 (0.84, 1.29)	0.36	28

RR (95% CI) in blue color. * $p < 0.05$; [#] not compared. [&] In mepolizumab; smell was assessed by the Sniffin' Sticks Screening-12 test and not UPSIT, and nasal blockage was assessed by the visual analog scale score and not UPSIT so that there were no data for the meta-analysis. WMD, weighted mean difference; RR, risk ratio; CI, confidence interval; NPS, nasal polyp score; SNOT-22, Sino-Nasal Outcome Test-22; UPSIT, University of Pennsylvania Smell Identification Test; NCS, nasal congestion score; AEs, adverse events; RCT, randomized controlled trial.

Network Meta-Analysis

Table 3 shows the result of the NMA, represented by WMD or RR with 95% CI.

NPS: The NMA showed that compared with the placebo, omalizumab, dupilumab, and mepolizumab significantly reduced the NPS (WMD: −1.17, 95% CI: [−1.95, −0.39]; WMD: −1.84, 95% CI: [−2.68, −1.01]; WMD: −1.22, 95% CI: [−2.32, −0.11], respectively). However, there were no significant differences among omalizumab, dupilumab, and mepolizumab.

SNOT-22: Compared with the placebo, omalizumab and dupilumab significantly reduced the SNOT-22 in NMA (WMD: −15.62, 95% CI: [−19.79, −11.45]; WMD: −18.95, 95% CI: [−21.71, −16.19], respectively), while mepolizumab did not (WMD: −11.40, 95% CI: [−25.44, 2.64]). There were no significant differences among omalizumab, dupilumab, and mepolizumab in terms of SNOT-22.

UPSIT: In NMA, compared with placebo, omalizumab and dupilumab significantly improved UPSIT (WMD: 3.84, 95% CI [2.19, 5.50]; WMD: 10.96, 95% CI: [9.72, 12.19], respectively). Omalizumab was inferior to dupilumab with regard to UPSIT (WMD: −7.12, 95% CI: [−9.18, −5.05]). There were no data for mepolizumab as its subjects' smell was assessed by Sniffin' Sticks Screening-12 test and not UPSIT [13].

NCS: Compared with the placebo, omalizumab and dupilumab significantly reduced NCS in NMA (WMD: −0.76, 95% CI [−1.12, −0.39]; WMD: −0.83, 95% CI: [−1.16, −0.50], respectively). There was no significant difference between omalizumab and dupilumab in terms of NCS (WMD: 0.07, 95% CI [−0.42, 0.57]). There were no data for mepolizumab as its subjects' nasal blockage was assessed by visual analog scale score and not NCS [13]. AEs: There were no significant differences among all interventions in the patients' AEs.

Surface under the Cumulative Ranking Curve and the Mean Rank

Figure 3 and online suppl. Table 3 present the ranking of treatments based on SUCRA. Dupilumab had the best efficacy in terms of NPS, SNOT-22, UPSIT, and NCS for SUCRA values of 0.900, 0.916, 1.000, and 0.807, respectively. Omalizumab ranked second in efficacy in terms of

Table 3. WMD for NPS, SNOT-22, UPSIT, and NCS and RR for AEs NMA

Variables	WMD or RR (95% CI)			
NPS	Omalizumab			
	0.67 (−0.47, 1.81)	Dupilumab		
	0.05 (−1.30, 1.40)	−0.63 (−2.01, 0.76)	Mepolizumab	
	−1.17 (−1.95, −0.39)*	−1.84 (−2.68, −1.01)*	−1.22 (−2.32,−0.11)*	Placebo
SNOT-22	Omalizumab			
	3.33 (−1.67, 8.33)	Dupilumab		
	−4.22 (−18.87, 10.42)	−7.55 (−21.86, 6.75)	Mepolizumab	
	−15.62 (−19.79, −11.45)*	−18.95 (−21.71, −16.19)*	−11.40 (−25.44,2.64)	Placebo
UPSIT	Omalizumab			
	−7.12 (−9.18, −5.05)*	Dupilumab		
	_#	–	Mepolizumab	
	3.84 (2.19, 5.50)*	10.96 (9.72, 12.19)*	–	Placebo
NCS	Omalizumab			
	0.07 (−0.42, 0.57)	Dupilumab		
	–	–	Mepolizumab	
	−0.76 (−1.12, −0.39)*	−0.83 (−1.16, −0.50)*	–	Placebo
AEs	Omalizumab			
	0.99 (0.53, 1.86)	Dupilumab		
	0.66 (0.26, 1.68)	*0.66 (0.27, 1.63)*	Mepolizumab	
	0.74 (0.46, 1.20)	*0.75 (0.50, 1.12)*	*1.13 (0.50,2.54)*	Placebo

RR (95% CI) in *blue color*; * $p < 0.05$; # not compared. WMD, weighted mean difference; RR, risk ratio; CI, confidence interval; NPS, nasal polyp score; SNOT-22, Sino-Nasal Outcome Test-22; UPSIT, University of Pennsylvania Smell Identification Test; NCS, nasal congestion score; AEs, adverse events; NMA, network meta-analysis.

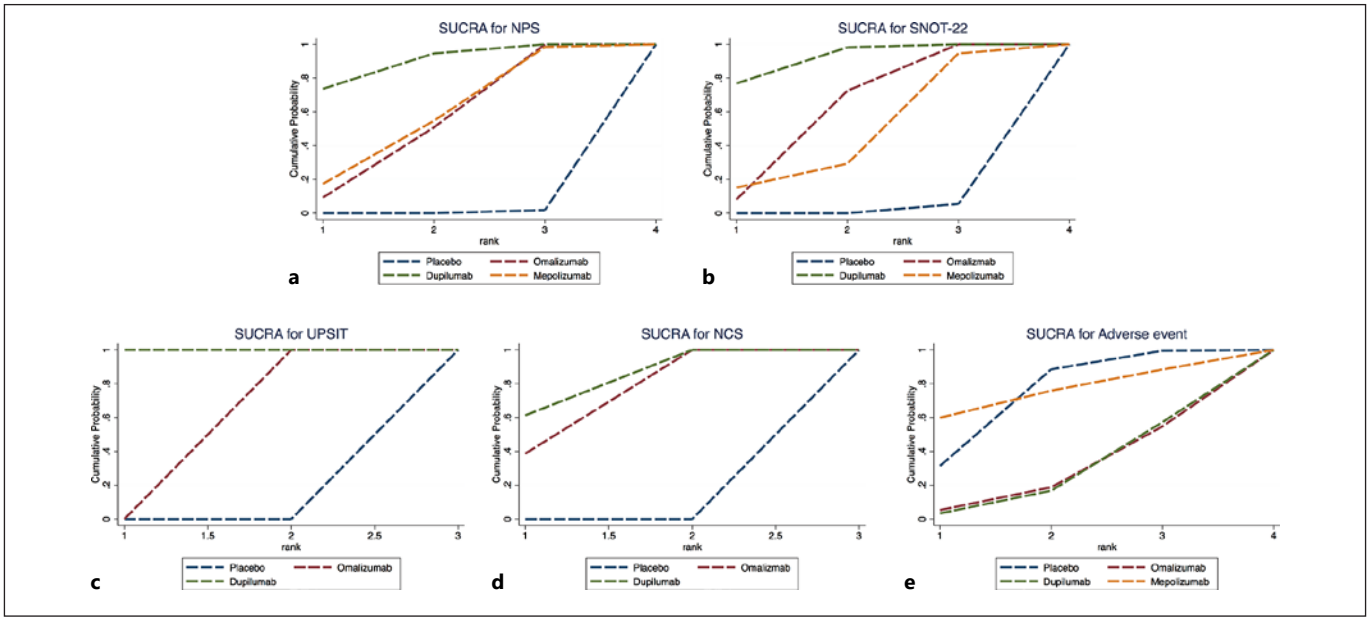


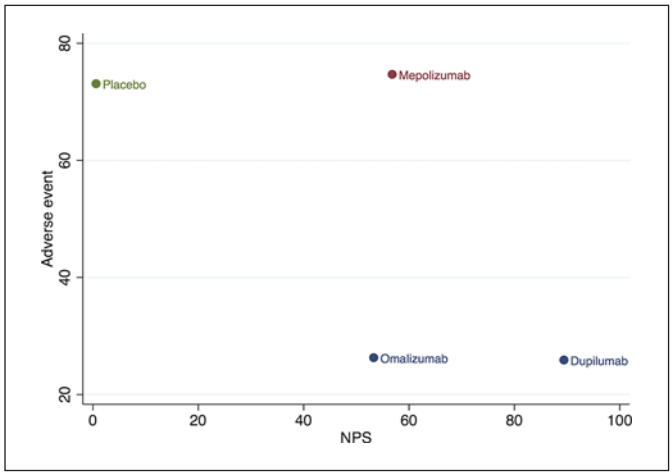
Fig. 3. Surface under the cumulative ranking curve for the outcomes: NPS (**a**), SNOT-22 (**b**), UPSIT (**c**), NCS (**d**), and AEs (**e**). NPS, nasal polyp score; SNOT-22, Sino-Nasal Outcome Test-22; UPSIT, University of Pennsylvania Smell Identification Test; NCS, nasal congestion score; AEs, adverse events; SUCRA, surface under the cumulative ranking curve.

SNOT-22, UPSIT, and NCS for SUCRA values of 0.606 0.500, and 0.693, respectively. Omalizumab had a low risk of AEs for SUCRA values of 0.263. Mepolizumab ranked second in efficacy in terms of NPS for SUCRA values of 0.563 and had the highest risk of AEs for SUCRA values of 0.747. The placebo had the worse efficacy in terms of NPS, SNOT-22, UPSIT, and NCS for SUCRA values of 0.006, 0.019, 0.000, and 0.000, respectively.

Figure 4 indicates the efficacy (NPS) and safety (AEs) in all the treatments. Dupilumab had the best efficacy and safety. Mepolizumab ranked second in efficacy, but it had the worst safety. Omalizumab had better efficacy than placebo and ranked second in safety.

Sensitivity Analysis

The exclusion of 1 RCT decreased the degree of heterogeneity in some analyses, but the aggregated results did not change substantially.



Color version available online

Fig. 4. Efficacy (NPS) and safety (AEs) in all the treatments. NPS, nasal polyp score; AEs, adverse events.

Discussion

Principal Findings

This systematic review and NMA identified 9 RCTs with 1,190 participants, evaluating the efficacy and safety of dupilumab, mepolizumab, and omalizumab in CRSwNP. It showed that all biologics were more efficacious than the placebo and were safe in adults with CRSwNP. Moreover, based on the efficacy (NPS) and safety (AEs), dupilumab had the best efficacy and safety; omalizumab had a better outcome than mepolizumab when efficacy and safety were combined, although mepolizumab had better efficacy than omalizumab.

Comparison with Other Studies

In this NMA, dupilumab and mepolizumab were superior to placebo in terms of NPS, which was consistent with the systematic review by Chong et al. [22]. Additionally, our results showed that omalizumab was superior to placebo with regards to NPS, SNOT-22, UPSIT, and NCS. Because the study by Gevaert et al. [16] had not yet been published at that time, systematic reviews by Chong et al. [22] and Hong et al. [23] showed that they were uncertain about the effects of omalizumab based on their available evidence.

Although the indirect type of comparisons was crude, Lipworth's study showed that changes in NPS were greater in absolute or percentage terms for dupilumab than for omalizumab [24]. Additionally, dupilumab had consistently greater improvements in key CRSwNP outcomes versus omalizumab at week 24 in an indirect treatment comparison [25]. Similar to their results, our result based on SUCRA indicated that dupilumab was superior to omalizumab with regards to NPS, SNOT-22, UPSIT, and NCS. This may reflect that the mechanism of action in dupilumab acts higher up the type 2 inflammatory cascade than that of omalizumab by blocking signaling of IL-4 and IL-13 and accordingly has been shown to suppress levels of fractional exhaled nitric oxide and IgE in patients with asthma [26, 27].

Implication for Future Research and Clinical Practice

There were 9 RCTs included in this systematic review and NMA, which recruited 1,190 patients with moderate to severe CRSwNP. It was certain that the patients in the biologics group experienced significant improvements in efficacy (NPS, SNOT-22, UPSIT, and NCS) and had no increased risk of AEs. Therefore, a further large number of trials would not be required to change the comparisons.

Moreover, according to the ranking of biologics based on SUCRA for the efficacy (NPS) and safety (AEs), dupilumab which is approved for the treatment of CRSwNP by FDA [28], is the best choice. Omalizumab is the second best option.

Cough, bronchitis, arthralgia, accidental overdose, and injection-site reactions were slightly more frequent in the dupilumab group, but the most common AEs (nasopharyngitis, worsening of nasal polyps and asthma, headache, epistaxis, and injection-site erythema) were more frequent with placebo [11]. Most common AEs in the omalizumab group were headache, injection-site reactions, arthralgia, dizziness, and upper abdominal pain,

but no anaphylaxis, Churg-Strauss syndrome, and/or hypereosinophilic syndrome was observed [16]. Most frequent AEs in the mepolizumab group were headache and nasopharyngitis [13].

To now, it is still unknown that biologics are effective in patients with less severe CRSwNP and safety in the long term. Thus, further studies are required to evaluate their efficacy and their safety in patients with less severe diseases by a long time follow-up. Moreover, a cost-effectiveness analysis for biologics therapies in CRSwNP is called for [29].

Because this NMA is based on indirect evidence, further studies should also focus on the head-to-head comparison between biologics in patients with CRSwNP. Some studies indicated that benralizumab [30] and reslizumab [31] were effective in CRSwNP, but they did not meet our inclusion criteria and cannot be recommended by our study. Moreover, although type 2-targeted treatments are effective for CRSwNP, there still lacks sufficient evidence about non-type 2 inflammation-targeted treatment approaches [32], and our further studies should also focus on this.

Limitations of the Study

Despite the strict methodology of this systematic review and NMA using PRISMA guidelines, certain limitations should be considered. First, studies recruited participants with moderate to severe CRSwNP as more than half of the participants had asthma as comorbidity or inhaled asthma therapy. Thus, there is no evidence on whether or not patients with less severe disease (without asthma) would benefit. Second, 9 RCTs included in our study were all in adults so that there were no data for children. Finally, because of only 2–3 studies for each biologic, there is insufficient data to make funnel plots [33].

To the best of our knowledge, this was the first NMA to compare different biologics in patients with CRSwNP. Based on indirect evidence of the efficacy (NPS) and safety (AEs), dupilumab is the best choice for CRSwNP and omalizumab is the second best option. The findings from this study may help guide physicians in the choice of biologics for treatment of CRSwNP. A head-to-head comparison between biologics in patients with CRSwNP is needed.

Statement of Ethics

This network meta-analysis followed the guidelines of the PRISMA statement.

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. Wu and Y. Zhang performed the literature search, assessed study details, and evaluated the study quality supported by W. Kong and X. Wang. R. Zheng, L. Yuan, and H. Qiu performed the statistical analyses. Q. Wu wrote the first draft of the manuscript with the support of X. Huang and Q. Yang, 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 supplement file.

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