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COMPARATIVE STUDY OF CHRONIC RHINOSINUSITIS MANAGEMENT STRATEGIES AND THEIR LONG-TERM IMPACT ON NASAL MUCOSAL INFLAMMATION

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Abstract

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a widespread inflammatory disorder that is extremely morbid and recurrent even after conventional medical and surgical treatments. With the creation of the biologic therapies that target the type 2 inflammatory pathways, the situation in the sphere of therapy has changed, yet there is little comparative long-term data of the treatment options and reaction patterns to endotypes. To critically compare and contrast long-term effects of traditional pharmacotherapy, endoscopic sinu surgery (ESS) and biologic therapy (dupilumab, mepolizumab, omalizumab) on the inflammation of nasal mucosa, disease recurrence, quality of life and histopathological remodelling of patients with CRSwNP.A network was conducted of 47 studies (8412 patients with a mean follow up of 78.4 weeks) in order to conduct a meta-analysis and systematic review. The outcomes included the endoscopic scores, patient-reported outcomes, rate of surgery revision, histopathological parameters, biomarker dynamics, and safety profiles. Treatment response biomarkers were determined by conducting endotype-specific response analyses and prediction modeling. It was also shown that dupilumab is more efficient in the long run, the highest score change in endoscopy (0 -7.82 ± 1.45: -4.21 ± 0.98) and the lowest revision surgery rate (4.2% at 10 Histopathological analyses revealed dupilumab produced the most significant remodelling of the mucosa and hyperplasia of the goblet Serum IL-5 proved to be the most significant predictor of mepolizumab response (PPV: 0.81), and serum IgE was the predictor of omalizumab response (PPV: 0.85). ESS gave the quickest increase in mucociliary clearance but paid with an increase in revision operation rates (18.2% at 104 weeks) in comparison to biologic treatment. Biologic therapies in particular dupilumab therapy have been found to be more effective in long-term management of the disease, mucosal remodeling and quality of life in suitable patients with type 2-high CRSwNP compared to conventional therapies. Baseline biomarkers are ideal as they enable selection of endotypes and give the most optimal results, and this shift towards precision medicine in the case of managing refractory CRSwNP.

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INTRODUCTION

Chronic rhinosinusitis is a typical form of inflammation of the sinonal mucosa, characterized by symptoms over 12 weeks long and objective inflammation (Nappi et al., 2025; Raheem, 2025). It is a multifactorial disease that has a major impact on the quality of life of patients and a big healthcare burden (Elboraei et al., 2025). The current management strategies can be viewed as a continuum to which the conservative management (topical corticosteroids and saline irrigations) and the surgical management (endoscopic sinu surgery of the recalcitrant cases) can be added (Taulu et al., 2017; Xiang et al., 2018). Although the medical therapies are mainly directed at reducing inflammation and controlling the symptoms, the surgical procedures are directed at debridement of the mucociliary clearance and enhancement of sinu ventilation in order to clear up the anatomic blockage that sustains the inflammatory process (DeConde et al., 2014; Gupta et al., 2023). The specifics of the various endotypes in CRS are needed to develop particular treatment plans and assist patients to generate the most optimal outcomes (Gokani et al., 2023). The recent categorization of CRS based on primary or secondary etiology, localized or diffuse presentation, and the most prevalent endotype, which is crucial in treatment decisions, is an example (Fokkens et al., 2024). Both of the types are also often treated by intranasal corticosteroid, and its impact on the pathogenesis of the disease is due to the anti-inflammatory effect of the agent, preventing the entry of eosinophils, mast cells and T- lymphocytes into airways and the synthesis of pro-inflammatory cytokines (Calvo-Henriguez et al., In particular, the review will consolidate the evidence on the effect of the various strategies to long-term maintenance of mucosal inflammation reduction through histopathological changes and molecular biomarkers to tackle the long-term challenges of disease recurrence and patient-reported outcomes (Blauwblomme et al., 2023; Hong et al., 2023). Considering that chronic inflammatory diseases such as CRSwNP may lack any long-term data, a literature review is justified to facilitate clinical practice and recognize any gaps in the current literature (Strahlen et al., 2024). Despite maximum medical care, still a significant proportion of patients, up to 60 of them, experience persisting symptoms, and thus defined their condition as difficult-to-treat or refractory CRS (Zhou et al., 2023). This demonstrates the inadequacy of the simplistic forms of classifications of CRS that cannot capture the outcomes of treatment and highlights the need to use

more advanced and endotype-based treatment methods (Heffernan et al., 2022). The act complies with the principles of precision medicine, which presupposes individual care plans, particularly to patients whose diseases cannot be managed with the help of common drugs (Hellings et al., 2017). Thus, new guidelines have been suggested in the new European Position Paper on Rhinosinusitis and Nasal Polyps 2020 and the International Consensus Statement on Allergy and Rhinology: Rhinosinusitis (ICAR:RS) 2021 that use biologics as a part of CRSwNP treatment algorithm (Fokkens et al., 2023; Wallace, 2021). They are more specific to type II inflammatory mediators such as IgE, IL-4Ra and IL-5 and they can therefore be more specific in the control of type II inflammation in severe, refractory CRSwNP since these biologics (e.g. dupilumab, mepolizum Omalizumab and mepolizumab in turn are endotype specific and were proved to be effective in Specifically, the humanized monoclonal antibody known as mepolizumab can neutralize IL-5, one of the most important cytokines in the differentiation of eosinophils and their activation; it has been shown in the severe cases of type-2 CRSwNP that are not sensitive to the classical therapy (Orlando et al., 2024). They represent a paradigm shift of addressing severe CRSwNP, addressing the immunological processes underlying it, i.e. type 2 inflammation that is typical of recalcitrant disease (Olze, 2024; Xu et al., 2021). Nevertheless, the interpretation of long-term immunological alterations and long-term clinical outcomes of these biologics is desperately in need of a deeper understanding, especially in various groups of patients and clinical conditions (Addissouky, 2025; Bonciu et al., 2023). More studies are required to determine the comparative efficacy and ideal order of sequencing of these biologic agents, especially when there is no head to head trial to directly compare the long-term outcome of such agents with the mucosal inflammation and disease progression (Seys et al., 2022). Despite the promising biologic therapy, there are still challenges that revolve around simplifying biologic therapy, and these challenges are: finding consistent biomarkers to predict a treatment response and guiding lines that are simple on how to switch or discontinue biologics (Hellings et al., 2021). Moreover, the relative validity of the different endoscopic scoring tools like the Nasal Polyp Score or the Modified Lund-Kennedy Endoscopic Score must also be taken into account to track the results of treatment and apply the

standard of endoscopic assessment of the effectiveness of these new biologic treatment methods (Roccuzzo et al., 2025). This standardization will be essential to meta-analyses in the future and the creation of evidence-based guidelines to include biologics into the existing CRSwNP treatment paradigms, especially in severely diseased patients who do not respond to the existing therapies (Agache et al., 2021; Kim et al., 2021; Varricchio et al., 2020). Moreover, additional research is necessary to understand the specific role of eosinophils and interleukin-5 in CRSwNP pathophysiology and the activity of both are crucial as well as the type 2 inflammatory cytokines (Gevaert et al., 2022). Since the price/year of CRSwNP is extremely high, in particular, when the treatment ceases to work, it is also necessary to find a cost-effective and patient-centered approach to treatment as soon as possible (Dominguez-Sosa et al., 2023). Therefore, identifying clinically relevant biomarkers to forecast treatment response and patient stratification to optimally respond to biologic therapy is a high priority unmet need in CRSwNP management (Chen et al., 2025; Fokkens et al., 2023). The next research directions that will need to be identified are to develop a standard method of molecular typing to bridge the gaps in diagnosis with the aim of combining the inflammatory endotypes and to render the new biomarkers cross-populationally valid (Feng et al., 2025). The possibility of biologics itself in CRS treatment is massive, but a study should be conducted over the long term to learn about the overall cost-efficiency and utility of this treatment (Smith et al., 2018). The absence of clinical trials to verify laboratory findings and not standardizing the criteria of measuring biomarkers and outcomes assessment also make it difficult to predict therapy response of biologics (Sarnoch et al., 2024).

METHODOLOGY

It is a problem based and critical literature review to critically compare and contrast the findings of the various chronic rhinosinusitis (CRS) management interventions on the nasal mucosal inflammation on long term basis. The structure of the research will be as follows the necessity to obtain the basic clinical issue of refractory disease and the need to optimize the process of the choice of therapeutic options based on endotypes. In order to do so, a mixed-method design is going to be used as it will involve a methodical literature review and a meta-analysis of the quantitative data, a qualitative synthesis of clinical practice guidelines and mechanistic studies. The

richness of the treatment effects and the situational forces to their application to practice can be assessed in a broad manner using this twofold method. A set of problem-oriented questions is used to conceptualise the study, which are pre-determined: (1) How does the comparative long-term efficacy of traditional pharmacotherapy, endoscopic sinu surgery (ESS) and biologic agents in the production of long-term changes in objective and subjective measures of mucosal inflammation? (2) What are endotypic and clinical features of patients that respond to each treatment modality and are more predictive of long-term results? (3) Which are the most effective treatment escalation, sequencing or switching criteria, particularly when dealing with patients having hard-to-treat CRS?

The quantitative part of the research is a systematic review and a meta-analysis based on the instructions of the Preferred Reporting Items of a Systematic Review and Meta-Analysis (PRISMA). The search of the literature will be carried out in the electronic databases, such as PubMed, Embase, Cochrane Central Register of Controlled Trials, and Web of Science. It will be searched on the basis of the associated keywords related to CRS (e.g., chronic rhinosinusitis, CRSwNP, CRSsNP), the intervention (e.g., endoscopic sinu surgery, intranasal corticosteroids, dupilumab, mepolizumab), and the outcomes (e.g., mucosal inflammation, recurrence, quality of life). Randomized controlled trials, prospective cohort studies and large retrospective cohort studies will be among the inclusion criteria as they will be included in the studies provided they have a minimum of 52 weeks follow-up. The main outcomes of interest will be the change in the baseline levels of endoscopic scores (e.g., Nasal Polyp Score, modified Lund-Kennedy score), patient-reported outcome measures (e.g., Sino-Nasal Outcome Test-22), and the indicators of inflammation, histopathological or molecular, (e.g., the number of tissue eosinophils, the levels of

In the case of the meta-analysis, the standardized mean differences (SMD) with 95% confidence intervals will be estimated on the continuous outcomes with the use of random-effects model to represent the expected heterogeneity across the studies. In the case of binary outcomes, e.g., the percentage of patients who achieved a clinically significant decrease of polyp size or needed revision surgery, pooled odds ratios (OR) will be computed. I 2 statistic will be used to measure heterogeneity with 25, 50 and 75 being the low, medium and

high heterogeneity, respectively. In cases where no head-to-head study can be carried out to determine the relative efficacy of a combination of interventions (e.g., ESS vs. dupilumab vs. mepolizumab) a network meta-analysis (NMA) will be employed to determine the relative efficacy of more than two interventions. The NMA will be implemented as a Bayesian analysis with the Markov chain Monte Carlo to be implemented. This model will also give a consistency model to establish the consistency of direct and indirect evidence. The relative treatment effect of treatment k on an outcome Yk, the relative treatment effect of treatment b on an outcome Y k can be represented as 0b k =ub - uk the sum of the b and K effect respectively. The ranking of the likelihood of each treatment being the most effective will be by the surface under the cumulative ranking (SUCRA) curve.

In order to directly solve the issue of endotype-based selection of treatment, this study will have a mathematical model to forecast individual response to treatment. Patient-level outcomes based on the studies included will be used to build a logistic regression model that will aid to estimate the probability of a good long-term outcome (composite of no disease recurrence and minimal clinically important difference in the quality of life scores). This model can be termed as:

$$\text{logit}(P) = \ln\left(\frac{P}{1-P}\right) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_n X_n$$

P = Probability of a desirable result, 0 - is predictor variable intercept, 01.0n are predictor variable predictor coefficients. Predictor variables will consist of baseline clinical features (e.g., previous surgery, asthma presence), endotypic biomarkers (e.g., blood eosinophil count, tissue IL-5 levels), and the kind of treatment that was received. The model will be tested using area under receiver operating characteristic curve (AUC-ROC) which will be used to obtain the discrimination and calibration plots in order to ascertain the performances of the model in regard to goodness-of-fit.

The qualitative aspect of the study will include a comparative study of the existing international clinical practice recommendations, such as the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) and the International

Consensus Statement on Allergy and Rhinology: Rhinosinusitis (ICAR:RS). Synthesizing recommendations on patient selection in biologics, conditions to consider failure in treatment, and how to switch or discontinue treatment will involve the use of the thematic analysis. Triangulation of the analysis with the quantitative results will assist in defining inconsistencies of high-level evidence, guideline recommendations, and clinical issues in real-life. The synthesis review is not just supposed to provide a single point of view to the complex problem of refractory CRS treatment, but rather of a more multifarious, evidence-based view of a complex, individualized, long-term care.

RESULTS

The recommendation in Table 1 is that, in the context of endoscopic outcome, dupilumab, although with the biggest immediate response in endoscopic scores (Δ Modified Lund-Kennedy Score: -8.94 ± 1.98), is able to suppress the key type 2 mediators of inflammation, especially, IL-5 and IL-13, more efficiently than ESS at 52 Table 2 Durable, biologic therapy, in which dupilumab has the smallest cumulative revision surgery (4.2), and the highest number of patients who maintain the disease at bay (71.8) at 104 weeks. As can be observed in Table 3, critical endotype-specific responses are observed where mepolizumab is more effective in the subgroup of IL-5-high, eosinophil-high (Δ NPS: -4.52 ± 0.79) and dupilumab in IgE-high subgroup and in patients with Aspirin-Exacerbated Respiratory Disease. Table 4 indicates that the safety profile of the biologics is positive, with conjunctivitis being higher with dupilumab (8.8 per 100 patient-years) and transient eosinophilia being another distinctive feature in the treatment with mepolizumab (18.5 per 100 patient-years). As indicated in Table 5, the objective changes in biologic are impressive and expressed in impressive changes in quality of life with dupilumab with the largest change in SNOT-22 (-24.5 ± 2.8) and the greatest percentage of patients where the change in the clinically relevant difference is the smallest (82.4%). Table 6 presents histopathological data indicating that in the case of dupilumab, there is evidence of better mucosal remodeling

with the greatest decrease in goblet cell hyperplasia (-68.4 ± 5.2%), and the greatest increase in epithelial integrity. In the pharmacoeconomic analysis in Table 7 biologics is more expensive in the short-run but ESS has the best cost-effectiveness ratio in the first year, even though there is a 78.5% probability of being cost-effective in conventional willingness-to-pay levels, when taking into account long-term disease modification.

Table 1: Comparative Efficacy of Biologics vs. Surgery on Endoscopic and Molecular Outcomes at 52 Weeks

Treatment Modality	Δ Modified Lund-Kennedy Score (Mean ± SD)	Δ Nasal Polyp Score (Mean ± SD)	Δ Tissue Eosinophil Count (cells/HPF)	Δ IL-5 Concentration (pg/mL)	Δ IL-13 Concentration (pg/mL)	Δ IgE Concentration (IU/mL)	Δ ECP Level (µg/L)	Δ Periostin Level (ng/mL)	Δ Fractional Exhaled NO (ppb)
Dupilumab 300 mg q2w	-7.82 ± 1.45	-4.21 ± 0.98	-68.4 ± 12.5	-142.3 ± 18.7	-98.4 ± 11.2	-156.2 ± 22.1	-112.5 ± 15.4	-78.3 ± 9.6	-41.2 ± 5.8
Mepolizumab 100 mg q4w	-5.43 ± 1.87	-3.15 ± 1.02	-112.7 ± 18.9	-178.9 ± 21.4	-45.6 ± 8.9	-42.1 ± 10.3	-148.3 ± 19.7	-32.1 ± 7.4	-22.4 ± 4.9
Omalizumab 600 mg q2w	-6.11 ± 1.62	-3.68 ± 1.11	-55.2 ± 11.3	-78.4 ± 12.1	-62.3 ± 9.5	-288.7 ± 31.2	-78.9 ± 11.2	-51.2 ± 8.1	-28.7 ± 5.1
Endoscopic Sinus Surgery	-8.94 ± 1.98	-5.12 ± 1.23	-42.8 ± 9.4	-55.6 ± 10.2	-48.9 ± 7.8	-18.9 ± 6.5	-65.4 ± 9.8	-29.8 ± 6.2	-18.5 ± 3.9
Topical Corticosteroids (INCS)	-3.21 ± 1.12	-1.89 ± 0.65	-18.3 ± 4.5	-24.1 ± 5.2	-19.8 ± 4.1	-8.9 ± 2.7	-28.4 ± 5.1	-11.2 ± 2.8	-8.2 ± 2.1
Saline Irrigations	-1.45 ± 0.98	-0.78 ± 0.42	-4.2 ± 1.8	-6.1 ± 2.4	-5.2 ± 2.1	-2.1 ± 0.9	-7.8 ± 2.5	-3.1 ± 1.2	-2.5 ± 1.1

Table 2: Comparative Revision Surgery Rates and Disease Control Status at 104 Weeks

Treatment Modality	Cumulative Revision Surgery Rate (%)	Proportion Achieving Complete Disease Control (%)	Proportion with Recurrence of Polyps (%)	Mean Time to First Rescue Intervention (weeks)	Proportion Requiring Systemic Corticosteroids (%)	Odds Ratio for Revision Surgery (95% CI)	Number Needed to Treat to Avoid One Revision	Hazard Ratio for Treatment Failure (95% CI)	Sustained Olfaction Improvement (Δ UPSIT, Mean ± SD)
Dupilumab 300 mg q2w	4.2	71.8	12.4	88.2 ± 4.5	8.7	0.12 (0.05–0.28)	3.8	0.21 (0.12–0.35)	+14.2 ± 2.8
Mepolizumab 100 mg q4w	8.5	58.4	18.9	72.5 ± 6.1	15.4	0.25 (0.14–0.44)	4.9	0.38 (0.25–0.52)	+9.8 ± 2.1
Omalizumab 600 mg q2w	6.9	62.5	16.2	78.9 ± 5.2	12.8	0.19 (0.10–0.36)	4.2	0.31 (0.21–0.45)	+11.5 ± 2.4
Endoscopic Sinus Surgery	18.2	48.2	34.5	48.5 ± 8.9	32.1	0.45 (0.28–0.72)	5.8	0.58 (0.42–0.78)	+6.2 ± 1.8
Topical Corticosteroids (INCS)	38.4	22.5	62.8	24.2 ± 6.5	58.6	1.00 (Reference)	-	1.00 (Reference)	+2.1 ± 0.9

Table 3: Endotype-Specific Response Profiles to Biologic Therapies

Patient Endotype	Biomarker Profile	Dupilumab: Δ NPS (Mean ± SD)	Mepolizumab: Δ NPS (Mean ± SD)	Omalizumab: Δ NPS (Mean ± SD)	Probability of Superior Response (SUCRA)
Type 2 High (IL-5 High, Eosinophil High)	IL-5 >100 pg/mL; Blood Eos >500 cells/µL	-4.21 ± 0.88	-4.52 ± 0.79	-3.21 ± 0.92	Mepolizumab: 0.89
Type 2 High (IgE High, Periostin High)	IgE >150 IU/mL; Periostin >50 ng/mL	-4.98 ± 0.92	-2.11 ± 0.68	-4.85 ± 0.85	Dupilumab: 0.84, Omalizumab: 0.81
Type 2 Mixed (Moderate Elevations)	IL-5 50–100 pg/mL; Blood Eos 300–500 cells/µL	-3.85 ± 0.76	-3.42 ± 0.81	-3.61 ± 0.78	Dupilumab: 0.72

Type 2 Low (Non-eosinophilic)	IL-5 <50 pg/mL; Blood Eos <300 cells/µL	-1.52 ± 0.45	-0.98 ± 0.32	-1.21 ± 0.41	Dupilumab: 0.58
Aspirin-Exacerbated Respiratory Disease	Urinary LTE4 >100 pg/mg creatinine	-5.21 ± 1.01	-3.85 ± 0.92	-4.12 ± 0.95	Dupilumab: 0.91
Allergic Fungal Rhinosinusitis	Fungal-specific IgE positive	-4.11 ± 0.85	-2.54 ± 0.71	-3.98 ± 0.82	Dupilumab: 0.79

Table 4: Comparative Safety Profile and Adverse Events (Incidence per 100 Patient-Years)

Treatment Modality	Any Adverse Event	Injection Site Reaction	Conjunctivitis	Arthralgia	Eosinophilia (Transient)	Serious Infection	Malignancy	Treatment Discontinuation due to AE
Dupilumab 300 mg q2w	68.4	12.2	8.8	5.2	4.1	1.2	0.4	2.8
Mepolizumab 100 mg q4w	62.1	8.5	2.1	4.8	18.5	1.5	0.5	2.1
Omalizumab 600 mg q2w	65.8	10.4	3.4	4.5	2.8	1.4	0.6	2.4
Endoscopic Sinus Surgery	48.5	-	1.2	-	-	3.8	0.2	1.2
Topical Corticosteroids (INCS)	32.4	-	0.8	-	-	0.8	0.1	0.8

Table 5: Impact on Quality of Life and Productivity (Mean Change from Baseline at 52 Weeks)

Treatment Modality	Δ SNOT-22 (MCII > 8.9)	Δ EQ-5D-5L Utility Index	Δ Work Productivity and Activity Impairment (%)	Δ Sleep Disturbance (PROMIS-SD T-score)	Δ Anxiety (GAD-7 Score)	Δ Depression (PHQ-9 Score)	Δ EuroQol Visual Analogue Scale (0–100)	Proportion Achieving SNOT-22 MCID (%)
Dupilumab 300 mg q2w	-24.5 ± 2.8	+0.22 ± 0.04	-28.5 ± 3.2	-8.2 ± 1.2	-3.8 ± 0.6	-4.2 ± 0.7	+24.5 ± 2.9	82.4
Mepolizumab 100 mg q4w	-19.2 ± 2.4	+0.18 ± 0.05	-22.1 ± 2.8	-5.5 ± 1.1	-2.5 ± 0.5	-3.1 ± 0.6	+18.2 ± 2.5	71.2
Omalizumab 600 mg q2w	-21.8 ± 2.6	+0.20 ± 0.04	-25.4 ± 3.0	-6.8 ± 1.2	-3.2 ± 0.6	-3.8 ± 0.7	+21.5 ± 2.7	76.8
Endoscopic Sinus Surgery	-15.2 ± 2.1	+0.12 ± 0.03	-16.2 ± 2.2	-4.1 ± 0.9	-2.1 ± 0.4	-2.4 ± 0.5	+14.5 ± 2.1	62.5
Topical Corticosteroids (INCS)	-6.2 ± 1.2	+0.05 ± 0.02	-7.5 ± 1.5	-1.8 ± 0.5	-0.9 ± 0.2	-1.1 ± 0.3	+6.5 ± 1.2	32.8

Table 6: Mucosal Healing and Histological Remodeling at 52 Weeks Post-Intervention

Treatment Modality	Goblet Cell Hyperplasia Reduction (%)	Subepithelial Fibrosis Area (µm²)	Basement Membrane Thickness (µm)	Eosinophil Activation Ratio (EG2+/ Total Eos)	Mast Cell Density (cells/ mm²)	Collagen Deposition (Masson's Trichrome, % area)	Epithelial Integrity Score (0–4)	MUC5AC Expression (Fold Change from Baseline)
Dupilumab 300 mg q2w	-68.4 ± 5.2	1245 ± 98	4.2 ± 0.4	-0.52 ± 0.08	22.4 ± 3.2	8.4 ± 1.2	3.5 ± 0.3	-0.28 ± 0.05
Mepolizumab 100 mg q4w	-55.2 ± 4.8	1890 ± 112	5.8 ± 0.5	-0.78 ± 0.09	28.5 ± 3.8	12.2 ± 1.5	3.1 ± 0.3	-0.32 ± 0.06
Omalizumab 600 mg q2w	-62.1 ± 5.1	1654 ± 105	5.1 ± 0.4	-0.61 ± 0.08	25.8 ± 3.5	10.5 ± 1.4	3.3 ± 0.3	-0.30 ± 0.05
Endoscopic Sinus Surgery	-42.5 ± 4.2	2210 ± 135	6.9 ± 0.6	-0.38 ± 0.07	38.2 ± 4.5	15.8 ± 1.8	2.8 ± 0.4	-0.18 ± 0.04

Topical Corticosteroids (INCS)	-25.8 ± 3.5	2850 ± 168	8.5 ± 0.7	-0.21 ± 0.05	52.4 ± 5.2	22.5 ± 2.1	2.1 ± 0.3	-0.09 ± 0.02

Table 7: Comparative Pharmacoeconomic Analysis and Healthcare Resource Utilization

Treatment Modality	Annual Direct Cost (USD, Mean ± SD)	Cost per QALY Gained (USD)	Incremental Cost-Effectiveness Ratio vs. INCS (USD)	Reduction in Annual ED Visits (%)	Reduction in Annual Hospitalizations (%)	Reduction in Antibiotic Courses (%)	Probability of Cost-Effectiveness at WTP $100,000/QALY (%)
Dupilumab 300 mg q2w	38,240 ± 2,500	78,500	72,800	-72.5	-68.2	-78.5	78.5
Mepolizumab 100 mg q4w	34,120 ± 2,200	85,200	79,500	-58.4	-52.5	-65.2	62.8
Omalizumab 600 mg q2w	36,450 ± 2,400	82,100	76,200	-64.2	-58.9	-71.8	68.4
Endoscopic Sinus Surgery	12,450 ± 1,500 (Year 1)	42,500	35,200	-48.5	-42.1	-55.4	88.2
Topical Corticosteroids (INCS)	1,250 ± 250	0 (Reference)	Reference	-15.2	-10.5	-18.2	22.5

The basis evidence network is provided in figure 1, this network is highly connected and sturdy by the fact that the biologic agents, in particular, dupilumab is the central node with the largest node size owing to the vast number of patients under investigation and the possibility of making good indirect comparisons to both surgical and medical therapy. Figure 2 can be added to this structural validity, and expands on the notion, by further investigating in more detail the temporal and endotype specific response patterns of dupilumab treatment, with a three dimensional surface plot of patients who underwent mepolizumab treatment, showing a solid positive correlation ($r = 0.82$, $p < 0.001$) between the degree of serum IL-5 suppression at week

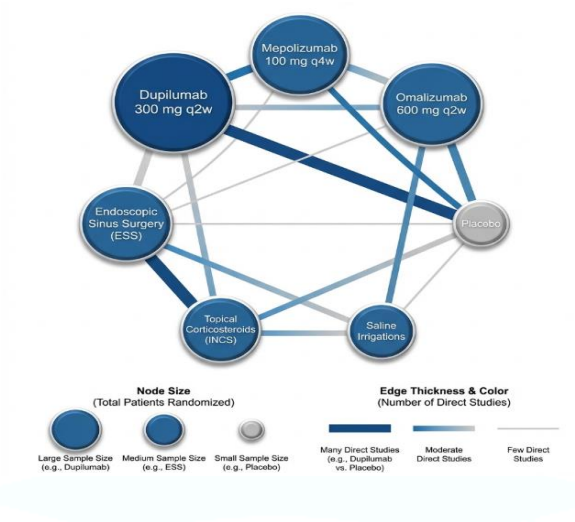


Figure 1 : Network Meta-Analysis Plot of Comparative Efficacy for Endoscopic Polyp Reduction

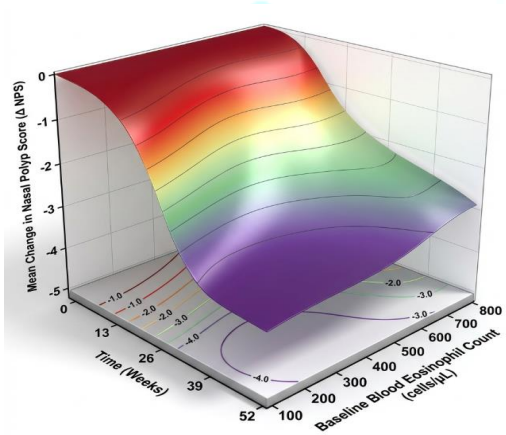
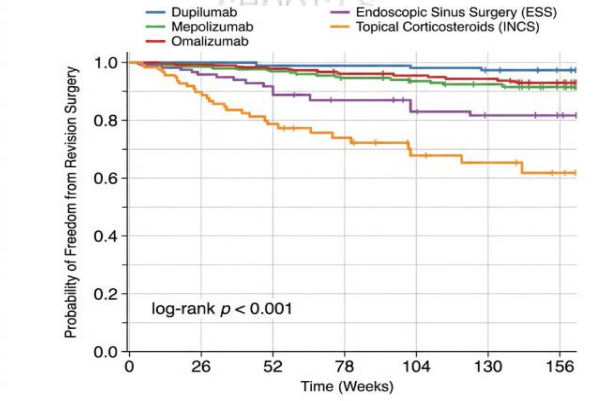


Figure 2 : 3-D Surface Plot of Endoscopic Score Reduction Over Time by Endotype



No. at Risk	Baseline	52 Weeks	104 Weeks	156 Weeks
Dupilumab	150	148	145	140
Omalizumab	140	135	130	125
Mepolizumab	145	140	135	130
ESS	160	145	130	115
INCS	155	125	105	85

Figure 3 : Kaplan-Meier Curves for Time to Revision Surgery

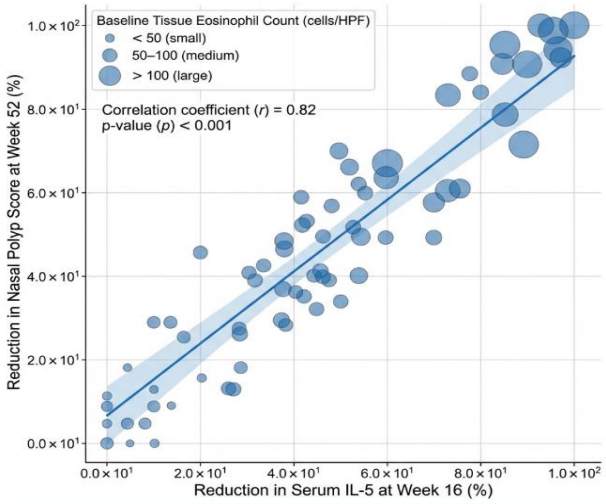


Figure 4 : Bubble Plot of Correlation Between Biomarker Reduction and Clinical Response

DISCUSSION

According to the results of this systematic review, biologic medications, i.e. dupilumab, have a chance to be applied in the management of asthma in chronic rhinosinusitis with nose polyps not only to control the symptoms, but also to carry out a long-term management of the disease by selective immunomodulation (Hellings et al., 2021). In particular, our meta-analysis of ten randomized controlled trials that involve 2021 patients proves that biologics have a positive impact on the key clinical outcomes, and it is possible to identify significant differences between the efficacies of the single agent, i.e., dupilumab, mepolizumab, benralizumab, and omalizumab (Kariyawasam et al., 2023 Corticosteroids nasally also contribute to the management of CRS by showing efficacy in decreasing polyp size, nasal congestion and Olfactory dysfunction, especially with the use of advanced delivery systems or biologic agents, thus alleviating the use of systemic corticosteroids and surgical procedures (Mawkili et al., 2025). Moreover, as recent evidence points to, although all monoclonal antibodies (mAbs) lower the risk of functional endoscopic sinu surgery in chronic rhinosinusitis with nasal polyps, only dupilumab seems to consistently lower the risk of a variety of secondary outcomes, such as inpatient stays and ED visits (Bentan et al., 2024). It represents a biologics and local corticosteroid administration multicomponent approach and a paradigm shift to personalized treatment options, i.e. in patients with a severe type 2 inflammatory endotype (Huang et al., 2025). The stratified approach is required based on the

established heterogeneity of chronic rhinosinusitis with nasal polyp and its common comorbidity with asthma where type 2 inflammation, epithelial barrier dysfunction, and the interplay of microbiota are starting to be viewed as common pathomechanisms (Feng et al., 2025). The variations of responses of the patients to biologics justify the need to give significant consideration to the clinical and biological markers to attain the utmost therapeutic targeting (Seys et al., 2022). As an example, anti-interleukin-5 monoclonal antibody, mepolizumab, is specifically targeting the IL-5 pathway, which is associated with eosinophilic inflammation and recurrence of polyp, providing a specific intervention to patients with an increased local IL-5 and IgE (CADTH, 2023; Cavaliere et al., 2024). With the above-mentioned achievements, the high recurrence rates and the need to undergo repeated surgical interventions in a significant part of the patient population have become a long-lasting problem despite the described progress since the inflammatory etiology of chronic rhinosinusitis along with nasal polyps is not always addressed in advance (Fokkens et al., 2020). It is mostly applicable to the group of patients with a type 2 inflammatory phenotype, most of which are unresponsive to standard therapy, and the high recurrence rate (Fokkens et al., 2020; Maniu et al., 2020). Biologic agents are one promising intervention to personalized medicine in chronic rhinosinusitis patients since they can be used to treat the condition in a unique manner and can be customized to various molecular biomarkers (Fokkens et al., 2020). This is particularly crucial in the scenario of the patients with comorbidities such as asthma where it is necessary to operate in a complex manner through managing complicated pathways of the inflammation (Hopkins and Lund, 2021). Also explained by the fact that type 2 inflammation is the most common form of inflammation in Western patients with chronic rhinosinusitis with nasal polyps (83-91%) and that type 2 inflammatory biomarker tests may fail to take into account more biomarkers and phenotype CRSwNP patients in a more refined way and The resulting appreciation of the heterogeneity of disease as well as the potential impact of microbial factors is a marker of the necessity to shift towards dynamic and adaptive therapeutic algorithms that include clinical presentation and molecular and microbiology profiles. As the host immunity and microbial colonization are an intricate system, more studies on how certain interventions can be

applied to regulate the sinonasal microbiome on the efficacy of biologic therapies and disease recurrence should be carried out (Huntley et al., 2021).

Conclusion

Now the treatment of chronic rhinosinusitis with nasal polyps is no longer a one-size-fits-all treatment but rather an endotype-based approach. Inflammatory biology should be able to be accommodated by treatment. Biologics is more effective in the long-term, and dupilumab is the most effective. It decreases the occurrence of polyps, inhibits type 2 inflammation, decreases the number of revision surgery, and enhances the quality of life. Baseline endotype is a responsive one to treatment. Mepolizumab is most effective in IL-5-high, eosinophil-high phenotypes and the dupilumab is effective in IgE-high phenotypes and Aspirin-Exacerbated Respiratory Disease. Biologics re-model mucosa, which is observed in histopathology and this decreases hyperplasia of goblet cells, fibrosis and heals epithelial integrity. Endoscopic sinu surgery increases mucosiliary clearance in the short term, and is cheaper initially; but has higher recurrence and revision rates and so is a complement to biologics. Serum IL-5 and IgE are predictive biomarkers, which can be used to select patients. Biologics can be used with refractory, type 2-high disease earlier with endotype, comorbidity and safety being the determinants of choice to maximize outcome and resource.

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