Biologic treatment for severe chronic rhinosinusitis with nasal polyps: a systematic review and meta-analysis*

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Abstract

Background: Chronic rhinosinusitis with nasal polyps is often severe, debilitating and difficult to treat. Biologics that target key inflammatory pathways have the potential to treat this disease; this study aimed to evaluate their effectiveness.

Methodology: Systematic review and meta-analysis of randomised controlled trials of biologics in chronic rhinosinusitis with nasal polyps. Primary outcomes were extent of disease, objective disease severity and disease-specific quality of life, with outcomes measured at different end-of-treatment timepoints in different studies (range 16-52 weeks).

Results: Eleven trials were identified with 2035 participants. Ten studies reported change in polyp size, estimating a reduction of -1.25 in the treatment group. Six studies reported reduction in Lund-Mackay score where the pooled mean difference was -4.90. Five studies included peak nasal inspiratory flow with a pooled mean difference of 33.54, indicating improved nasal airflow. Seven studies reported change in olfactory score with an overall pooled effect of 6.56 suggesting improved olfaction. The SNOT-22 score in nine studies gave an overall pooled effect of -14.53, indicating improved quality of life.

Conclusions: Biologics can be effective in treating nasal polyps, with reduction in polyp size and extent of disease, and improved sense of smell and quality of life. There is significant heterogeneity in the outcomes for individual biologics, highlighting the need for further studies.

Key words: health-related quality of life, interleukins, olfactory disorders, sinonasal tract

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is often severe and difficult to treat. Disease recurrence due to poor response to medical therapy, often leading to frequent sinonasal surgery, is common. CRSwNP has a distinct clinical phenotype and specific immunological subtype (endotype), often with high T2 inflammation characterised by excess IgE and eosinophilic tissue states [1]. Interleukin (IL)-5 drives eosinophil production and survival whilst IL-4 and IL-13 promote eosinophilia and drive

IgE production, along with the induction and maintenance of T2 inflammation. All can drive structural tissue change (remodelling). There is an urgent unmet clinical need to provide more effective treatment for CRSwNP.

Biologics are molecules synthesised within cells of living organisms and modified to target key human molecular mediators and receptors. Biologics direct a disease process by modulating a specific biological mechanism. CRSwNP and asthma are

strongly co-associated, and biologic efficacy in T2-high asthma has driven the extension of their use to CRSwNP [2]. Randomised controlled trials (RCTs) support their clinical efficacy in CRSwNP.

Biologics are expensive; understanding the comparative efficacy can help guide judicious utilization and limit unnecessary financial burden on healthcare systems. There is a compelling need to place biologics in a clinically relevant setting to deliver optimal benefit. We thus undertook a systematic review and meta-analysis of biologics in CRSwNP to understand what practical impact these drugs may have on current tertiary rhinology practice.

Materials and methods

Search strategy and selection criteria
Inclusion and exclusion criteria were predefined.

Types of studies
RCTs, quasi-RCTs and cross-over trials of 12 weeks or longer duration were included to allow insight into the efficacy of extended treatment.

Types of participants
Symptomatic CRSwNP despite standard treatment. Studies were excluded if participants had a known aetiology for their sinus disease e.g. cystic fibrosis/immunodeficiency.

Intervention
Monoclonal antibodies used for the treatment of CRSwNP.

Comparison
Placebo, no treatment or current standard of care.

Databases searched
MEDLINE (1946 – 9 November 2021), EMBASE (1980 – 9 November 2021), Global Health (1973 - 9 November 2021), the Cochrane Library, including the Central Register of Controlled Trials (on 9 November 2021), and clinicaltrials.gov (on 9 November 2021).

Search strategy
Search terms based on disease terminology related to sinonasal disease, clinical outcomes with biologics in CRSwNP and patient reported outcome measures (PROMs) (Appendix 1). Endnote version X8 reference software found and removed duplicates. The reference lists of studies selected for full-text analysis were assessed for additional studies not identified within the original search.

Study selection
At least two reviewers reviewed titles and abstracts and read full-text articles. Any remaining duplicates were excluded at this stage (Figure 1). Conflicts were resolved by discussion. PROSPE-
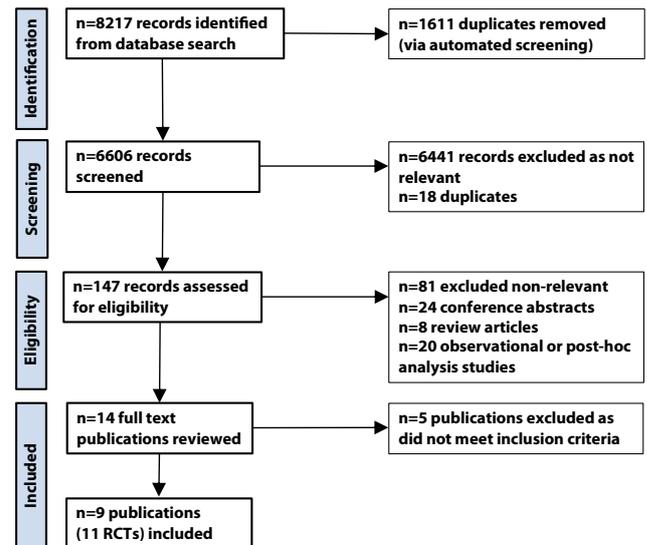

Figure 1. PRISMA flow diagram for study selection of meta-analysis of randomised controlled trials of biologic agents in chronic sinusitis with nasal polyps (CRSwNP).

RO registration:
https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021288356.

Institutional permission was not required.

Data analysis
Studies that met the inclusion criteria had relevant data extracted by two independent reviewers using a standardised data form. Outcomes were assessed at different time points in different studies, ranging from 16-52 weeks (Table 1).

Primary outcomes
- Extent of disease:
    o nasal polyp score (NPS)
    o radiological scoring with Lund-Mackay score (LMS)
- Objective disease severity:
    o peak nasal inspiratory flow (PNIF)
- Formal olfactory testing (University of Pennsylvania Smell Identification Test, UPSIT)
- Health-related quality of life (QoL) measured with validated disease-specific QoL scores e.g. sinonasal outcome test-22 (SNOT-22)

Secondary outcomes
- Subjective disease severity measured with validated patient-reported symptom scores e.g., visual analogue scale (VAS) for overall disease severity and/or specific symptoms of nasal congestion, discharge.

Table 1. Summary of characteristics of randomised controlled studies included in meta-analysis.

Randomised controlled trial	Subjects active / placebo	Mean age (years) active / placebo	Asthma % active / placebo	N-ERD % active / placebo	Intervention	Follow-up / outcomes measured (weeks)	Outcome measures
Bachert et al. 2022 [13]	413 (207 / 206)	50·1 / 50·2	68·6% / 67·0%	30·0% / 29·1%	Benralizumab 30 mg SC every 4 weeks x 3 then every 8 weeks to 40 weeks	40 / 40	NPS LMS SNOT-22 NBS Time to surgery and/ or SCS use
Tversky et al. 2021 [9]	24 (12/12)	49·8 / 50·8	83·0% / 100%	25·0% / 67·0%	Benralizumab 30 mg SC every 4 weeks x 3 doses then once after 8 weeks	24 / 24	NPS LMS UPSIT SNOT-22 NBS
Bachert et al. 2019 [10]: SINUS-24	276 (143 / 133)	52·0 / 50·0	57·0% / 59·0%	32·0% / 29·0%	Dupilumab 300 mg SC every 2 weeks to 24 weeks	48 / 24	NPS LMS PNIF UPSIT SNOT-22 Disease severity VAS NCS Nasal discharge score Time to surgery or SCS use
Bachert et al. 2019 [10]: SINUS-52	448 (150 / 145 / 153)*	51·0 / 53·0 / 53·0*	57·0% / 63·0% / 59·0%*	23·0% / 28·0% / 29·0%*	Dupilumab 300 mg SC every 2 weeks to 52 weeks OR Dupilumab 300mg SC every 2 weeks to 24 weeks then every 4 weeks to 52 weeks*	52 / 24	NPS LMS PNIF UPSIT SNOT-22 Disease severity VAS NCS Nasal discharge score Time to surgery or SCS use
Bachert et al. 2016 [14]	60 (30 / 30)	47·4 / 49·3	53·3% / 63·3%	20·0% / 30·0%	Dupilumab 600 mg SC loading dose then 300 mg weekly to 16 weeks	32 / 16	NPS LMS PNIF UPSIT SNOT-22 Disease severity VAS NCS Nasal discharge score
Han et al. 2021 [11]	407 (206 / 201)	48·6 / 48·9	68·8% / 74·0%	22·0% / 31·0%	Mepolizumab 100 mg SC every 4 weeks to 52 weeks	52 / 52	NPS PNIF UPSIT SNOT-22 Nasal obstruction VAS Time to surgery
Bachert et al. 2017 [4]	105 (54 / 51)	51·0 / 50·0	81·0% / 75·0%	Data not available	Mepolizumab 750 mg IV every 4 weeks x 6 doses	25 / 25	NPS PNIF SNOT-22 Disease severity VAS Nasal obstruction VAS Nasal discharge VAS
Gevaert et al. 2020 [12]: POLYP 1	138 (72 / 66)	50·0 / 52·2	58·3% / 48·5%	22·2% / 16·7%	Omalizumab 75 mg – 600 mg SC every 2 – 4 weeks to 24 weeks†	24 / 24	NPS UPSIT SNOT-22 NCS

Randomised controlled trial	Subjects active / placebo	Mean age (years) active / placebo	Asthma % active / placebo	N-ERD % active / placebo	Intervention	Follow-up / outcomes measured (weeks)	Outcome measures
Gevaert et al. 2020 [12]: POLYP 2	127 (62 / 65)	49·0 / 51·0	61·3% / 60·0%	38·7% / 32·3%	Omalizumab 75 mg – 600 mg SC every 2 – 4 weeks to 24 weeks[†]	24 / 24	NPS UPSIT SNOT-22 NCS
Gevaert et al. 2013 [15]	23 (15 / 8)	50·0 / 45·0	100% / 100%	53·0% / 50·0%	Omalizumab SC every 2 – 4 weeks to 16 weeks with maximum total dose 375mg[†]	16 / 16	NPS LMS NCS Nasal discharge score

N-ERD = non-steroidal exacerbated respiratory disease; SC = subcutaneous; NPS = nasal polyp score; LMS = Lund-Mackay score; SNOT-22 = sinonasal outcome test-22; NBS = nasal blockage score; SCS = systemic corticosteroids; UPSIT = University of Pennsylvania smell identification test; PNIF = peak nasal inspiratory flow; VAS = visual analogue scale; NCS = nasal congestion score. *SINUS-52 had 2 active groups (with different dosing regimes) - the first 2 results are both active groups and the third is the placebo group. [†] omalizumab dose and frequency calculated based on pre-treatment serum immunoglobulin E (IU/ml) and body weight (kg).

Risk of bias assessment was conducted using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB2) (Appendix 2) [3].

Differences between treatment and control groups were estimated via a mean difference. Standardising these mean differences to Hedge's g was necessary for nasal congestion and discharge scores due to inconsistency in the scale of reported outcomes. Where possible, these outcomes were derived from the 'difference from baseline' summaries to control for the potential confounding effect, or otherwise from follow-up summary only; both effect estimates are statistically comparable and are therefore combined in the same meta-analyses. In one study [4], differences from baseline were not reported thus outcomes were derived from follow-up measurements only and combined with all other studies. The outcomes of 'time to surgery' and 'time to systemic corticosteroid (SCS)' were synthesised from reported hazard ratios and combined with relative risks where studies reported these comparable outcomes in a binary format. Where associated standard errors were not given, they were derived from reported confidence intervals (CI). Data not presented numerically were extracted from presented figures using plot digitising software (plotdigitizer.sourceforge.net).

Inverse-variance random-effects methods were used for all analyses to account for possible heterogeneity. The heterogeneity variance (τ^2) was calculated using the restricted maximum likelihood method [5], which measures the amount of additional variation that exists in a meta-analysis relating to differences in the design of conduct of the studies. We present the I^2 statistic [6], which measures heterogeneity proportionally to random error and test for the presence of heterogeneity via the Q-test. Prediction intervals were calculated as a supplement to evaluate

the range of biologic effects that are plausible. Results were synthesised separately for each outcome overall, with subgroup analyses for individual drugs. Forest plots are presented. Analyses were carried out in R (version 4.0.4) using the package metafor (version 3.0.2) [7]. 95% CI and prediction intervals are reported for all pooled estimates; the significance level was set at 5%.

Results

The search returned 8217 results. Screening identified 14 records for full-text review; nine of these met the inclusion criteria, reporting 11 different trials (Figure 1). All 11 were randomised double blind placebo-controlled trials including 2035 patients. For one study [8] extraction of relevant data failed as results were only presented graphically; it was subsequently excluded, leaving 10 RCTs in eight publications including 2021 patients (1096 active intervention and 925 placebo). Characteristics of the included studies are summarised in Table 1. Intranasal steroids were continued in addition to biologic agents on all trials. There was no significant difference between treatment and control groups with regards to age, sex, asthma or N-ERD status and this data was not available for subgroup analysis. The overall risk of bias was low (Figure 2).

Ten studies [4, 9-15] reported change in NPS from baseline, estimating a larger reduction of -1.25 (95% CI -1.68 to -0.81, p<0.001) in the treatment group compared to control (Figure 3a), meaning that the treatment group had a greater reduction in polyp size. Considerable heterogeneity exists in the overall meta-analysis (τ^2= 0.414, I^2= 88.6%, p<0.001). The associated 95% prediction interval was -2.58 to 0.09, suggesting the range of possible estimated mean differences is largely negative. A statistically significant proportion of this heterogeneity can be explained through subgroup analysis by investigative drug (test for differences in

As percentage (intention-to-treat)
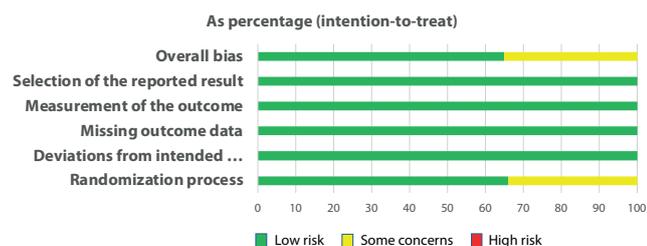
Figure 2. Risk of bias assessment for studies included in the meta-analysis.

subgroups: τ^2= 0.367, I^2=91.7%, p<0.001). The studies evaluating dupilumab [10, 14] showed a much larger subgroup effect than the other drugs, producing a pooled effect of -1.89 (95% CI -2.15 to -1.64); this effect is significantly larger than equivalent pooled effects of benralizumab and mepolizumab (p<0.001) but non-significant compared with omalizumab (p=0.385). However, of the omalizumab studies, one [15] produced a much larger effect than the other two resulting in considerable heterogeneity (τ^2= 0.876, I^2= 92.1%, p<0.001).

Across six studies using benralizumab [9, 13], dupilumab [10, 14] and omalizumab [15], the pooled mean difference in change in LMS was -4.90 (95% CI -7.37 to -2.44, p<0.001), with high heterogeneity (τ^2= 8.243, I^2= 93.9%, p<0.001) (Figure 3b). This indicates greater improvement in radiological disease extent in the treatment group. The prediction interval (95% PI -11.05 to 1.24) suggests small harmful effects, namely worsening disease, may be possible in individual studies. This heterogeneity can be reduced considerably when studies are grouped by investigative drug (p<0.001). The two studies investigating benralizumab [9, 13] showed a borderline significant effect (-1.47, 95% CI -3.10 to 0.16, p=0.078), whereas the dupilumab studies [10, 14] showed a much larger beneficial effect (-6.94, 95% CI -9.04 to -4.83, p<0.001).

Five studies evaluating dupilumab [10, 14] and mepolizumab [4, 11] reported change in PNIF from baseline. There was a significant overall pooled mean difference; those in the treatment group experienced a 33.54 L/min (95% CI 26.31 to 40.76, p<0.001) larger increase in PNIF than those in the control group (Figure 3c). Little evidence of heterogeneity was observed overall (τ^2=18.51, I^2=27.56%, p=0.310), with a narrow prediction interval suggesting the range of potential estimated effects is entirely positive (95% PI 22.43 to 44.64). However, the three studies involving dupilumab [10, 14] showed a slightly larger pooled effect (effect=37.81, 95% CI 30.98 to 44.64) than the two studies investigating mepolizumab (effect=23.93, 95% CI 12.61 to 35.25) [4, 11] with this difference just crossing the statistical significance threshold (p=0.040).

Seven studies assessed olfaction, using the University of

Pennsylvania Smell Identification Test (UPSIT) [9-12, 14] (Figure 3d). The overall pooled effect was 6.56 (95% CI 2.69 to 10.43, p<0.001), suggesting an overall improvement in olfaction, although with considerable heterogeneity between studies (τ^2=25.32, I^2=94.70%, p<0.001). The associated prediction interval includes negative effects (95% PI -4.04 to 17.15) which suggests that some studies may have found worsening olfaction. Most of the heterogeneity can be explained when studies are grouped by investigative drug (p<0.001); the three involving dupilumab [10, 14] showed a large pooled effect (effect=10.93, 95% CI 9.69 to 12.17), while the benralizumab (p=0.306) [9] and mepolizumab (p=0.678) [11] studies were non-significant overall.

Nine studies [4, 9-14] reported change in disease-specific QoL using SNOT-22 scores (Figure 3e). The overall pooled effect was -14.53 (95% CI -18.28 to -10.79, p<0.001) with moderate heterogeneity between studies (τ^2=21.48, I^2=69.23%, p=0.001), indicating a significant improvement in QoL. The associated 95% prediction interval was -24.36 to -4.71. Some heterogeneity can be explained by splitting studies by the intervention drug (p<0.001); this is mainly due to smaller non-significant effect sizes being observed in the two benralizumab studies (effect=-4.57, 95% CI -9.69 to 0.55, p=0.080) [9, 13]. Mepolizumab, dupilumab and omalizumab studies reported similar positive intervention effects [4, 10-12, 14].

Three dupilumab [10, 14] and one mepolizumab [4] studies reported change in overall subjective disease severity using a VAS. This resulted in a statistically significant overall pooled mean difference of -2.71 (95% CI -3.33 to -2.09, p<0.001) (Figure 3f), with a lower VAS indicating improvement in disease severity. Moderate heterogeneity was observed overall (τ^2=0.432, I^2=49.33%, p=0.143) and the associated prediction interval for the pooled effect was -3.76 to -1.66. The effect was smaller in the mepolizumab study (effect=-1.80, 95% CI -2.90 to -0.7) [4] compared to those investigating dupilumab (effect=-2.99, 95% CI -3.43 to -2.57) [10, 14]; this difference between subgroups just crossed the threshold of statistical significance (p=0.047).

Ten studies evaluated subjective nasal congestion scores on various scales (standardised effect =-0.75, 95% CI -0.96 to -0.54), showing a trend towards improvement (Figure 3g) [4, 9-15]. Heterogeneity is partly explained when studies are separated by drug (p=0.009) with benralizumab and dupilumab studies showing the largest improvement. Five studies assessed subjective discharge (standardised effect=-0.83, 95% CI -1.00 to -0.67), again with a trend to improved symptom scores [4, 10, 14, 15] (Figure 3h). No significant differences were found between studies separated by drug (p = 0.510).

Two additional time to event outcomes were reported, with
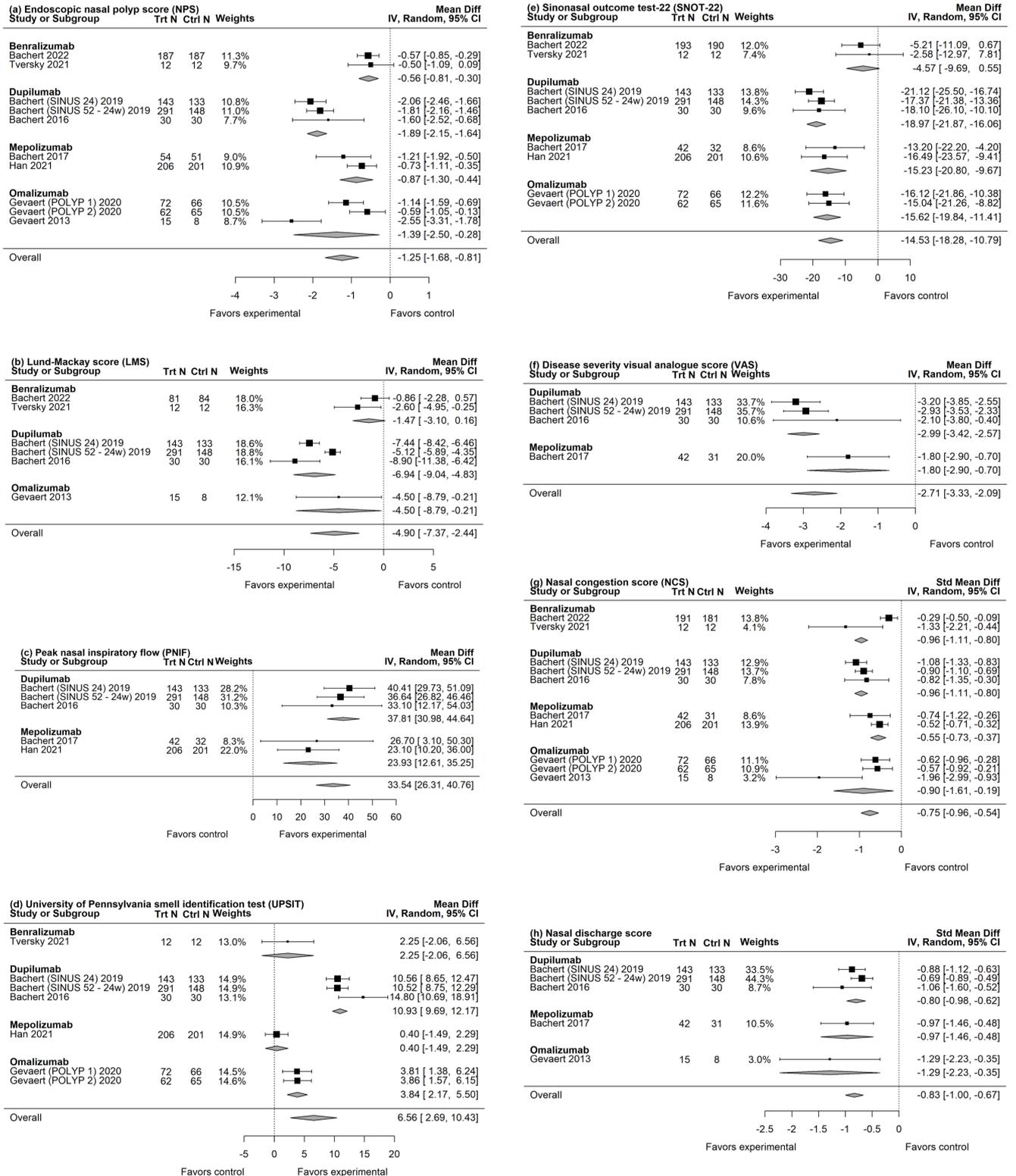
Figure 3. Forest plots showing meta-analyses of mean difference in the following outcomes: a) endoscopic nasal polyp score (NPS); b) Lund-Mackay score (LMS); c) peak nasal inspiratory flow (PNIF); d) University of Pennsylvania smell identification test (UPSIT); e) sinonasal outcome test-22 (SNOT-22); f) disease severity visual analogue score (VAS); g) nasal congestion score (NCS); and h) nasal discharge score with biologic use.
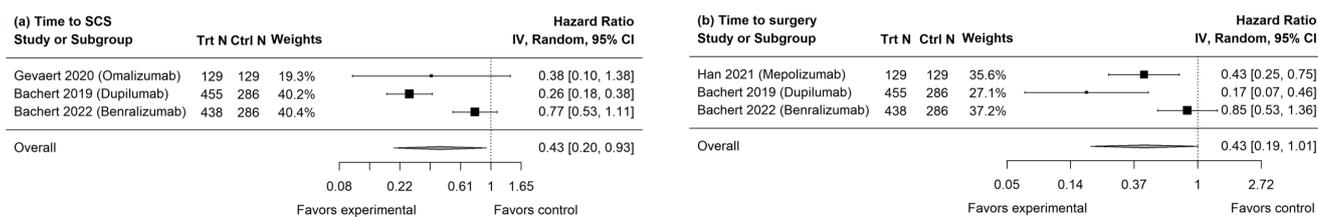
Figure 4. Forest plots showing meta-analyses of: a) a) time to systemic corticosteroids (SCS); and b) time to surgery with biologic use.

relevant data obtained from a post-hoc analysis in the case of dupilumab [16] (Figure 4). These were time to systemic cortico-steroid (SCS) use [10, 13, 16] and time to surgery for nasal polyps [11, 13, 16], resulting in hazard ratio pooled effects of 0.43 (95% CI 0.20 to 0.93) and 0.43 (95% CI 0.19 to 1.01), respectively. These results show an increased time to surgery and/or SCS use in the biologic treatment groups with placebo and treatment group Kaplan-Meier curves beginning to diverge as early as four weeks with dupilumab [10, 16] and after 24 weeks with benralizumab [13].

Discussion

This meta-analysis analysed key clinical outcome measures in a total of 2021 patients with CRSwNP enrolled in 10 RCTs of at least 12 weeks duration of treatment with the biologics benrali-zumab [9, 13], dupilumab [10, 14], mepolizumab [4, 11] and omalizumab [12, 15]. The overall results confirm improvements in disease outco-mes that are relevant to patient care, but the analysis also shows that individual biologics differ in clinical efficacy. None of the studies reported any serious adverse events. Our work allows insight into how biologics may impact patients with CRSwNP in a real-world setting. It shows that biologics modulated disease with improvements in clinical outcomes, although these were measured at different time points in different studies, ranging from 16 weeks to 52 weeks. In addition, some studies included patients who had previously undergone surgery and required revision surgery despite ongoing medical treatment [4, 9, 11] whilst others included subjects who had failed medical treatment but had not necessarily undergone surgery [10, 12-15] so might be considered to have less severe disease. Some biologics perfor-med better than others. However, high heterogeneity in efficacy was present, and no studies directly compared one biologic to another.

Relieving nasal obstruction is a key aim of treatment; this symp-tom is often assessed objectively by NPS, with which there is some correlation. NPS significantly improved with all biologics compared to placebo. There was considerable heterogeneity overall; such variability is likely caused by inherent differences in study design such as the investigative drug, duration of treatment and/or follow-up period. Differences between study groups such as patient heterogeneity could act as a further con-

founding factor, particularly as prescription of certain drugs may be heavily associated with other key patient characteristics such as age. For that reason, we calculated the associated 95% pre-diction interval, that is the expected range of true effects; this showed that the possible estimated mean differences in NPS are largely negative, supporting a definite reduction in polyp size. Subgroup meta-analysis confirmed that statistically significant heterogeneity exists between drug groups. Dupilumab demon-strated the largest subgroup effect for NPS reduction compared to other biologics.

The reduction in LMS confirmed decreased radiological extent of disease, again with high heterogeneity. Here the predic-tion interval suggested that the LMS may sometimes worsen which raises the possibility that biologics may not be beneficial in some individuals, with ongoing inflammation leading to worsening disease. Such negative outcomes highlight the need for close vigilance when establishing any patient on a novel immunomodulatory intervention. On subgroup meta-analysis the dupilumab studies again showed the largest effect [10, 14]. Surprisingly, studies using benralizumab, which leads to rapid and complete eosinophil depletion and might thus be expected to significantly impact inflammation in CRSwNP, considered to be an eosinophil-driven process, demonstrated a statistically significant improvement in only the LMS [9, 13]. Such findings provide mechanistic insight into the immunological cytokines, cells and signalling pathways in CRSwNP [17].

Improvement in PNIF was only reported for dupilumab [10, 14] and mepolizumab [4, 11]. Any decrease in NPS should be associa-ted with improved nasal airflow. Little heterogeneity was seen between the studies of both biologics, confirming a real impro-vement in PNIF and suggesting PNIF is a robust tool with which to measure clinical response to treatment. Blocking IL-4/IL-13 with dupilumab seems to carry a greater impact in improving PNIF than eosinophil depletion although in subgroup analysis this difference was just significant.

Smell loss is a distressing symptom. It is well recognised that human self-assessment of olfactory function is unreliable [18]. Psychophysical testing is the gold standard. Thus, objective

olfactory testing (using UPSIT) based RCT outcomes only were thus extracted and analysed. Whilst the pooled meta-analysis confirmed significant improvement in olfaction, again there was considerable heterogeneity between studies. Here, the associated predicted intervals also demonstrated negative effects, perhaps indicative of drug inefficacy in certain patients, with ongoing disease impacting olfaction rather than the biologic itself having a detrimental effect. Subgroup meta-analysis showed that dupilumab had the greatest impact on olfaction [10,14] whilst benralizumab and mepolizumab had no significant effect [9,11]. This finding is substantiated by Mullol et al's post-hoc analysis of the olfactory outcomes seen with dupilumab in the SINUS-24 and SINUS52 studies [19]. They reported a rapid and sustained improvement in olfaction with dupilumab treatment, irrespective of prior surgical treatment or coexisting asthma or N-ERD. Such findings provide mechanistic insights into smell loss in CRSwNP [20, 21]. Smell loss is often considered a purely conductive problem, whereby nasal obstruction due to polyp mass prevents olfactant molecules from reaching olfactory mucosa, but direct cytotoxic inflammation of the olfactory mucosa also occurs [22]. Blocking IL-5 (mepolizumab), IL-5R (benralizumab) and IL-4/IL-13 via IL-4Rα (dupilumab) decreased NPS and improved PNIF, yet only IL-4Rα inhibition led to marked improvement in smell, suggesting that olfactory mucosal inflammation is the key driver of smell loss. IL-4/IL-13-driven signalling seems particularly relevant to olfactory dysfunction [20].

Improvement in disease-specific QoL was reported with all four biologics. There was overall moderate heterogeneity between studies. Whilst mepolizumab, dupilumab and omalizumab demonstrated similar effects [4, 10-12, 14], benralizumab [9, 13] reported only non-significant effects and when analysed individually demonstrated only a borderline significant effect overall. Further post-hoc analysis of the SINUS-24 and SINUS-52 studies confirmed that dupilumab led to a significant improvement in disease-specific and overall health-related QOL [23], and similar improvements have been reported with other biologics [24].

Subgroup analysis of the improvement in overall subjective disease severity was only reported for dupilumab [10, 14] and a single mepolizumab study [4]. This analysis further supports the overall dominant efficacy of dupilumab in CRSwNP, with difference in subgroups just crossing the threshold of statistical significance. The secondary outcomes of subjective nasal congestion score with mepolizumab, dupilumab and omalizumab, and discharge score in relation to mepolizumab and dupilumab, were overall improved, supporting the roles for IL-5, IL-4/IL-13 and IgE in CRSwNP [25].

Delay in SCS use and/or time to surgical intervention is not a strict measure of disease outcome as such decisions are often made based on patient symptoms in real life. However, this data provides insight into the clinical efficacy of biologics. The reported data suggests that, with a reduction of 57% in SCS use and 39% in the need for surgery, biologics slow disease progression and improve clinical outcomes. The reduction in surgery, and comorbidities from SCS overuse [26], along with improvement in associated asthma [27], must all be factored into future biologic cost-effectiveness calculations. Patients often regard avoiding recurrent systemic steroids and surgery as the most important clinical outcomes for them.

Our study has many strengths, most notably the high quality RCTs. The wealth of relevant outcomes evaluated in this analysis pointed broadly towards a single consensus which adds credence to our conclusions. The consistency of these reported outcomes between studies meant we could perform separate meta-analyses without standardising the effect estimates in most cases and thus may have reduced the level of statistical heterogeneity. The risk of bias assessment was reassuring. Predicted intervals helped determine whether an effect was real or not, and subgroup analysis allowed us to reduce heterogeneity. Clinical trials with high patient numbers may achieve more conservative results as the testing of the intervention is on a larger scale. Funnel plot analysis for each outcome to evaluate how the study effect relates to size (data not shown) found no evidence of funnel plot asymmetry. However, such analyses were underpowered given the small number of included studies, and most were of comparable size.

A strength of meta-analysis is the drawing together of results from different research teams. The main limitation in this analysis is that the biologics were often evaluated by the same research teams using similar study designs and protocols, as demonstrated in the dupilumab studies [10, 14] and heterogeneity could be influenced by such factors.

Given our strict inclusion criteria we excluded several studies (Appendix 3) [8, 28-32]. Wu et al's recent meta-analysis of omalizumab perhaps assumed that the standard deviations for each outcome were the same for both treatment and placebo arms [33]. Their risk of bias assessments was also more lenient than our evaluation.

Ongoing Cochrane reviews have not interpreted previous RCTS of biologics in CRSwNP in the context of a clinically relevant setting [34, 35]. A recent network meta-analysis of biologics in CRSwNP (to 4th August 2021) included RCTs regardless of duration, proof-of-concept status, and where CRSwNP outcome data was extracted from what were primarily studies in severe asthma [36]. Many of these studies did not meet our inclusion criteria, specifically set to identify RCTs relating to biologics for

CRSwNP in a setting more comparable with clinical practice. This network meta-analysis is informative but the applicability to everyday practice is limited, particularly as outcomes related to prolonged biologic intervention alone were not reported. The RCTs included compared a single intervention with placebo and there is limited utility of network analytical techniques with few indirect comparisons to be made.

It is important to interpret outcome data in terms of everyday clinical practice. CRSwNP is clinically heterogeneous and associated with varying endotypes [37]. It is disappointing that none of the clinical studies attempted to evaluate clinically homogenous subgroups or recruit based on biomarkers such as serum eosinophils. The percentage of subjects with asthma ranged from 48.5% in some studies to 100% in others, and that of subjects with non-steroidal exacerbated respiratory disease (N-ERD) from 16.7% to 67%; these differences are highly likely to impact outcome given the higher recurrence rates in these patients, especially those with N-ERD. Therefore, an important question is whether the biologic studies have been undertaken in the appropriate patient sub-groups relevant to clinical practice. Overall there was no significant difference between placebo and treatment groups in baseline characteristics such as age, sex, asthma and N-ERD status, and too few studies were available to provide meaningful subgroups for meta-analysis. In the case of many of these characteristics, there was too little variation in samples to identify any association with the outcomes.

Our meta-analysis aimed to assess the outcomes of biologic treatment on objective measures of sinonasal disease and the symptoms associated with CRSwNP. We therefore did not assess the impact of biologic treatment for this indication on asthma outcomes, which were reported in some of the included RCTs. Given that asthma was frequently seen in the included patient cohorts, as discussed above, and can be in itself an indication for biologic treatment, it would have been interesting to see if the asthma outcomes mirrored the improvement seen in sinonasal measures.

It is likely that the meta-analysis outcomes would have less statistical variance if the studies had been undertaken in more homogeneous patient groups with regards to both clinical subtypes and endotypes of disease [38]. This and a standardised interventional trial protocol with clinically relevant treatment and follow-up times would provide more homogeneous data sets for meta-analysis. Future studies must address the need to understand clinical outcomes in specific subgroups of CRSwNP and in relation to disease severity. This is essential if we are to target the right drug to the right patient. With affordable genomic sequencing on the horizon, such ambitions to deliver personalised care are near reality. Identification of disease traits and associated biomarkers that predict clinical treatment response with a particular biologic must be prioritised.

Conclusion

In summary, we confirm the clinical efficacy of biologics in treating CRSwNP. Subgroup analysis suggests that dupilumab has a more significant effect than the other biologics. However, as variable inclusion criteria were used for both the active and control groups in each trial, it is difficult to draw firm conclusions as to the efficacy of individual biologics at this stage. The drugs appear to be clinically relevant in CRSwNP refractory to standard treatment. However, future studies should explicitly address the heterogeneity of disease. Only then will it be possible for clinicians to fully understand how to apply biologics cost-effectively to achieve the best patient outcomes.

Authorship contribution

HHK and JR conceptualised the review, screened abstracts, extracted and reviewed data and wrote the final draft. DL performed the statistical analysis and edited the final draft. DC, TJ, PS, MD and SBG screened abstracts, extracted data and edited the final draft. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Conflict of interest

HHK has undertaken paid advisory board work for Sanofi and Novartis and paid lecture work for AstraZeneca and GSK. SBG has undertaken paid advisory board work for GSK. The other authors declare no conflicts of interest.

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SUPPLEMENTARY MATERIAL

Appendix 1. Search strategy.

Search terms were based on disease terminology related to sinonasal disease (sinusitis or rhinosinusitis*, paranasal sinus disease*, rhinitis*) or disease therapy (biologic*, biological therap*/factor*/intervention*/drug therap*/monoclonal antibod* or mAb, immunotherapy or immunomodulation or monoclonal antibod*, terms specific to individual biologics or cytokine-based therapy). We searched for reported clinical outcomes with biologics in chronic rhinosinusitis and patient reported outcome measures (PROMS) using the term PROMS or patient reported outcome measure* OR quality of life OR questionnaire OR survey OR valid*OR develop*.

To maximise findings specific to CRSwNP, we used a 'proximity searching' approach with the term chronic rhinosinusitis ADJ2 nasal polyp*, to replace both phrases with and without nasal polyps. The ADJ2 operator finds terms in any order and with one word (or none) between them, as in this way the search will have picked up both phrases and combinations of such phrases.

Appendix 2. Risk of bias.

Risk of bias assessment was conducted using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB2). This tool assesses six domains of bias, including different aspects of trial design, conduct and reporting, then uses an algorithm to generate an overall risk of bias judged as "low", "some concerns" or "high". The domains are randomisation process; effect of assignment to intervention; effect of adhering to interventions; missing outcome data; measurement of outcome; and selection of reported result. The information extracted from each study included: authors, study design and duration, treatment drug and dosage, number of participants, mean age, inclusion and exclusion criteria, outcome measures, and relevant outcome results.

Appendix 3. Studies excluded at full text screening stage.

Two RCTs related to omalizumab were excluded. Wahba et al. [28] gave treatment for less than 12 weeks. Hayashi et al. [29] was really a mechanistic study of omalizumab in NERD generally, rather than CRSwNP specifically, and did not report the clinical outcomes predefined for our meta-analysis other than SNOT-22. In the Pinto study [8], data extraction for analysis was not possible for NPS or other clinical outcomes without making several assumptions on standard deviations. This finding and the relatively small numbers enrolled into the study (n=7) led to its exclusion from the meta-analysis. A recent meta-analysis by Wu et al., incorporating these studies in omalizumab, perhaps assumed that the standard deviations for each outcome were the same for both treatment and placebo arms [33]. We felt that the conclusions in their detailed analysis should be interpreted with caution because of this, as well as their lenient risk of bias assessments of the published RCTs compared to our evaluation. We excluded a study of mepolizumab in CRSwNP as treatment duration was only two months [30]. We did not include the Bachert et al. 2017 study [4] when analysing time-to-event outcomes for surgery, because in that study this outcome was a binary event measured at a set timepoint of 4 weeks after the last dose of mepolizumab and therefore not compatible with the reported outcomes in the other included RCTs. The Takabayashi et al. [31] benralizumab study was excluded based on duration of treatment for only 8 weeks. Short duration of biologic delivery also excluded one reslizumab (anti-IL-5) study in CRSwNP [32].