Therapeutic outcomes of biologic switching in chronic rhinosinusitis with nasal polyps: a systematic review and meta-analysis

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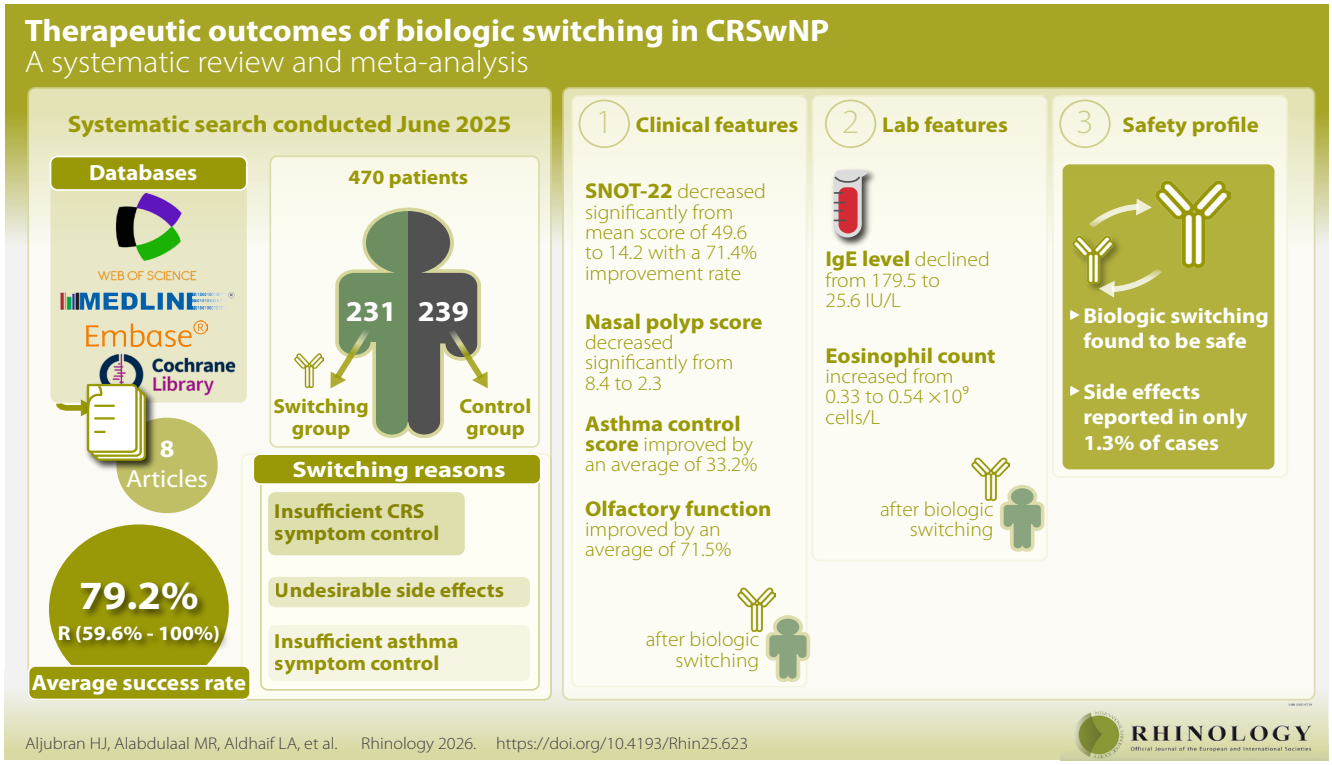


Abstract

Background: Biological therapy is a newer line of treatment that has been utilized in practice for patients with chronic rhinosinusitis with nasal polyps, showing excellent results. However, some patients with chronic rhinosinusitis with nasal polyposis (CRSwNP) do not respond to this therapy. Hence, this study aims to evaluate the efficacy and safety of biological switching in these patients.

Methodology: Using the Web of Science, Cochrane, MEDLINE, and Embase databases, we analyzed studies involving biological switching in CRSwNP patients published up to June 2025. The studies were extracted, and data were pooled for meta-analysis.

Results: Of 3,367 studies identified, eight studies (involving 470 patients) were included in the systematic review, four of which were included in the meta-analysis. The results showed that the most common reason for switching was insufficient CRS symptom control (59.7%), followed by undesirable side effects (10.8%). The findings demonstrated dramatic effects of biological switching in terms of the SNOT-22 score, with a mean improvement of 71.4%. In addition, studies that switched patients to dupilumab showed significant improvement after switching in both SNOT-22 and nasal polyp scores. Overall, the success rate of biological switching ranged from 59.6% to 100%, with an average success rate of 79.2%.

Conclusions: This review demonstrated the effect of biological switching as an option for patients with refractory CRSwNP or those experiencing biological side effects. These findings highlight a new therapeutic alternative that can serve as a fundamental choice when managing CRSwNP patients.

Key words: chronic rhinosinusitis, nasal polyposis, biological therapy, switching

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a chronic inflammatory condition affecting approximately 2–4% of the population in Western countries. Type 2 inflammation is the most prevalent underlying mechanism, present in about 85% of patients, and involves cytokines such as interleukin (IL)-4, IL-5, and IL-13, along with prominent eosinophilic infiltration [1,2]. The condition often coexists with asthma, a connection explained by the unified airway hypothesis, which proposes that the upper and lower airways share similar type 2 inflammatory pathways [3]. In addition to asthma, other common comorbidities include allergic rhinitis and NSAID-exacerbated respiratory disease (NERD). Patients with both CRSwNP and asthma often experience a greater symptom burden, and management sometimes become more complex when the two conditions coexist [4,5]. The inflammatory nature of CRSwNP continues to pose a significant challenge for otolaryngologists, as many patients fail to achieve full symptom relief despite available treatments [6]. Even after sinus surgery or the use of topical corticosteroids, a considerable number of individuals remain symptomatic and show only partial disease resolution [7]. In response, multiple biological agents were recently examined in treating this condition. Recent real-world studies have demonstrated that most patients with CRSwNP respond favorably to biologic therapy; however, a minority of patients may exhibit suboptimal response, for whom switching between biologic agents has been proposed as a potential management strategy. Nevertheless, evidence regarding biologic switching remains limited [8–11]. Existing studies are generally small, retrospective, and variable in follow-up duration [9,12,13]. Some studies suggest that outcomes may vary depending on the sequence of biologics used, yet the absence of comparative trials and consistent outcome measures limits evidence-based recommendations [10,11,14]. This study aims to systematically evaluate the clinical effectiveness and safety of switching biologic therapies in patients with CRSwNP, focusing on outcomes such as symptom control, nasal polyp size, and quality of life.

Materials and methods

Protocol and registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and followed the Cochrane Review methods, The protocol was registered in PROSPERO on February 3, 2025 (CRD42025648431).

Information sources

A complete literature search was conducted using four electronic databases: MEDLINE (ProQuest, Ann Arbor, MI, USA), Embase (OvidSP), the Cochrane Central Register of Controlled Trials (OvidSP), and Web of Science (Clarivate). The search was confined to studies published in English-language. The publishing date range was set from inception to June 2025. Furthermore, the reference lists of all eligible studies were reviewed, and Google Scholar was searched to identify any potentially relevant research not recorded in the primary databases.

Search strategy

To guarantee comprehensive coverage of relevant studies, two sets of keyword categories were generated. The first group focused on terms related to CRSwNP, while the second includes terms associated with biologic treatments and treatment switching. Keywords were determined by evaluating the titles, abstracts, and full texts of relevant publications from the initial screening phase. The complete list of search terms and database-specific strategies is provided in Table S1.

Eligibility criteria

Studies were eligible if they were involved patients who switched from one biologic agent to another, and reported outcomes, such as symptom improvement, polyp size reduction, sinus inflammation, or adverse events. Only randomized controlled trials, case-control studies, and prospective or retrospective cohort studies were considered. Meanwhile, studies were excluded if they did not involve a switching intervention, lacked a confirmed CRSwNP diagnosis, failed to report relevant outcomes, or conducted on non-human sample. Additional exclusions included review articles, case reports, conference abstracts, editorials, expert opinions, non-English publications, and studies with high risk of bias. Studies involving pediatric populations or alternative comparators unrelated to biologic switching, were also excluded.

Selection process

All identified studies were imported into Rayyan software to examined for duplicates [15]. Then, the data was divided into two parts in which (L.D. and D.A.) screened the first part and (R.H. and Z.W.) screened the second part independently using a three-step process of the eligible articles. Any disagreements between reviewers on study inclusion were handled through discussion. If consensus could not be reached, another reviewer (H.J.) was consulted to make the final decision. Data extraction was later conducted to extract the most important and relevant outcomes, including study characteristics, participant demographics, biological therapy details (type, dose, frequency, duration, primary and secondary biological therapy), control group, primary outcomes (Sinonasal Outcome Test-22 [SNOT-22], Lund-Mackay score, Nasal Polyp Score, and olfactory function), and secondary outcomes (asthma control, IgE level, and eosinophil count).

Study quality assessment

The quality of the included studies was appraised using the

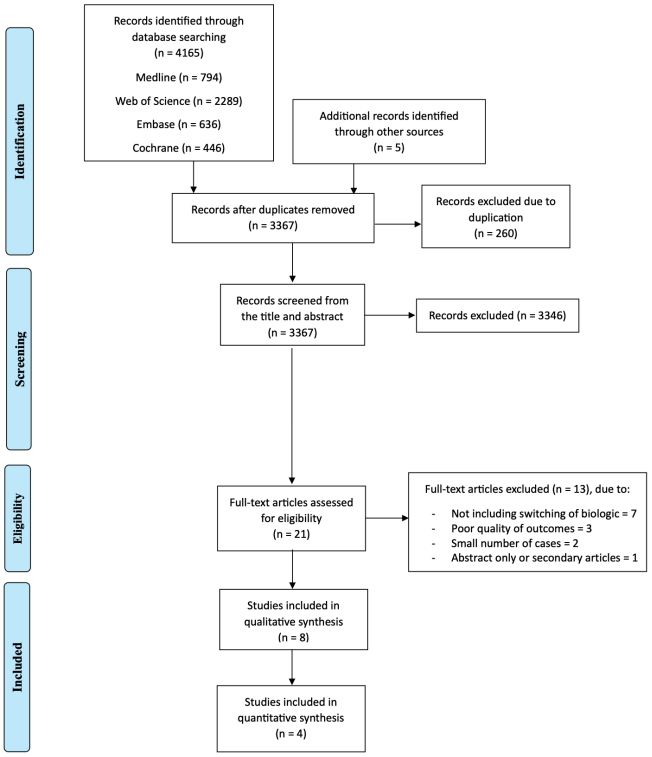


Figure 1. PRISMA flow-diagram of the search process.

Joanna Briggs Institute (JBI) critical appraisal tools, with instruments selected according to the specific study design [16,17]. Two reviewers independently assessed the studies, addressing domains such as participant selection, measurement validity, control of confounding variables, and the methodological integrity of the statistical procedures applied. Each item was rated as "yes," "no," "unclear," or "not applicable." Based on the responses, studies were classified as having low, moderate, or high risk of bias. A summary of the risk of bias assessments is provided in Table S2.

Statistical analysis

The included data in this study was analyzed using the RevMan (version 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Using the random effect model, forest plots were pooled and generated. Moreover, Higgins I^2 statistics was used to evaluate heterogeneity across included studies, with $I^2 > 50\%$ being considered significant. Due to the limited number of included studies, subgroup analyses or meta-regression to explore sources of heterogeneity were not performed. Additionally, inclusion of fewer than 10 studies eliminated the need for evaluation of publication bias. A p-value of less than 0.05 was considered significant in all data.

Results

Study selection

A total of 3,367 unique articles were identified from four different databases. After screening the title and abstract of each study, a total of 21 studies were eligible for full-text screening. From these studies, only eight studies were included in the final review, in which the remaining studies were excluded for the reasons detailed in the PRISMA diagram (Figure 1) [8–10,12–14,18,19].

Quality and bias assessment of the included studies

The quality of the included studies was evaluated according to the JBI critical appraisal tools. Further assessment can be found in Table S3. Most of the included studies were found to have an intermediate risk of information bias, while two studies were labeled to have low risk. In terms of selection bias, most studies involved low risk, except for two studies in which they were labeled as an intermediate risk. Meanwhile, there was variety in terms of confounding, as four studies had low risk, three had intermediate risk, and one study had high risk. In terms of the quality of statistical analysis, most of the studies had low risk, except for two studies labeled as high risk. Further details are included in Table S4.

Studies and population characteristics

The eight studies involved after the three-screening processes included 470 patients, in which they were further divided into case group (231 patients) and control group (239 patients). The case group included patients who were switched to another biological treatment, while the control group included patients who remained in their initial biological therapy, though not all the included studies involved patients in the control group. The publication year of the included studies was found to be between 2020 and 2025. Moreover, most of the studies were published in Europe, while one study was published in Japan and one study in Australia. Furthermore, all the eight included studies were retrospective cohort studies. The included studies have differences in terms of the baseline characteristics, which are detailed in Table 1.

Biological therapy features

This section provides details of the initial and second biological therapies used in the included studies, as shown in Table 2. The duration of the initial biological therapy was ranging between 6-20.5 months, while it was ranging between 6-18 months in the second biological therapy used. Regarding the type of initial biological therapy, it was varied across the included studies, as multiple biologics were used. Similarly, there were multiple biological agents used as a second therapy, though half of the studies switched all their patients into dupilumab (50%). The reason for switching varied across the studies, with insufficient CRS symptom control as the most common reason (59.7%).

Overall biological switching outcomes

Most of the included studies followed the EPOS/EUFOREA

Table 1. Baseline characteristics of the included articles.

Author	Country	Sample size (total; case group)	Mean age	Female %	Diagnosis	Asthma %	Mean number of previous FESS
Retrospective observational study							
Sacks, et al. (2025)	Australia	50; 21	Case: 46.1 ± 10.8 Control: 55.3 ± 12.8	Case: 57 Control: 55	Eosinophilic CRS	Case: 100 Control: 100	NR
Domínguez-Sosa, et al. (2024)	Spain	42; 21	Case: 48.1 ± 12.1 Control: 52.5 ± 11.9	Case: 57.1 Control: 28.6	CRSwNP	Case: 100 Control: 90.5	Case: 2 Control: 2
Dorling, et al. (2024)	Canada	225; 36	Case: 54.9 ± 15.4 Control: 50.9 ± 13.9	Case: 58.3 Control: 42.3	CRSwNP	Case: 91.7 Control: 80.4	Case: 2.37 Control: 2.25
Rosso, et al. (2024)	Italy	20; 20	54 ± 8.9	NR	CRSwNP	100	2.02
Habenbacher, et al. (2024)	Switzerland	4; 4	54 ± 1.6	100	CRSwNP	75	2
Otten, et al. (2023)	Netherlands Italy Germany	94; 94	48.9 ± 13.4	44.7	CRSwNP	91.5	NR
Brkic, et al. (2023)	Austria	17; 17	47.4 ± 40.3	58.8	CRSwNP	94.1	2
Hamada, et al. (2020)	Japan	18; 18	69.0 ± 11.7	55.6	Eosinophilic CRS	100	NR

CRS: Chronic rhinosinusitis; CRSwNP: Chronic rhinosinusitis with nasal polyposis; FESS: Functional endoscopic sinus surgery; NR: not reported.

guidelines to define the success of biological switching, as seen in Table 2. Generally, the success rate of switching from one biologic agent to another ranged from 59.6% to 100%, with an average success rate of 79.2% (Figure 2). Among the included studies, three studies in which all patients were switched to dupilumab reported an average success rate of 84.4%. In contrast, one study in which all patients were switched to benralizumab reported a success rate of 61.1%.

Clinical outcomes of biological switching

Regarding SNOT-22, five studies reported scores both before and after biologic switching. The mean SNOT-22 score before switching was 49.6, which decreased to 14.2 after switching, representing a 71.4% improvement. Among these five studies, four reported SNOT-22 outcomes after switching all patients to dupilumab, comprising a total of 79 patients. Our pooled analysis showed that biologic switching was associated with a significant reduction in SNOT-22 scores in patients with CRSwNP (34.39; 95% CI: 9.97–58.8; p = 0.006; Figure 3A). However, substantial heterogeneity was observed among the included studies (I^2 = 96%).

Overall, biologic switching demonstrated effectiveness in improving patients' clinical condition. Several included studies also reported improvements in olfactory function when the initial biologic therapy failed. For example, three studies reported an average 71.5% improvement in olfactory function following biologic switching. In addition to improvements in CRSwNP outcomes, some studies also observed improvements in asthma-related outcomes after switching biologics. Specifically, some studies reported an average 33.2% improvement in the Asthma Control Test score. However, one study in which patients were switched to benralizumab reported an increase in asthma exacerbations, rising from 0.6 to 0.8 episodes per year.

Endoscopic and laboratory outcomes of biological switching

Regarding the endoscopic findings, the nasal polyp score was reported by five studies, showing a 72.9% improvement rate, with mean scores decreasing from 8.4 before switching to 2.3 after switching. The pooled analysis of the four studies that switched their patients to dupilumab demonstrated a significant improvement in nasal polyp score after switching (1.62; 95% CI: 0.49–2.75; p = 0.005; Figure 3B), although there was substantial heterogeneity among these studies (I^2 = 89%). Regarding laboratory findings, three studies that switched patients to dupilumab reported an increase in eosinophil count, rising from 0.33 to 0.54 $\times 10^9$ cells/L after switching. Meanwhile, two studies reported a decline in IgE levels after switching to dupilumab, with mean levels decreasing from 179.5 to 25.6 IU/L.

Safety and side effects

Biological switching was found to be safe, as there were only minimal reported side effects (such as one facial xeroderma, one psoriasis, and one thrombocytopenia), with an average side effect of 1.3% among the included studies.

Discussion

The current high recurrence rates of CRSwNP despite standard treatment highlight the need for new therapeutic approaches

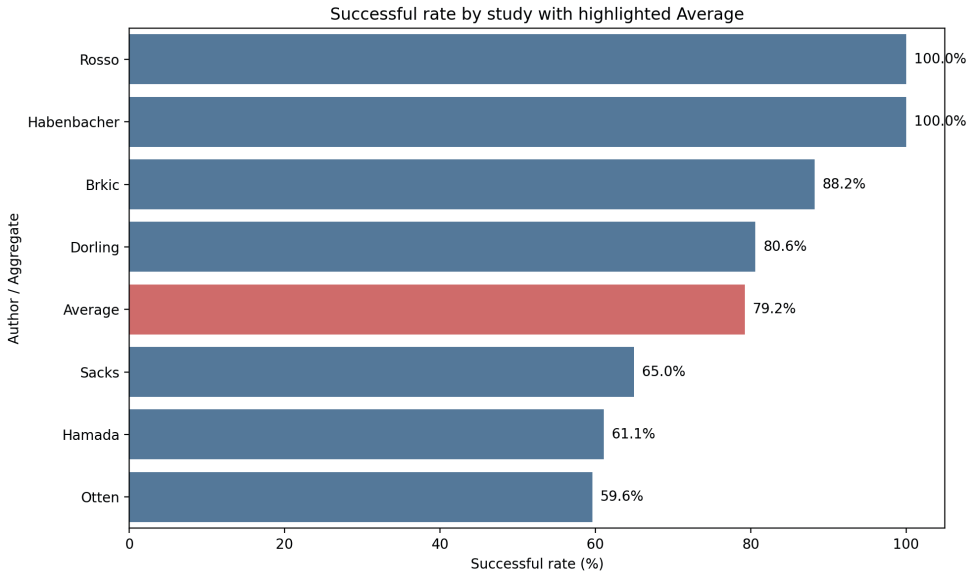
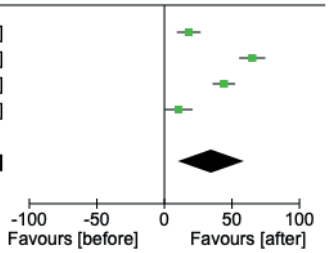


Figure 2. Distribution of the successful rate among the included studies after biologic switching.

Study or Subgroup	Before Mean	Before SD	Before Total	After Mean	After SD	After Total	Weight	Mean difference IV, Random, 95% CI
Brkic, et al. (2023)	33	11.11	17	15	14.81	17	25.1%	18.00 [9.20 , 26.80]
Domínguez-Sosa, et al. (2024)	71	21.11	21	6	8.15	21	24.9%	65.00 [55.32 , 74.68]
Rosso, et al. (2024)	56	14.81	20	12	11.85	20	25.2%	44.00 [35.69 , 52.31]
Sacks, et al. (2025)	30.5	16.6	21	20.1	18	21	24.8%	10.40 [-0.07 , 20.87]
Total (Wald[a])			**79**			**79**	**100.0%**	**34.39 [9.97 , 58.80]**

Test for overall effect: Z = 2.76 (P = 0.006)

Heterogeneity: Tau² (REML[b]) = 597.80; Chi² = 76.94, df = 3 (P < 0.00001); I² = 96%



Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Figure 3. Forest plot of the change in (A) SNOT-22 and (B) nasal polyp score after switching to dupilumab.

[20]. Recently, biologic agents targeting specific type 2 inflammatory pathways have been introduced, including omalizumab, mepolizumab and benralizumab, and dupilumab. These agents offer effective control of CRSwNP by reducing polyp size, improving symptom scores, and decreasing the need for surgical intervention [21–23]. Despite their overall effectiveness, treatment responses vary considerably among patients, leading to consideration of biologic switching as a potential strategy, although current guidelines on switching biologics in CRSwNP remain limited.

Generally, biologic therapy is indicated in CRSwNP patients with persistent nasal polyposis after endoscopic sinus surgery who meet at least three of five criteria: evidence of type 2 inflammation, need for systemic corticosteroids, significantly impaired quality of life, substantial loss of smell, or comorbid asthma [24]. Several biologics have been approved for CRSwNP, including dupilumab, omalizumab, and mepolizumab by the United States Food and Drug Administration (FDA) [25]. Dupilumab was the first approved biologic for CRSwNP as an add-on maintenance therapy for adults with severe disease inadequately controlled by corticosteroids. It is a fully human monoclonal antibody that inhibits IL-4Rα, blocking IL-4 and IL-13 signaling pathways, and has been shown to improve quality of life, endoscopic outcomes, and olfactory function, particularly in patients who previously failed other biologics [26,27].

Mepolizumab, an anti-IL-5 monoclonal antibody, reduces eosinophil activation and survival and is effective in patients with hypereosinophilia and eosinophilic asthma. It provides a reduction in polyp burden and nasal obstruction in eosinophilic cases [28,29]. Omalizumab, an anti-IgE monoclonal antibody, is an effective option for CRSwNP, particularly in allergic disease and in the presence of comorbid asthma, improving endoscopic

Table 2. Biological therapy features, post-treatment surveillance, and key findings of the included studies.

CRS: Chronic rhinosinusitis; NA: not applicable; NR: not reported.

	Control group			Switching group						
Author	Population	Biological therapy	Duration (months)	Initial biological therapy	Duration (months)	Second biological therapy	Duration (months)	Transition reason	Successful rate	Definition of success	Key findings
Retrospective observational study											
Sacks, et al. (2025)	Patients remained on initial biologics	Benralizumab: 100%	> 6	Benralizumab 100%	> 6	Dupilumab: 100%	NR	Insufficient CRS symptom control: 100%	65%	Based on EUFOREA response criteria	- Overall, there was a 65% successful switching to dupilumab. - 54.4% reduction in SNOT-22 after switching vs 60.3% increase in the control group. - 56.7% improvement in modified Lund-Kennedy score after switching vs 94.6% increase in the control group. - 71% reduction in tissue eosinophilia after switching. - 69.5% improvement in Asthma Control Symptoms after switching.
Dominguez-Sosa, et al. (2024)	Patients remained on initial biologics	Dupilumab: 100%	12	Benralizumab: 14.3% Omalizumab: 4.8% Mepolizumab: 80.9%	NR	Dupilumab: 100%	12	Insufficient CRS symptom control: 85.7% Insufficient asthma symptom control: 14.3%	NR	NR	- Biologic-pretreated patients and biologic-naive patients showed similar post-dupilumab findings. - 91.5% improvement in SNOT-22 after switching vs 91.4% in the control group. - 100% improvement in Nasal Polyp Score after switching vs 83.3% in the control group. - 80% improvement in Visual Analogue Scale in both groups. - 35.6% improvement in total IgE level after switching vs 61.2% in the control group. - There was a significant increase in the mean eosinophil count after switching.
Dorling, et al. (2024)	Patients remained on initial biologics	Dupilumab: 58.2% Mepolizumab: 40.2% Benralizumab: 1.1% Tezepelumab: 0.5%	19.59	Dupilumab: 30.6% Mepolizumab: 44.4% Omalizumab: 11.1% Benralizumab: 11.1% Reslizumab: 2.8%	15.28	Dupilumab: 30.6% Mepolizumab: 41.7% Omalizumab: 11.1% Benralizumab: 13.9% Reslizumab: 2.8%	NR	Insufficient CRS symptom control: 47.2% Insufficient asthma symptom control: 5.5% Side effects: 27.8% (54.5% of the dupilumab patients) insurance issues: 16.7% comorbid eczema: 2.8%	80.6%	Based on EUFOREA response criteria	- Overall, there was an 80.6% successful switching to another biological therapy. - Insufficient CRS symptom control was the most common cause of switching. - 2.8% of the patients required dual biologics therapy to control their symptoms. - 16.7% of the patients required another biologic switching to control their symptoms. - There was no improving in patients who were switched to another biological therapy in the same class.
Rosso, et al. (2024)	NA	NA	NA	Omalizumab Mepolizumab Benralizumab	15.1	Dupilumab: 100%	18	Insufficient CRS symptom control: 100%	100%	NR	- Overall, there was a 100% successful switching to dupilumab. - 78.6% improvement in SNOT-22 after switching. - 100% improvement in Nasal Polyp Score after switching. - 20% increase in mean eosinophil count after switching. - 93.3% improvement in total IgE level after switching. - 20% improvement in Asthma Control Test after switching. - 75% improvement in the olfactory function after switching.
Habenbacher, et al. (2024)	NA	NA	NA	Dupilumab: 50% Omalizumab: 25% Mepolizumab: 25%	NR	Dupilumab: 50% Mepolizumab: 25% Omalizumab: 25%	6	Insufficient CRS symptom control: 75% Side effects (joint pain): 25% (dupilumab)	100%	Based on EUFOREA response criteria	- 100% of the patients had successful switching for another biological therapy. - Insufficient symptom control was the cause of switching in 75% of patients. - 68.7% improvement in SNOT-22 after switching. - 81% improvement in Nasal Polyp Score after switching. - 53.8% improvement in the smell function after switching.
Otten, et al. (2023)	NA	NA	NA	Dupilumab: 17% Omalizumab: 35.1% Mepolizumab: 28.7% Benralizumab: 9.6% Reslizumab: 9.6%	15	Dupilumab: 48.9% Omalizumab: 4.3% Mepolizumab: 28.7% Benralizumab: 9,6% Reslizumab: 8.5%	16	Insufficient CRS symptom control: 45.7% Insufficient asthma symptom control: 16% Insufficient CRS and asthma symptom control: 24.5% Side effects: 13.8% (56.3% of the dupilumab patients)	59.6%	Based on EUFOREA response criteria	- Overall, there was a 59.6% successful switching to another biological therapy. - Insufficient CRS symptom control was the most common cause of switching. - 7.4% of the patients required dual biologics therapy to control their symptoms. - The combination of anti-IL5 with dupilumab showed a reduction in the mean eosinophil count. - 25.5% of the patients required another biologic switching to control their symptoms. - There was no improving in patients who were switched from anti-IL5 to another.
Brkic, et al. (2023)	NA	NA	NA	Omalizumab: 100%	11.4	Dupilumab: 100%	11.7	Insufficient CRS symptom control: 94% Side effects (joint pain): 6%	88.2%	Based on EUFOREA response criteria	- Overall, there was an 88.2% successful switching to dupilumab. - 54.5% improvement in SNOT-22 after switching. - 100% improvement in Nasal Polyp Score after switching. - 23.4% decrease in mean eosinophil count after switching. - 10.2% improvement in Asthma Control Test after switching. - 85.7% of the patients had improvement in the olfactory function after switching.
Hamada, et al. (2020)	NA	NA	NA	Mepolizumab: 100%	20.5	Benralizumab: 100%	16	NR	61.1	(1) No exacerbation or (2) No exacerbation and discontinued oral corticosteroids	- 61.1% of the patients showed successful switching from mepolizumab to benralizumab. - There was no significant change in Lund-Mackay score after switching. - Asthma exacerbation increased from 0.6 to 0.8 episodes per year after the switching mepolizumab to benralizumab.

findings and patient-reported outcomes [22]. Benralizumab (anti-IL-5R) has also shown the ability to reduce polyp size and nasal congestion; however, its overall impact has been less comprehensive, and it has not received approval for use in CRSwNP [30].

To evaluate the efficacy of biologic agents, the updated EPOS/EUFOREA guidelines have defined specific response criteria for these therapies [24]. These criteria include a reduction in nasal polyp size, a decrease in the need for systemic corticosteroids, improvement in quality of life, enhancement of the sense of smell, and reduction in other related comorbidities. Each criterion is used to categorize the overall response as follows: no response (0 criteria met), poor to moderate response (1–3 criteria met), and good to excellent response (4–5 criteria met). According to these guidelines, two initial evaluation periods are recommended—after 6 months and 1 year—followed by annual assessments [24]. Based on these criteria, several management strategies are suggested for patients showing no response, including discontinuation of therapy, switching to another biologic agent, or considering revision surgery. For those with a poor to moderate response, the next step depends on the patient's preference: they may continue the same biologic if partial benefit is observed or, if no significant improvement occurs, switch to another agent, undergo revision surgery, or receive a short course of systemic corticosteroids. Finally, patients demonstrating a good to excellent response are advised to continue with the same biologic therapy [31].

According to the EPOS/EUFOREA guidelines, biologic switching is a potential strategy for CRSwNP patients with inadequate symptom control. In the eight real-world studies included in this review, EPOS/EUFOREA guidelines was followed to define the success of biological switching. Specifically, many patients continued to experience a high sinonasal symptom burden despite ongoing therapy. For instance, approximately 85.7% of cases in one study reported a SNOT-22 score above 50 and a nasal polyp score of 5 or higher while receiving their initial biologic agent [19]. Another common reason for switching was worsening asthma control during treatment. In one study, the Asthma Control Questionnaire score remained ≥ 1.5 in roughly 34% of patients, indicating inadequate asthma improvement under the original biologic therapy [19]. In some cases, switching was also necessitated by adverse events or insurance-related issues [8].

The efficacy of some biologics has been more limited in specific subgroups. Omalizumab showed reduced effectiveness in patients without clear allergic triggers for their nasal polyps (the "non-allergic" endotype of CRSwNP) [8]. Similarly, IL-5 pathway inhibitors often provided incomplete control of nasal polyposis over the long term, with approximately 65% of patients receiving anti–IL-5 or IL-5R agents eventually requiring a switch due to persistent sinonasal symptoms [32]. A particularly noteworthy finding across studies involved patients with NERD, a challenging phenotype representing roughly 44–50% of certain cohorts. Nearly all NERD patients who had failed IL-5 blockade responded favorably when switched to dupilumab [8,19]. This near-universal response underscores the potent therapeutic effect of targeting the IL-4/IL-13 pathway in altering the disease trajectory in refractory CRSwNP cases.

When switching from one biologic to another, an interim "wash-out" period of approximately 4–8 weeks is commonly recommended. This practice is based primarily on pharmacokinetic reasoning rather than definitive clinical trial evidence. The rationale is that allowing several weeks between treatments gives the first biologic time to clear from the patient's system, thereby minimizing potential overlap or interference between therapies. For instance, a brief hiatus may permit any anti-drug antibodies formed during treatment with the initial biologic to diminish before initiating the new agent—anti-drug antibodies were detected in roughly 11% of omalizumab non-responders in one study [34]. Similarly, a wash-out period is thought to lower the risk of unforeseen immunologic interactions when switching between biologics with different mechanisms of action, such as transitioning from an anti-IgE antibody to an IL-4/IL-13 inhibitor. Theoretically, this interval also facilitates clearer interpretation of treatment outcomes, ensuring that any observed improvement can be attributed to the new biologic rather than residual effects of the previous one [34]. However, the optimal duration of the wash-out period remains uncertain, and clinical practice varies widely. While a 4–8-week interval is frequently advised and pharmacologically plausible, the decision ultimately depends on clinical judgment and patient-specific factors in the absence of conclusive data. In case of switching from mepolizumab to dupilumab, some reports suggest switching without a prolonged interval between treatments, which may help minimize the risk of treatment-associated hypereosinophilia during the initial months of dupilumab therapy [35].

Given the lack of clear, evidence-based guidelines on the optimal timing and criteria for switching between biologic therapies, several essential factors must be carefully considered before making such a decision. The first step is to confirm that the patient has been fully adherent to the prescribed biologic regimen and that comorbidities are well managed (such as ensuring that individuals with NERD completely avoid NSAIDs). It is also important to recognize that certain biologics are more effective for specific conditions, and thus the selection should be guided by disease characteristics rather than drug availability alone. Overall, the choice of therapy should be individualized based on patient-specific clinical factors, as summarized in Table 3. When a biologic fails to provide adequate control, switching within the same class is generally discouraged. Current evidence supports the use of dupilumab as a suitable alternative for patients unresponsive to anti–IL-5 or anti-IgE agents, especially in those with concomitant asthma or NERD, since it targets both upper and lower airway inflammation. Mepolizumab is preferred

Table 3. Consideration in choosing the best biologic switching agent in CRSwNP patients based on the patient-specific factors.

Patient factors	Preferred biological agent	Rational
High serum IgE	Omalizumab	Targets IgE-mediated inflammation
High blood or tissue eosinophils	Mepolizumab	Reduces eosinophilic inflammation
Elevated IgE and eosinophils	Dupilumab	Broader type-2 blockade (IL-4/13)
Bronchial asthma	Dupilumab	Improves both upper and lower-airway symptoms
Persistent loss of smell	Dupilumab	Most robust improvement in olfaction function
Aspirin-exacerbated respiratory disease	Dupilumab	Broader type-2 blockade (IL-4/13)
Intolerable side effects on Dupilumab	Mepolizumab or Omalizumab	Narrows inflammatory targeting

in patients with elevated eosinophil counts, whereas omalizumab remains effective for those with asthma and high IgE levels. Dupilumab can be replaced by mepolizumab or omalizumab in cases of intolerance or adverse effects. Other biologics are not recommended as second-line options due to limited efficacy and lack of FDA approval, although benralizumab has shown a 61.1% success rate following mepolizumab failure [12]. In rare refractory cases, dual biologic therapy may be considered, but further research is needed to define treatment failure criteria, optimal switching strategies, and biomarker-based algorithms for individualized biologic selection [13].

This study has several key limitations. First, the included studies used heterogeneous endpoints, defining treatment success differently—for example, one used a 40-point SNOT-22 improvement, while another required 60 points—making cross-study comparisons difficult. Second, the pooled analyses showed substantial statistical heterogeneity which may be attributed to differences among the included studies in terms of baseline disease severity, prevalence of comorbid asthma or NERD, prior exposure to different biological agents, and variations in follow-up duration. Third, short follow-up periods limited insights into long-term treatment durability after biologic switching. Also, the primary and secondary outcomes were not analyzed according to the reason for biologic switching (e.g., lack of disease control or adverse effects). Subgroup analysis was not feasible due to the limited number of studies and because most studies did not separate patients based on the indication for switching. Another limitation relates to the imbalance in the distribution of biologic agents among switching cases. Approximately two-thirds of the reported switches involved dupilumab, which may reflect prevailing prescribing patterns or availability rather than true comparative superiority over other biologic therapies. Finally, all studies were retrospective, with variable criteria and protocols for determining therapy switches. Collectively, these limitations highlight the need for cautious interpretation of our findings and underscore the importance of future prospective, standardized research to validate these observations.

Conclusion

Biologic switching offers a valuable therapeutic option for patients with refractory CRSwNP when the initial biologic fails to adequately control symptoms. Among the available agents, dupilumab appears to be the most effective for switching, showing a high success rate; however, other biologics should also be considered in specific clinical scenarios. Selecting the most appropriate biologic remains challenging, as no standardized, evidence-based criteria currently exist. Therefore, the choice of a subsequent biologic should be individualized according to patient-specific factors. These findings highlight the need for future prospective, controlled studies to confirm these observations and to clarify the optimal timing for switching therapy.

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Author contributions

Study concepts: AM, HJJ; Study design: HJJ, MRA; Data acquisition: HJJ, MRA; Quality control of data and algorithms: LAD, DMM, RMH, ZSW, FOD; Data analysis and interpretation: LAD, DMM, RMH, ZSW, FOD; Statistical analysis: HJJ, MRA; Manuscript preparation: HJJ, MRA, LAD, DMM, RMH, ZSW, FOD; Manuscript editing: AM, HJJ, MRA; Manuscript review: all the authors.

Conflict of interest

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SUPPLEMENTARY MATERIAL

Table S1. Keywords used to identify the possible included studies.

#	Search strategy steps in Medline database	Search strategy keywords in Medline database
1	Biologics keywords	Monoclonal antibodies OR Biologic OR Biologics OR Biological therapy OR Immunoglobulins OR Interleukins OR IL-5 OR IL-4 OR IL-13 OR Interferons OR Omalizumab OR IgE Receptors OR IgE OR Anti-IgE antibodies OR Anti-IgE OR Dupilumab OR Mepolizumab OR Reslizumab OR Benralizumab
2	Chronic rhinosinusitis keywords	Chronic rhinosinusitis with nasal polyps OR Chronic rhinosinusitis without nasal polyps OR Chronic rhinosinusitis OR Chronic sinusitis OR Recalcitrant chronic rhinosinusitis OR Refractory chronic rhinosinusitis OR Nasal polyposis
3	Merged	1 AND 2
#	**Search strategy steps in Embase database**	**Search strategy keywords in Embase database**
1	Biologics keywords	Monoclonal antibodies OR Biologic OR Biologics OR Biological therapy OR Immunoglobulins OR Interleukins OR IL-5 OR IL-4 OR IL-13 OR Interferons OR Omalizumab OR IgE Receptors OR IgE OR Anti-IgE antibodies OR Anti-IgE OR Dupilumab OR Mepolizumab OR Reslizumab OR Benralizumab
2	Chronic rhinosinusitis keywords	Chronic rhinosinusitis with nasal polyps OR Chronic rhinosinusitis without nasal polyps OR Chronic rhinosinusitis OR Chronic sinusitis OR Recalcitrant chronic rhinosinusitis OR Refractory chronic rhinosinusitis OR Nasal polyposis
3	Merged	1 AND 2
#	**Search strategy steps in Cochrane database**	**Search strategy keywords in Cochrane database**
1	Biologics keywords	Monoclonal antibodies OR Biologic OR Biologics OR Biological therapy OR Immunoglobulins OR Interleukins OR IL-5 OR IL-4 OR IL-13 OR Interferons OR Omalizumab OR IgE Receptors OR IgE OR Anti-IgE antibodies OR Anti-IgE OR Dupilumab OR Mepolizumab OR Reslizumab OR Benralizumab
2	Chronic rhinosinusitis keywords	Chronic rhinosinusitis with nasal polyps OR Chronic rhinosinusitis without nasal polyps OR Chronic rhinosinusitis OR Chronic sinusitis OR Recalcitrant chronic rhinosinusitis OR Refractory chronic rhinosinusitis OR Nasal polyposis
3	Merged	1 AND 2
#	**Search strategy steps in Web of Science database**	**Search strategy keywords in Web of Science database**
1	Biologics keywords	Monoclonal antibodies OR Biologic OR Biologics OR Biological therapy OR Immunoglobulins OR Interleukins OR IL-5 OR IL-4 OR IL-13 OR Interferons OR Omalizumab OR IgE Receptors OR IgE OR Anti-IgE antibodies OR Anti-IgE OR Dupilumab OR Mepolizumab OR Reslizumab OR Benralizumab
2	Chronic rhinosinusitis keywords	Chronic rhinosinusitis with nasal polyps OR Chronic rhinosinusitis without nasal polyps OR Chronic rhinosinusitis OR Chronic sinusitis OR Recalcitrant chronic rhinosinusitis OR Refractory chronic rhinosinusitis OR Nasal polyposis
3	Merged	1 AND 2

Table S2. Joanna Briggs Institute (JBI) critical appraisal checklists which were used to assess the risk of bias among the included articles.

Cohort	Question	Low risk of bias	Intermediate risk of bias	High risk of bias
Information bias	2,3,7,8,9,10	Answer Yes 5/6 times	Answer Yes 3/4 times	Answer Yes 0/1/2 times
Selection bias	1,6	Answer Yes 2 times	Answer Yes 1 times	Answer Yes 0 times
Confounding	4,5	Answer Yes 2 times	Answer Yes 1 times	Answer Yes 0 times
Statistical quality	11	Answer Yes 1 times		Answer Yes 0 times

Table S3. The results of the different JBI questionnaires (questionnaire for cohort studies).

Cohort	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
Hamada	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	UC	Yes
Habenbacher	Yes	Yes	Yes	UC	No	Yes	Yes	Yes	Yes	NA	Yes
Domínguez-Sosa	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes
Otten	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	UC	No	UC
Dorling	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	UC	No	No
Rosso	No	No	Yes	Yes	UC	Yes	Yes	Yes	UC	No	Yes
Sacks	Yes	Yes	Yes	Yes	Yes	Yes	Yes	UC	UC	No	Yes
Brkic	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes

Available on: https://jbi.global/critical-appraisal-tools. Abbreviations: NA=not applicable, Q=question, RCT=randomized controlled trial, UC=unclear

Table S4. Assessment of bias of all included studies.

Author	Information bias	Selection bias	Confounding	Statistical quality
Hamada, et al. (2020)	+/-	+/-	+	+
Habenbacher, et al. (2024)	+	+	-	+
Domínguez-Sosa, et al. (2024)	+/-	+	+/-	+
Otten, et al. (2023)	+/-	+	+	-
Dorling, et al. (2024)	+/-	+	+/-	-
Rosso, et al. (2024)	+/-	+/-	+/-	+
Sacks, et al. (2025)	+/-	+	+	+
Brkic, et al. (2023)	+	+	+	+

Abbreviations: (+) Low risk of bias, (+/-) intermediate risk of bias, (-) high risk of bias, (NA) not applicable.