Role of biological medicines in chronic rhinosinusitis with nasal polyps - Systematic review and meta-analysis

Review Article

Authors

João Vila-Real-Fernandes
Faculdade Ciências da Saúde, Universidade da Beira Interior, Covilhã, Portugal

Rui Cerejeira
Faculdade Ciências da Saúde, Universidade da Beira Interior, Unidade de Otorrinolaringologia da Beira Interior (UOBI) Covilhã, Portugal

Rafaela Veloso-Teles
Faculdade Ciências da Saúde, Universidade da Beira Interior, Unidade de Otorrinolaringologia da Beira Interior (UOBI), Covilhã, Portugal

Correspondência:
João Vila-Real-Fernandes
jpvrf12@gmail.com

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Abstract

Introduction: Chronic rhinosinusitis with nasal polyps is an inflammatory disease associated with high morbidity and quality of life impairment. The aim of this article is to evaluate the efficacy of new monoclonal therapies in the control of disease refractory to the available therapies and to discuss the multiple factors that should be taken into consideration in the use of these types of drugs.
Methods: Systematic review with meta-analysis on the efficacy of biological therapies in chronic rhinosinusitis with nasal polyps. It was also assessed, through a review of the relevant literature, the cost-benefit of biologic treatments.
Results: In total, the meta-analysis included 11 randomized clinical trials that evaluated 4 monoclonal antibodies and all antibodies showed improvement in quality of life and a positive impact on the extent of the disease, despite its huge economical burden.
Conclusion: In this systematic review, we were able to verify that dupilumab was the monoclonal antibody with the greatest impact, both on quality of life and on the extent of the disease. However, further studies are needed in the future to better assess the long-term effect of these new therapies. Furthermore, given the economic impact of its use, it is imperative to efficiently assess which patients benefit the most from biologic therapies.

Keywords: chronic rhinosinusitis; nasal polyps; monoclonal antibodies; biologics

Introduction

According to the EPOS2020 - European Position Paper on Rhinosinusitis and Nasal Polyps 2020 [1], chronic rhinosinusitis (CRS), with or without nasal polyps, is an inflammation of the nasal cavity and paranasal sinuses and is clinically defined in adults by the presence of two or more symptoms, one of which must be nasal obstruction/congestion or anterior/posterior rhinorrhea, with the other symptoms being pain/pressure in the face

and hyposmia or anosmia. In addition, the diagnosis requires endoscopic signs of the disease (nasal polyps and/or mucopurulent rhinorrhea draining from the middle meatus and/or edema/ mucus obstruction primarily in the middle meatus) and/or changes in computed tomography (CT) (changes in the mucosa of the osteomeatal complex and/or paranasal sinuses). For the diagnosis of CRS to be valid, the symptoms must be present for a minimum period of 12 weeks. CRS with nasal polyps (CRSwNP) is characterized by the presence of bilateral nasal polyps detected by nasal endoscopy in addition to the above described criteria[1,2].

CRS is a disease with a high impact in terms of morbidity of the affected population and the health costs associated with the disease itself and with the periods of work absenteeism[3]. With regard to its epidemiology, two studies were conducted based on nasal endoscopy in Portugal. In the first study, conducted in the north of Portugal, a group of 200 Caucasian cadavers was analyzed and the prevalence of nasal polyps was found to be 5.5%[4]. In the second study, conducted in 2018, the prevalence of CRSwNP among 215 textile industry workers was 8.8%, that is, significantly higher than that found among 101 retail sales workers (0%). This suggests a correlation between occupational exposure to dust and the occurrence of nasal polyposis[5].

In another study conducted by the same group of researchers, the rate of relapse in 85 patients who underwent surgery and follow-up for a minimum period of nine months while receiving intranasal glucocorticoids was 31%[6]. In these patients, aspects such as occupational exposure to dust and the concomitant presence of non-IgE mediated asthma were identified as the predictive factors for disease relapse. A systematic review of the role of functional endoscopic sinus surgery (FESS) in the treatment of CRSwNP showed that disease recurrence after FESS varied between 4% and 60%, with a median of 20% in all studies; in the case of revision surgery, the interval was 3% to 42% with a median of 6%[7]. This implies that there is a considerable percentage of patients who have recurrent disease even after all the conventional medical measures and surgical interventions have been used[6]. This is the group of patients that is expected to benefit from a potential biological therapy.

CRS has been classified into two distinct clinical phenotypes, CRS with nasal polyps and without nasal polyps. Despite the knowledge that inflammation is at the base of this disease, the elucidation of the underlying mechanisms remains unsatisfactory. It is believed that CRS is a clinical syndrome that corresponds to the common final manifestation of multiple pathophysiological pathways that affect the nasal cavities and paranasal sinuses. It is known that there is an association between CRS without nasal polyps and type 1 inflammation and in the case of CRSwNP, a stronger association with type 2 inflammation. This type 2 inflammation is more frequently associated with an increase in inflammatory factors, including IL-4, IL-5, IL-13, and IgE, and these mediators may serve as potential therapeutic targets for the novel biological treatment of CRSwNP[3].

One of the first biological therapies introduced was omalizumab. It acts as a human monoclonal anti-IgE antibody that binds to free IgE molecules, thereby decreasing their circulating levels. In turn, this reduction leads to a decrease in the rate of IgE binding to its receptor in basophils and mast cells, thus inhibiting their degranulation and subsequent release of cytokines and inflammatory mediators[8].

IL-5 plays a role in differentiation, chemotaxis, and eosinophil survival, and eosinophils play an important role in type 2 inflammation. Monoclonal antibodies such as mepolizumab act as anti-IL-5 therapy as they have a high affinity for IL-5. The therapeutic target of benralizumab is the IL-5 receptor, which is expressed on the surface of both eosinophils and basophils. It can inhibit the binding of IL-5 to its receptors and thus causes cytotoxicity mediated by antibody-dependent cells (8).

IL-4 and IL-13 activate type 2 inflammatory

responses via the synthesis of IgE and related cell types. They share a common receptor, IL-4Rα, and act as two essential mediators in Th2 cell differentiation. Dupilumab is a monoclonal antibody against IL-4Rα and there are great expectations regarding its effect on the control of the inflammatory process that underlies CRSwNP (8).

Materials and Methods

This systematic review and meta-analysis were conducted in 2022 (the last date of the search was February, 2), using the PRISMA 2020 checklist (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) and PubMed database. In addition, the included randomized clinical trials (RCTs) were searched on the website www.clinicaltrials.gov. Only articles written in Portuguese and English were included. Because this was a systematic review, there was no need to obtain approval from the ethics committee. A protocol was written, submitted, and approved in PROSPERO (CRD42022308005).

In this review, articles published between 2011 and 2021 were considered. The bibliographic search was performed by three independent researchers using a sequence of terms (rhinosinusitis OR "chronic rhinosinusitis" OR "nasal polyps" OR "nasal polyposis") AND ("monoclonal antibodies" OR biologics OR humanized) AND (treatment OR therapy OR management). The selection of the studies was performed by three researchers and started with a simple reading of the titles and abstracts. Subsequently, in the first step, those articles that did not address the topic of biological therapies in CRSwNP were excluded and in the second step, all articles that were not RCTs were excluded. Subsequently, the full texts of the RCTs were reviewed and checked to ensure that they met the following inclusion criteria:

- Population aged 18 years and over
- Presence of CRSwNP
- Refractoriness to treatment with glucocorticoids and/or previous surgery for nasal polyps (more than a three-month interval) with relapse
- Bilateral nasal polyp score (NPS) ≥5, with a score ≥ 2 for each nostril.

Concurrently, exclusion criteria were also established, namely:

- Patients with cystic fibrosis, allergic fungal rhinosinusitis, ciliary dyskinesia, antrochoanal polyps, and nasal polyps associated with malignant sinonasal conditions.

The Cochrane risk-of-bias tool was used to assess the risk of bias (9).

Data extraction and review were performed by three researchers and any disagreement was resolved by discussion . At this stage, data were extracted on the population of each study and group (control vs placebo), treatment duration, treatment used, and respective protocol, as well as the means and standard deviations (for both groups) of the parameters used in the meta-analysis. The parameters evaluated in the meta-analysis included analysis of health-related quality of life, measured using the Sinonasal Outcome Test-22 (SNOT-22 test) (10), with a scale 0-110, and minimum clinically significant difference of 9 (11), in which “higher means worse”; and of disease extension, measured using the Nasal Polyp Score (NPS) (12), an endoscopic visual scale scoring from 0 to 8, in which, for each nostril: 0 = without polyps and 4 = large polyps; and the Lund Mackay Score (13), a scale scoring from 0 to 24, in which “higher means worse”, which uses CT of the paranasal sinuses to assess the extension of CRS. These results were analyzed using the Review Manager 5.4.1 softwar e in the form of tables comparing the different parameters using continuous data. Inverse variance was used as the statistical method, random effects were used as the analysis model, and the mean difference was used as a measure of effect. The confidence interval (CI) was set at 95% and heterogeneity was measured for all comparisons. The results were considered significant when $P<0.05$. The safety of the trials was analyzed according to the reported adverse events, their severity, and their association with the intervention compared to the placebo.

To perform the cost-benefit analysis of the biological medications, a review of the pertinent literature was conducted in PubMed using the terms “biologics”, “cost-effectiveness”, “dupilumab”, “monoclonal antibodies”, “chronic rhinosinusitis”, and “nasal polyps”. In addition, other articles were identified through a review of the lists of bibliographic references.

Results

This systematic review included ten studies, with the risk of bias being deemed “low” or “unclear” for most parameters. The risk of bias graph (Figure 1) shows the assessment of the review regarding each risk of bias parameter and the percentage refers to all the included studies. Figure 1 also shows the summary of the risk of bias with the assessment of each risk of bias parameter for each included study. Figure 2 presents the flow chart of the study. The search in PubMed yielded 1330 articles. Two additional articles from other sources were also included. Of the 1332 articles, four were duplicates and after a simple reading of the titles and abstracts, 1118 were excluded in the first phase, while 189 articles were excluded in the second phase. Twelve of the 21 articles whose full text was read were excluded, either because they did not meet the inclusion/exclusion criteria or because they addressed the same study. A total of nine articles were finally selected, with seven articles addressing one study per article and two articles addressing two studies per article [LIBERTY SINUS 24 and LIBERTY SINUS 52 are two different trials addressed in the same articles (14), as are POLYP 1 and POLYP 2 (15)], which makes a final total of 11 studies used in the meta-analysis. The inclusion criteria for the studies in the meta-analysis are described in Table 1.

Several monoclonal antibodies were tested in these 11 RCTs, namely: dupilumab, the focus of three RCTs (14,16); omalizumab, the focus of three RCTs (15,17); mepolizumab, the focus of three 3 RCTs (18–20), and benralizumab, the focus of two RCTs (21,22). The efficacy of these monoclonal antibodies was evaluated using the SNOT-22, NPS, and Lund Mackay Score instruments. The results are summarized in Table 2.

Dupilumab

The effects of dupilumab were analyzed in the following studies: Bachert 2016, LIBERTY SINUS 24, and LIBERTY SINUS 52 (14,16). The parameters SNOT-22, NPS, and Lund-Mackay Score were evaluated at 24 weeks in all three studies, while the SNOT-22 and NPS were additionally assessed at 52 weeks in the LIBERTY SINUS 52.

With regard to the impact on the quality of life, the use of dupilumab led to a mean difference of -19.61 (95% CI: -22.53, -16.69; P<0.00001) points in the SNOT-22 at 24 weeks in the three studies and of -22.38 (95% CI: -27.10, -17.66; P<0.00001) points at 52 weeks in the LIBERTY SINUS 52, compared to the use of the placebo.

With regard to the extension of the disease, the use of dupilumab led to a mean difference of -1.80 (95% CI: -2.25, -1.35, P<0.00001) points in the NPS and -7.00 (95% CI: -9.61, -4.39; P<0.00001) points in the Lund-Mackay Score at 24 weeks in the three studies, and to a mean difference of -2.34 (95% CI: -2.77, -1.91; P<0.00001) points in the NPS at 52 weeks in the LIBERTY SINUS 52, compared to the use of the placebo.

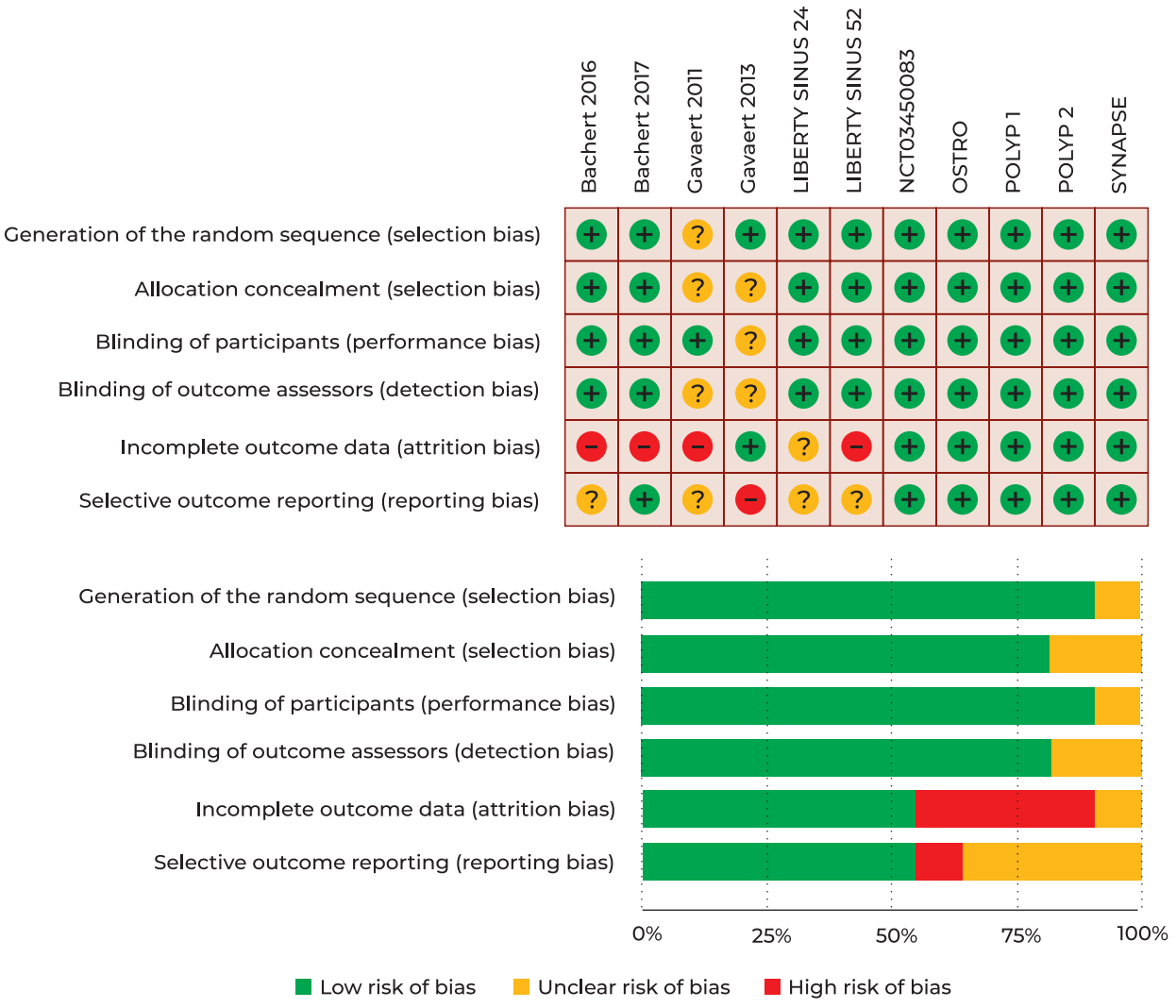
Omalizumab

The effects of omalizumab were evaluated in the studies of Gevaert 2013, POLYP 1, and POLYP 2 (15,17), with the SNOT-22 being used for evaluation in the studies POLYP 1 and POLYP 2, the NPS in the studies Gevaert 2013, POLYP 1, and POLYP 2, and the Lund-Mackay Score in the Gevaert 2013 study.

With regard to the impact on the quality of life, the use of omalizumab led to a mean difference of -15.62 (95% CI: -19.79, -11.45; P<0.00001) points in the SNOT-22 in the POLYP1 and POLYP2 studies, compared to the use of placebo.

With regard to the extension of the disease, the use of omalizumab led to a mean difference of -1.37 (95% CI: -2.30, -0.44; P=0.004) points in the

Figure 1
Risk of bias assessment graph and summary



NPS in the Gevaert 2013, POLYP 1, and POLYP 2 studies, compared to the use of placebo. The Lund-Mackay Score was only analyzed in the Gevaert 2013 study and the mean difference was -4.7 points, although this result was not statistically significant (P=0.06).

Mepolizumab

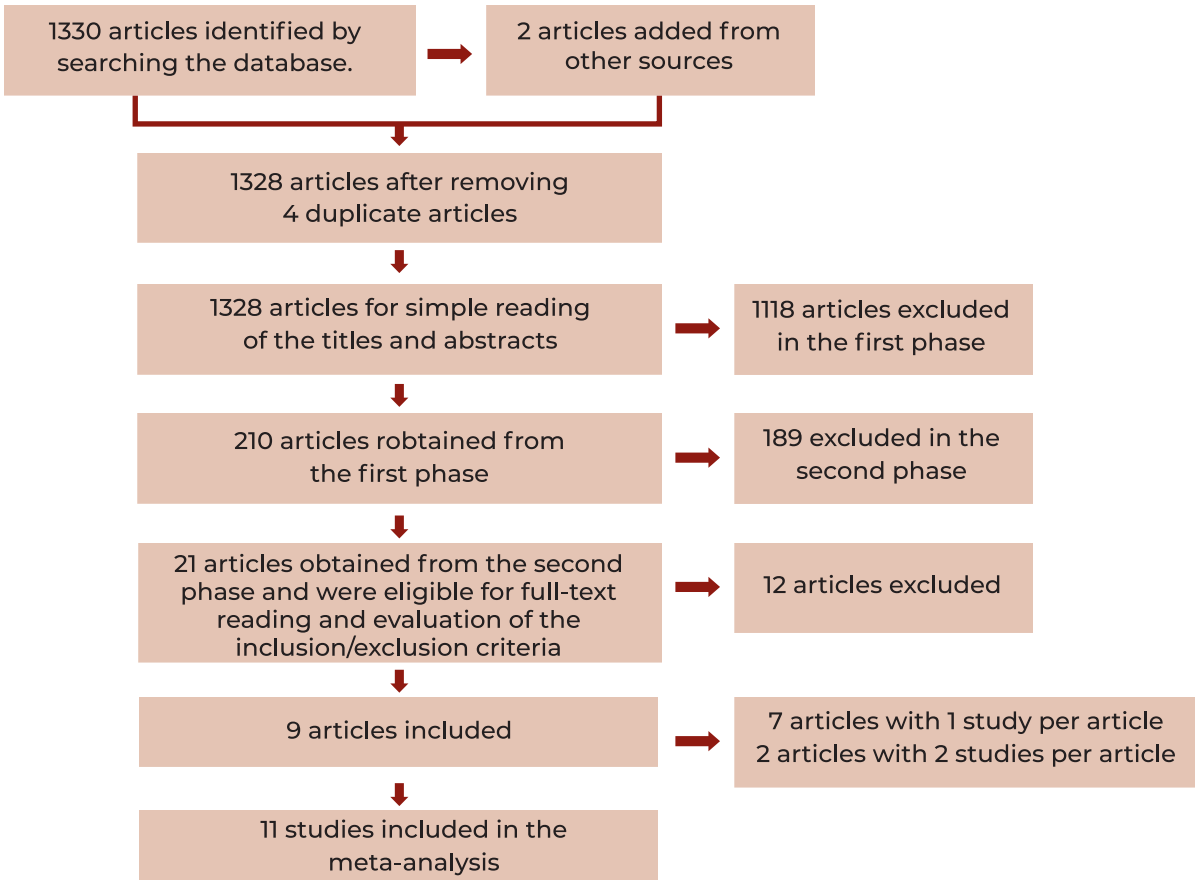
The effects of mepolizumab were evaluated in the Gevaert 2011, Bachert 2017, and SYNAPSE studies (18–20), and the SNOT-22 was used in the Bachert 2017 and SYNAPSE studies, while the NPS was used in the Gevaert 2011 and SYNAPSE studies. No study presented valid data for analysis regarding the Lund-Mackay Score. With regard to the impact on the quality of life, the use of mepolizumab led to a mean difference of -13.59 (95% CI: -17.77, -9.42; P<0.00001) points in the SNOT-22 in the Bachert 2017 and SYNAPSE studies, compared to the use of placebo.

With regard to the extension of the disease, the use of mepolizumab led to a mean difference of -0.85 (95% CI: -1.16, -0.54; P<0.00001) points in the NPS in the Gevaert 2011 and SYNAPSE studies, compared to the use of placebo.

Benralizumab

The effects of benralizumab were evaluated in the NCT03450083 and OSTRO studies (21,22) and the three parameters (SNOT-22, NPS, and Lund-Mackay Score) were evaluated by both studies. In terms of the impact on the quality of life, the use of benralizumab led to a mean

Figure 2
Flow chart of the PRISMA studies - Preferred Reporting Items for Systematic Reviews and Meta-Analysis



difference of -6.57 (95% CI: -12.20, 0.94; P=0.02) points in the SNOT-22 in the NCT03450083 and OSTRO studies, compared to the use of placebo. With regard to the extension of the disease, the use of benralizumab led to a mean difference of -0.54 (95% CI: -0.72, -0.35; P<0.00001) points in the NPS and -1.37 (95% CI: -3.10, -0.37; P=0.12) points in the Lund-Mackay Score in the NCT03450083 and OSTRO studies, compared to the use of placebo, although the result of the Lund-Mackay Score was not statistically significant.

Adverse effects

In most studies, the percentage of adverse effects was similar between the treatment and placebo groups. No study reported severe adverse effects associated with the treatment. The most common adverse effects were nasopharyngitis, headache, and injection site reaction.

Deaths during treatment were reported in some studies, but no death was related to the treatment.

Cost-benefit analysis of the biological medications

Rudmik *et al*. conducted a study in which FESS followed by postoperative medical treatment was compared to continued medical ("conventional") treatment for CRSwNP and concluded that FESS was a more cost-effective treatment strategy than continued medical therapy alone, with FESS having a total cost of $48,838,38 coupled to the production of a total of 20.50 quality adjusted life years (QALYs) and medical treatment alone having a total cost of $28,948,98 associated with the production of 17.13 QALYs[32]. The additional cost of FESS relative to continued medical treatment alone was $5,901,90 per QALY, an amount that is considered acceptable within

a budget limit of $25,000 per QALY provided to the patient[32]. The same conclusion was drawn in a different study, which demonstrated with 95% confidence that FESS was a more cost-effective alternative when the budget limit was $20,000[33].

In a more recent study, Scangas *et al*. conducted a cost-effectiveness analysis in which they compared FESS to the use of dupilumab using the economic Markov 10 states model. In this analysis, a cohort of 197 patients with CRSwNP who underwent FESS was compared to 293 patients with CRSwNP in the RCTs LIBERTY SINUS 24 and LIBERTY SINUS 52[14] who underwent treatment with dupilumab[34]. Using a time perspective of 36 years, Scangas *et al*. reported that surgical intervention achieved a total of 9.80 QALYs costing $50,436,99, whereas treatment with dupilumab achieved a total of 8.95 QALYs costing $536,420,22[34]. This led the authors to conclude that treatment with dupilumab was not only extremely expensive but was also less effective than FESS. They showed through unidirectional sensitivity analysis that for an annual cost of dupilumab above $855, FESS was more cost-effective regardless of the number of required revision surgeries [34].

Discussion

CRSwNP is a chronic disease that affects a significant number of patients with high associated comorbidity and heterogeneous features. The disease remains uncontrolled in a large number of patients, despite the use of topical and/or oral glucocorticoids or surgical treatment. In this meta-analysis, the efficacy of the different monoclonal antibodies used for the control of refractory disease was compared to that of conventional therapies.

The most effective antibody was dupilumab. With regard to the impact on the quality of life, this antibody achieved a reduction of -19.61 (P<0.00001) points in the SNOT-22 at 24 weeks, compared to the use of placebo. Considering that the SNOT-22 scale has a minimum clinically significant difference of 9 points[11], we concluded that this monoclonal antibody had a considerable impact on symptom improvement and the patients' quality of life. With the extension of the LIBERTY SINUS 52 study[14] to up to 52 weeks, a mean difference of -22.38 (P<0.00001) points was obtained in the SNOT-22, i.e., an even better result in the long term. With regard to the extension of the disease, a difference between the group that discontinued treatment at 24 weeks (-1.80 [P<0.00001] points in the NPS and -7.00 [P<0.00001] points in the Lund-Mackay Score) and the group that continued the treatment up to 52 weeks (-2.34 [P<0.00001] points in the NPS) was also observed, which indicates that the maximum potential of the monoclonal therapy has not yet been reached. The reduction obtained in disease extension was limited, with persistence of polyps, which means that complete remission of polyps was not achieved. Moreover, in patients who discontinued the treatment in the LIBERTY SINUS 24 (14) after 24 weeks, there was a gradual reoccurrence/worsening of symptoms. This reflects a need for the provision of chronic treatment with monoclonal antibodies in a continuous or intermittent manner to ensure successful outcomes over time.

The use of the remaining monoclonal antibodies also led to improvements, albeit less significant. This may be because the amount of medication, sample size , and duration of the intervention in the studies on omalizumab, mepolizumab, and benralizumab were considerably lower than those in the study on dupilumab. Therefore, further studies with larger samples and longer follow-up periods are necessary to better characterize the impact of these new therapies on CRSwNP.

With regard to the impact on the quality of life of omalizumab, mepolizumab, and benralizumab, there were significant reductions in the SNOT-22 compared to the use of placebo, but not as marked as with dupilumab. However, in the case of benralizumab, the SNOT-22 was below the minimum clinically significant difference; in addition, the results for disease extension were modest despite being significant, with only a

mean difference of -0.60 (P<0.00001) points in the NPS compared to the use of placebo. The use of omalizumab and mepolizumab led to a mean difference of -1.37 (P=0.004) and -0.85 (P<0.00001) points in the NPS, respectively, compared to the use of placebo. Although they were more effective than benralizumab, the impact was still not very significant considering the minimum score for inclusion in the study (bilateral NPS ≥5, with a score ≥ 2 for each nostril). The results of the analysis of the Lund-Mackay Score were not evaluated in the studies on mepolizumab. Although the results of the use of omalizumab and benralizumab were not statistically significant, they showed a trend towards a reduction in the Lund Mackay Score, with a mean difference of -4.7 (P=0.06) and -1.37 (P=0.12) points in the case of omalizumab and benralizumab, respectively, compared to the use of placebo.

A recently published study on this topic presented the same conclusions regarding dupilumab being the best choice for the control of CRSwNP. In that study, the authors also reported that omalizumab was the second best agent for the control of the disease and mepolizumab was the monoclonal antibody with the most adverse effects. [36]

The present study has some limitations, one being the fact that it appears that the maximum potential of monoclonal therapy has not been reached yet, which reflects the need for further studies with longer follow-up periods to obtain data on the therapeutic peak level and potential late adverse effects. In addition, it is not known how a change in the type of baseline inflammatory pattern may impact the individual and multiple body systems, and what adverse effects may subsequently appear.

Indications for biologicals and cost-effectiveness analysis of dupilumab

Among the antibodies studied in the RCTs included herein, only benralizumab does not have a formal indication from the Food and Drug Administration [23] and European Medicines Agency [24] as a potential therapeutic tool for the control of CRSwNP. All the other monoclonal antibodies, namely dupilumab, omalizumab, and mepolizumab are currently indicated by the Food and Drug Administration[25-27] and European Medicines Agency[28-30] for the treatment of severe uncontrolled CRSwNP despite the use of systemic glucocorticoids and/or surgery.

In an ideal world, health would not have an idealized value; however, one must consider the price of treatments. Thus, each therapy has an associated value, which is defined as its quality divided by its cost[3]. By using the Quality Adjusted Life Year (QALY), which equates to a person living one year in perfect health with the implementation of the novel therapy under study, it is possible to quantify the benefit of a given intervention through the number of QALYs it adds and estimate the value of the treatment using the cost inherent to each QALY added to the patient's life[3,31]. The results obtained in the review highlight the economic implications of the use of these new medications. There is no doubt that there is a high economic burden associated with CRSwNP and one, therefore, questions, whether society is ready to support the development of new biological medications when the therapeutic effects are achieved, remain fairly limited in comparison to the "conventional" medical and surgical treatments.

Criteria for the use of monoclonal antibodies in CRSwNP

With the knowledge of the cost involved in biological therapies and their innovative potential to control CRSwNP, it becomes imperative to define those patients who could benefit the most from these therapies.

In 2019, the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA)[35] organized a meeting of the multidisciplinary board of specialists to discuss the positioning of biologics in CRSwNP. In this meeting, the consensus reached was that for a patient to have an indication for biological therapy, he/she would need to have

Table 3
Criteria for the use of biological therapy in patients with chronic rhinosinusitis with nasal polyps

Criteria	Presence of bilateral nasal polyps with history of previous surgery	Presence of bilateral nasal polyps without history of previous surgery
- Type 2 inflammation - At least 2 courses of systemic glucocorticoids in the last year - Significant impact on the quality of life - Significant loss of the sense of smell - Diagnosis of asthma	3 criteria required	4 criteria required

Table 4
Criteria and classification of the response of patients with chronic rhinosinusitis with nasal polyps to biological therapy

Criteria	Classification
- Reduction in the size of the nasal polyps - Reduction in the need for systemic glucocorticoids - Increase in the quality of life - Improvement in the sense of smell - Reduction in the impact of comorbidities	0 criteria – without response; 1-2 criteria – poor response; 3-4 criteria – good response; 5 criteria – excellent response;

bilateral nasal polyps and three or four of the criteria presented in Table 3 depending on the presence or absence of previous surgery, respectively [35]. However, when a biologic is used for treatment, it is essential to assess the patient's response to avoid inappropriate treatments and unnecessary costs. Thus, in that meeting, it was proposed that for a response to biological therapy to be considered acceptable, the response to the five criteria (Table 4) needs to be assessed one year after the treatment. This response is classified according to the number of criteria that are met (see Table 4) and the treatment is discontinued if there is no response to it[35].

Conclusion

In this systematic review, dupilumab was found to be the monoclonal antibody with the most impact, both on the quality of life and disease extension. Further studies are necessary to better evaluate the long-term effect of these new therapies. However, given the costs inherent to their application, it is imperative to perform an effective and efficient assessment of which patients would benefit the most from biologics.

Conflicts of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

Data Confidentiality

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

Protection of humans and animals

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the 2013 Helsinki Declaration of the World Medical Association.

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Availability of scientific data

There are no datasets available, publicly related to this work.

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Table 1
Inclusion criteria and main characteristics of the randomized clinical trials included in the systematic review and meta-analysis

DUPILUMAB		
Studie		**BACHERT 2016**
Inclusion criteria	**Population under study**	CRSwNP
	Age (y)	18-65
	Refractoriness to treatment with glucocorticoids, and/or previous surgery for nasal polyps with relapse	Intranasal glucocorticoids for at least 8 weeks prior to screening, with refractoriness to treatment; 53.3%: ≥ 1 previous surgery for nasal polyps in the intervention group; 63.3%: ≥ 1 previous surgery for nasal polyps in the control group.
	NPS	Bilateral NPS ≥5 (≥ 2 in each nostril)
Duration		16 weeks
Intervention Protocol		The intervention group received 600 mg subcutaneous dupilumab as a loading dose, followed by 300 mg every week for 15 weeks; The control group received subcutaneous placebo every week for 16 weeks; All groups received 100 µg of mometasone furoate nasal spray in each nostril twice daily for the 4 weeks of preparation and continued with stable doses for the remainder of the study.
Total number of participants at the start of each trial		60
Studie		**LIBERTY SINUS 24**
Inclusion criteria	**Population under study**	CRSwNP
	Age (y)	≥18
	Refractoriness to treatment with glucocorticoids, and/or previous surgery for nasal polyps with relapse	Systemic glucocorticoids within the past 2 years (if not contraindicated); Previous surgery for nasal polyps.
	NPS	Bilateral NPS ≥5 (≥ 2 in each nostril)
Duration		24 weeks treatment and 24 weeks follow-up
Intervention Protocol		The intervention group received 300 mg of dupilumab subcutaneously every 2 weeks for 24 weeks; The control group received subcutaneous placebo every 2 weeks for 24 weeks; All groups received 100 µg of mometasone furoate nasal spray in each nostril twice daily during the 4-week preparation period, which was continued for the remainder of the study.
Total number of participants at the start of each trial		276
Studie		**LIBERTY SINUS 52**
Inclusion criteria	**Population under study**	CRSwNP
	Age (y)	≥18
	Refractoriness to treatment with glucocorticoids, and/or previous surgery for nasal polyps with relapse	Systemic glucocorticoids within the past 2 years (if not contraindicated); Previous surgery for nasal polyps.
	NPS	Bilateral NPS ≥5 (≥ 2 in each nostril)
Duration		52 weeks
Intervention Protocol		The intervention group received 300 mg of dupilumab subcutaneously every 2 weeks for 24 weeks and then every 4 weeks thereafter until a total of 52 weeks OR 300 mg of dupilumab subcutaneously every 2 weeks for 52 weeks; The control group received placebo subcutaneously every 2 weeks for 52 weeks; All groups received 100 µg of mometasone furoate nasal spray in each nostril twice daily during the 4-week preparation period, which was continued for the remainder of the study.
Total number of participants at the start of each trial		276

MEPOLIZUMAB		
Studie		**GEVAERT 2011**
Inclusion criteria	**Population under study**	CRSwNP
	Age (y)	≥18
	Refractoriness to treatment with glucocorticoids, and/or previous surgery for nasal polyps with relapse	Failure of conventional medical treatment; 75% - ≥ 1 previous surgery for nasal polyps in the intervention group; 80% - ≥ 1 previous surgery for nasal polyps in the control group.
	NPS	Bilateral NPS: Mean - 5.2 in the intervention group; Mean - 5.5 in the control group.
Duration		8 weeks of treatment and 40 weeks of follow-up
Intervention Protocol		The intervention group received 2 doses of 750 mg intravenous mepolizumab administered 28 days apart; The control group received 2 doses of intravenous placebo administered 28 days apart.
Total number of participants at the start of each trial		30
Studie		**BACHERT 2017**
Inclusion criteria	**Population under study**	CRSwNP
	Age (y)	18-70
	Refractoriness to treatment with glucocorticoids, and/or previous surgery for nasal polyps with relapse	Intranasal glucocorticoids for at least 3 months and/or a short regimen of oral corticosteroids; Previous surgery for nasal polyps.
	NPS	Bilateral NPS ≥5 (≥ 2 in each nostril)
Duration		24 weeks
Intervention Protocol		The intervention group received 750 mg of mepolizumab intravenously every 4 weeks for 24 weeks; The control group received placebo intravenously every 4 weeks for 24 weeks; All groups received 100 µg of fluticasone propionate nasal spray daily in each nostril for 10 to 14 days in preparation, which was continued for the remainder of the study
Total number of participants at the start of each trial		105
Studie		**SYNAPSE**
Inclusion criteria	**Population under study**	CRSwNP
	Age (y)	≥18
	Refractoriness to treatment with glucocorticoids, and/or previous surgery for nasal polyps with relapse	Intranasal glucocorticoids for at least 8 weeks prior to screening; Previous surgery for nasal polyps within the past 10 years.
	NPS	Bilateral NPS ≥5 (≥ 2 in each nostril)
Duration		52 weeks
Intervention Protocol		The intervention group received 100 mg of mepolizumab subcutaneously in the thigh, abdomen, or arm every 4 weeks for 52 weeks. The control group received placebo subcutaneously in the thigh, abdomen or arm every 4 weeks for 52 weeks; All groups received mometasone furoate nasal spray.
Total number of participants at the start of each trial		407

OMALIZUMAB		
Studie		**GEVAERT 2013**
Inclusion criteria	**Population under study**	CRSwNP
	Age (y)	≥18
	Refractoriness to treatment with glucocorticoids, and/or previous surgery for nasal polyps with relapse	Chronic rhinosinusitis and comorbid asthma for more than 2 years; 87% - ≥ 1 previous surgery for nasal polyps in the intervention group; 75% - ≥ 1 previous surgery for nasal polyps in the control group.
	NPS	Bilateral NPS: Mean - 6 in the intervention group; Mean - 6 in the control group.
Duration		6 weeks treatment and 4 weeks follow-up
Intervention Protocol		The intervention group received subcutaneous omalizumab. The dose and dosing frequency (every 2 weeks or every 4 weeks) of omalizumab were based on total serum IgE levels and body weight, with a maximum dose of 375 mg; The control group received subcutaneous placebo, with the same instructions as the intervention group.
Total number of participants at the start of each trial		23
Studie		**POLYP 1**
Inclusion criteria	**Population under study**	CRSwNP
	Age (y)	18-75
	Refractoriness to treatment with glucocorticoids, and/or previous surgery for nasal polyps with relapse	CRSwNP with inadequate response to conventional medical treatment; 54.2% - ≥ 1 previous surgery for nasal polyps in the intervention group; 60.6% - ≥ 1 previous surgery for nasal polyps in the control group.
	NPS	Bilateral NPS ≥5 (≥ 2 in each nostril)
Duration		24 weeks treatment and 4 weeks follow-up
Intervention Protocol		The intervention group received 75 mg to 600 mg omalizumab subcutaneously every 2 to 4 weeks (with dose and frequency determined by the total serum IgE level and body weight) for 24 weeks; The control group received subcutaneous placebo every 2 to 4 weeks (with dose and frequency determined by the total serum IgE level and body weight) for 24 weeks;All groups received 200 µg of mometasone furoate nasal spray twice daily (or once daily if intolerant to a twice daily regimen) during the preparation and treatment periods.
Total number of participants at the start of each trial		138
Studie		**POLYP 2**
Inclusion criteria	**Population under study**	CRSwNP
	Age (y)	18-75
	Refractoriness to treatment with glucocorticoids, and/or previous surgery for nasal polyps with relapse	CRSwNP with inadequate response to conventional medical treatment; 62.9% - ≥ 1 previous surgery for nasal polyps in the intervention 61.5% - ≥ 1 previous surgery for nasal polyps in the control group.
	NPS	Bilateral NPS ≥5 (≥ 2 in each nostril)
Duration		24 weeks treatment and 4 weeks follow-up
Intervention Protocol		The intervention group received 75 mg to 600 mg omalizumab subcutaneously every 2 to 4 weeks (with dose and frequency determined by the total serum IgE level and body weight) for 24 weeks; The control group received subcutaneous placebo every 2 to 4 weeks (with dose and frequency determined by the total serum IgE level and body weight) for 24 weeks; All groups received 200 µg of mometasone furoate nasal spray twice daily (or once daily if intolerant to a twice daily regimen) during the preparation and treatment periods.
Total number of participants at the start of each trial		127

BENRALIZUMAB		
Studie		**NCT03450083**
Inclusion criteria	**Population under study**	CRSwNP
	Age (y)	18-75
	Refractoriness to treatment with glucocorticoids, and/or previous surgery for nasal polyps with relapse	At least 1000 mg of oral prednisone (or equivalent) during the 12 months prior to symptom control; At least one previous surgery for nasal polyps.
	NPS	Severe bilateral nasal polyps with bilateral NPS ≥5
Duration		20 weeks
Intervention Protocol		The intervention group received 30 mg of benralizumab subcutaneously; The control group received subcutaneous placebo.
Total number of participants at the start of each trial		24
Studie		**OSTRO**
Inclusion criteria	**Population under study**	CRSwNP
	Age (y)	18-75
	Refractoriness to treatment with glucocorticoids, and/or previous surgery for nasal polyps with relapse	At least 1000 mg of oral prednisone (or equivalent) during the 12 months prior to symptom control; At least one previous surgery for nasal polyps.
	NPS	Severe bilateral nasal polyps with bilateral NPS ≥5
Duration		56 weeks
Intervention Protocol		The intervention group received 30 mg of benralizumab subcutaneously every 4 weeks for the first 3 doses and every 8 weeks for the last 5 doses; The control group received subcutaneous placebo every 4 weeks for the first 3 doses and every 8 weeks for the last 5 doses; All groups received 200 µg of mometasone furoate nasal spray twice daily in each nostril for a minimum of 4 weeks prior to randomization and throughout the remainder of the study.
Total number of participants at the start of each trial		410

CRSwNP – chronic rhinosinusitis with nasal polyps; NPS – Nasal Polyp Score

Table 2
Results of the meta-analysis comparing the intervention and placebo groups for the parameters evaluating the response to treatment with monoclonal antibodies in chronic rhinosinusitis with nasal polyps

Evaluated Parameter	Study or Subgroup	Intervention Group			Placebo Group			Mean Difference; Mean, IV, Random, 95% CI
		Mean	Standard Deviation	Total Participants	Mean	Standard Deviation	Total Participants	
DUPILUMAB								
SNOT-22	**Until 24 weeks**							
	Bachert 2016 (a)	12.8	11	30	30.2	19.6	30	-17.40 [-25.44,-9.36]
	LIBERTY SINUS 24	18.58	14.92	143	40.49	23.06	133	-21.91 [-26.53,-17.29]
	LIBERTY SINUS 52	23.89	23.89	295	42.16	23.26	153	-18.27 [-22.53,-14.01]
	Subtotal (95% CI)		**468**			**316**		**-19.61 [-22.53,-16.69]**
	Heterogeneity: Tau²=0.00; Chi²=1.62, df=2 (P=0,.44); I²=0% Test for overall effect: Z=13.17 (P<0,.00001)							
	Until 52 weeks							
	LIBERTY SINUS 52	21.67	19.16	150	44.05	22.66	153	-22.38 [-27.10,-17.66]
	Subtotal (95% CI)		**150**			**153**		**-22.38 [-27.10,-17.66]**
	Heterogeneity: Not applicable Test for overall effect: Z=9.29 (P<0,.00001)							
	Total (95% CI)		**618**			**469**		**-20.38 [-22.86,-17.89]**
	Heterogeneidade: Tau²=0.00; Chi²=2.58, df=3 (P=0,.46); I²=0% Test for overall effect: Z=16.08 (P<0,.00001) Test for differences between subgroups: Chi²=0.96, df=1 (P=0,.33); I²=0%							
NPS	**Until 24 weeks**							
	Bachert 2016 (a)	4	1.9	30	5.4	1.5	30	-1.40 [-2.27,-0.53]
	LIBERTY SINUS 24	3.75	1.98	143	5.94	1.44	133	-2.19 [-2.60,-1.78]
	LIBERTY SINUS 52	4.46	1.89	295	6.09	1.19	153	-1.63 [-1.92,-1.34]
	Subtotal (95% CI)		**468**			**316**		**-1.80 [-2.25,-1.35]**
	Heterogeneity: Tau²=0.10; Chi²=5.70, df=2 (P=0,.06); I²=65% Test for overall effect: Z=7.87 (P<0,.00001)							
	Until 52 weeks							
	LIBERTY SINUS 52	3.76	2.2	150	6.1	1.52	153	-2.34 [-2.77,-1.91]
	Subtotal (95% CI)		**150**			**153**		**-2.34 [-2.77,-1.91]**
	Heterogeneity: Not applicable Teste para efeito geral: Z=10.75 (P<0,.00001)							
	Total (95% CI)		**618**			**469**		**-1.94 [-2.36,-1.52]**
	Heterogeneity: Tau²=0.12; Chi²=10.73, df=3 (P=0,.01); I²=72% Test for overall effect: Z=9.10 (P<0,.00001) Test for differences between subgroups: Chi²=2.94, df=1 (P=0,.09); I²=65.9%							
Lund Mackay Score	**Until 24 weeks**							
	Bachert 2016 (a)	9.4	5.1	30	17.9	5.7	30	-8.50 [-11.24,-5.76]
	LIBERTY SINUS 24	10.89	4.82	143	18.97	4.51	133	-8.08 [-9.18, -6.98]
	LIBERTY SINUS 52	12.86	3.87	295	17.73	3.81	153	-4.87 [-5.62, -4.12]
	Subtotal (95% CI)		**468**			**316**		**-7.00 [-9.61,-4.39]**
	Heterogeneity: Tau²=4.64; Chi²=25.69, df=2 (P<0,.00001); I²=92% Test for overall effect: Z=5.25 (P<0,.00001)							
	Total (95% CI)		**468**			**316**		**-7.00 [-9.61,-4.39]**
	Heterogeneity: Tau2=4.64; Chi2=25.69, df=2 (P<0,.00001); I2=92% Test for overall effect: Z=5.25 (P<0,.00001) Test for differences between subgroups: Not applicable							

Evaluated Parameter	Study or Subgroup	Intervention Group			Placebo Group			Mean Difference; Mean, IV, Random, 95% CI
		Mean	Standard Deviation	Total Participants	Mean	Standard Deviation	Total Participants	
OMALIZUMAB								
SNOT-22	POLYP 1 (b,c)	-24.7	17.06	72	-8.58	16.9	66	-16.12 [-21.79,-10.45]
	POLYP 2 (b,c)	-21.59	17.72	62	-6.55	17.66	65	-15.04 [-21.20,-8.88]
	Total (95% CI)			**134**			**131**	**-15.62 [-19.79,-11.45]**
	Heterogeneity: Tau²=0.00; Chi²=0.06, df=1 (P=0,.80); I²=0% Test for overall effect: Z=7.34 (P<0,.00001)							
NPS	Gevaert 2013 (b,d)	-2.67	1.55	15	-0.12	0.03	8	-2.55 [-3.33,-1.77]
	POLYP 1 (b,c)	-1.08	1.36	72	0.06	1.3	66	-1.14 [-1.58,-0.70]
	POLYP 2 (b,c)	-0.9	1.34	62	-0.31	1.29	65	-0.59 [-1.05,-0.13]
	Total (95% CI)			**149**			**139**	**-1.37 [-2.30,-0.44]**
	Heterogeneity: Tau²=0.59; Chi²=17.91, df=2 (P=0,.0001); I²=89% Test for overall effect: Z=2.89 (P=0,.004)							
Lund Mackay Score	Gevaert 2013 (d)	-13.6	4.33	15	18.3	6.32	8	-4.70 [-9.60,0.20]
	Total (95% CI)			**15**			**8**	**-4.70 [-9.60,0.20]**
	Heterogeneity: Not Applicable Test for overall effect: Z=1.88 (P=0,.06)							
MEPOLIZUMAB								
SNOT-22	**Mean minimum square**							
	Bachert 2017 (e)	27.19	22.12	54	40.4	24.59	51	-13.21 [-22.17,-4.25]
	Subtotal (95% CI)			**54**			**51**	**-13.21 [-22.17,-4.25]**
	Heterogeneity: Not Applicable Test for overall effect: Z=2.89 (P=0,.004)							
	Mean							
	SYNAPSE (b)	-29.4	24.67	206	-15.7	23.93	201	-13.70 [-18.42,-8.98]
	Subtotal (95% CI)			**206**			**201**	**-13.70 [-18.42,-8.98]**
	Heterogeneity: Not Applicable Test for overall effect: Z=5.69 (P<0,.00001)							
	Total (95% CI)			**260**			**252**	**-13.59 [-17.77,-9.42]**
	Heterogeneity: Tau²=0.00; Chi²=0.01, df=1 (P=0,.92); I²=0% Test for overall effect: Z=6.38 (P<0,.00001) Test for differences between subgroups: Chi²=0.01, df=1 (P=0,.92); I²=0%							
NPS	Gevaert 2011 (b)	-1.3	1.72	20	0	0.94	10	-1.30 [-2.25,-0.35]
	SYNAPSE (b)	-0.9	1.9	206	-0.1	1.46	201	-0.80 [-1.13,-0.47]
	Total (95% CI)			**226**			**211**	**-0.85 [-1.16,-0.54]**
	Heterogeneity: Tau²=0.00; Chi²=0.95, df=1 (P=0,.33); I²=0% Test for overall effect: Z=5.38 (P<0,.00001)							

Evaluated Parameter	Study or Subgroup	Intervention Group			Placebo Group			Mean Difference; Mean, IV, Random, 95% CI
		Mean	Standard Deviation	Total Participants	Mean	Standard Deviation	Total Participants	
BENRALIZUMAB								
SNOT-22	NCT03450083 (b)	-19.2	2.6	12	-14.6	20.1	12	-4.60 [-16.07,6.87]
	OSTRO (b)	-15.1	33.55	207	-7.9	33.22	203	-7.20 [-13.66,-0.74]
	Total (95% CI)	**219**			**215**			**-6.57 [-12.20,0.94]**
	Heterogeneity: Tau^2=0.00; Chi^2=0.15, df=1 (P=0,.70); I^2=0% Test for overall effect: Z=2.29 (P=0,.02)							
NPS	NCT03450083 (b)	-0.9	0.2	12	-0.3	0.3	12	-0.60 [-0.80,-0.40]
	OSTRO (b)	-0.22	1.76	207	0.18	1.44	203	-0.40 [-0.71,-0.09]
	Total (95% CI)	**219**			**215**			**-0.54 [-0.72,-0.35]**
	Heterogeneity: Tau^2=0.00; Chi^2=1.11, df=1 (P=0,.29); I^2=10% Test for overall effect: Z=5.74 (P<0,.00001)							
Lund Mackay Score	NCT03450083 (b,c)	-4.2	2.69	12	-1.6	2.94	12	-2.60 [-4.85,-0.35]
	OSTRO (b)	-0.93	5.06	207	-0.2	4.2	203	-0.73 [-1.63,0.17]
	Total (95% CI)	**219**			**215**			**-1.37 [-3.10,0.37]**
	Heterogeneity: Tau^2=0.98; Chi^2=2.28, df=1 (P=0,.13); I^2=56% Test for overall effect: Z=1.54 (P=0,.12)							

SNOT-22 – Sinonasal Outcome Test-22; NPS – Nasal Polyp Score
IV –Inverse Variance
IC – Confidence Interval
(a) 16 weeks of follow-up;
(b) Change in the baseline;
(c) Standard deviation calculated from the standard error;
(d) Standard deviation calculated from the p-value;
(e) Standard deviation calculated from the confidence interval;