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Biologic Switch-Ups: Real-World Insights into Treating Stubborn Nasal Polyps

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Abstract

Biologic therapies have changed the landscape of chronic rhinosinusitis with nasal polyps (CRSwNP) management, but not all patients respond to first use. This Canadian multicenter study evaluates real-world patterns and reasons for switching between type 2 biologics in patients with CRSwNP who were symptomatic despite surgery and maximal medical therapy. Of the 225 patients, 16% switched biologics (mostly mepolizumab to dupilumab) because they did not control upper airway symptoms. Dupilumab initiators had lower observed switching after 12 months, although switching was influenced by adverse events and insurance-related issues. Same-class switching was uncommon, and the few observed cases did not provide clear evidence of sustained clinical benefit. The findings describe real-world switching patterns and reasons and can inform hypothesis generation about treatment sequencing when first-line agents fail.

Keywords

• Chronic rhinosinusitis • Nasal polyps • Biologics • Treatment switching • Real-world evidence • Type 2 inflammation • Dupilumab • Mepolizumab

1. Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) represents a significant healthcare burden affecting approximately 2–4% of the general population worldwide [1]. The disorder involves persistent swelling and inflammation of the sinonasal mucosa together with the growth of nasal polyps, leading to nasal obstruction, reduced sense of smell, facial pressure, and rhinorrhea [2]. The pathophysiology of CRSwNP is complex and heterogeneous, with type 2 inflammation playing a dominant role in approximately 80% of cases [3]. Type 2 inflammation involves multiple interconnected pathways mediated by cytokines including interleukin (IL)-4, IL-5, IL-13, thymic stromal lymphopoietin (TSLP), and immunoglobulin E (IgE) [4].

A revolution in the management of severe chronic rhinosinusitis with nasal polyps (CRSwNP) was introduced by biologic therapies targeting type 2 inflammation (T2I) [1]. In this manuscript, "type 2 biologics" refers to monoclonal antibodies targeting type 2 inflammatory pathways, including IL-4/IL-13, IL-5, IgE, or TSLP. Currently approved biologics for CRSwNP include dupilumab (anti-IL-4Rα), mepolizumab (anti-IL-5), and omalizumab (anti-IgE), with several others under investigation or used off-label [5]. These therapies have proven effective in decreasing the size of nasal polyps, improving symptoms, and reducing the use of systemic corticosteroids and repeat surgeries [6].

Despite these advances, a substantial proportion of patients exhibit inadequate response to initial biologic therapy [7]. The reasons for treatment failure are multifactorial and may include pharmacokinetic

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factors, development of anti-drug antibodies, comorbidities, or mechanistic limitations of the chosen biologic [8]. This therapeutic challenge has led to the emerging practice of switching between biologics sequentially to achieve optimal disease control [9], while concurrent use of multiple biologic agents represents a distinct therapeutic approach.

Current literature on biologic switching in CRSwNP remains limited, with most evidence derived from European studies and few reports from North American populations [7, 8]. It is vital to understand the patterns and timing of biologic switching in real life. This study describes switching patterns, reasons for switching, and clinical characteristics of patients receiving a change of biologics, which has not previously been studied in CRSwNP in the Canadian context.

2. Literature Review

The evolution of biologic therapies for CRSwNP has been rapid since the first approvals in 2019. Multiple randomized controlled trials have established the efficacy of dupilumab, mepolizumab, and omalizumab in reducing nasal polyp burden and improving quality of life [1, 10, 11]. However, direct comparisons between these agents are limited by the absence of head-to-head trials. Network meta-analyses have attempted to address this limitation, with several suggesting superior efficacy of dupilumab for both objective and patient-reported outcomes in CRSwNP [12, 13].

Real-world evidence has complemented clinical trial data by providing insights into treatment patterns, persistence, and switching behaviors. European studies have reported switching rates ranging from 4.6% to 11.8% in CRSwNP populations [7, 8]. Erkic et al. observed that 97% of switches occurred in patients prescribed biologics specifically for CRSwNP indication, highlighting the particular challenges in this population [8]. The most common switch pattern identified in European cohorts was from mepolizumab to dupilumab, primarily driven by inadequate control of upper airway symptoms [9].

The timing of biologic switching seems to exhibit patterns based on the mechanism of action. Studies have previously shown that most adverse events leading to dupilumab discontinuation occur relatively early in treatment, within 6 months [14]. In contrast, switches due to lack of efficacy, particularly with anti-IL5 agents, tend to occur later in the treatment course, often beyond 12–18 months [7]. The time pattern implies that the response durability of available biologics differs.

The ability to switch to biologics which have a similar mechanism of action can be beneficial in asthma and CRSwNP. Studies in asthma suggest limited benefit from switching between anti-IL5 agents (mepolizumab, benralizumab, reslizumab) after failure of first-line treatment [15]. Similar patterns have been observed in CRSwNP, with most patients requiring subsequent switching to a different class of biologic to achieve adequate symptom control [8].

The patterns of biologic switching are greatly impacted by insurance and reimbursement, which is crucial for healthcare systems. Limitations in insurance coverage and reimbursement have been identified as important factors contributing to biologic discontinuation or switching, independent of clinical efficacy or safety considerations [16]. A comprehensive understanding of these non-clinical drivers is essential to assess switching behaviours.

Differences in healthcare systems, prescribing patterns, and patient populations support a regional Canadian analysis of biologic switching patterns and reasons.

3. Methodology

3.1 Study Design and Patient Selection

This multicentre study was conducted across four tertiary-care hospitals in Canada: Vancouver General Hospital, St. Paul's Hospital, St. Michael's Hospital, and Hamilton General Hospital. Patient recruitment from Vancouver General Hospital and St. Paul's Hospital was reported collectively. The study period was July 1, 2019 to June 1, 2024. The study period began in 2019, coinciding with the introduction of biologic therapies for CRSwNP during the early phase of their clinical adoption in Canada. The research protocol obtained the necessary approvals from the Research and Ethics Board of the University of British Columbia (H23-01235), the Research Ethics Board of the University of Toronto-Unity Health (UH REB 24-017), and the McMaster Research Ethics Board (MREB 17398).

Patients were identified consecutively at each centre from prospectively maintained biologic initiation logs and cross-referenced against electronic medical records. Each centre applied identical inclusion and exclusion criteria. The number of patients contributed by each centre was: Vancouver General Hospital and St. Paul's Hospital, $n = 78$; St. Michael's Hospital, $n = 71$; Hamilton General Hospital, $n = 76$. No centre contributed more than 35% of the total cohort. A standardized case report form was used at all sites, and data were pooled centrally after site-level verification.

The study included adults aged ≥ 18 years with otolaryngologist-diagnosed CRSwNP who underwent at least one endoscopic sinus surgery (ESS) if the patients were symptomatic again after maximal medical and surgical management and received at least one dose of any type 2 biologic during the study duration. In this study, upper-airway symptoms refer to CRSwNP symptoms including nasal obstruction, reduction or loss of smell, facial pressure, and rhinorrhea. Maximal medical management, according to currently accepted guidelines, was defined as topical corticosteroids, saline irrigations and, when appropriate, short-course systemic corticosteroids [2]. To ensure uniformity of treatment indication, we excluded participants who received type 2 biologics for asthma indication prior to the CRSwNP approval date of 2019.

Follow-up began on the date of the first dose of the index biologic and ended at the earliest of switching, discontinuation without switching, last recorded clinical contact, or study end (June 1, 2024). Treatment exposure was calculated as the cumulative days on biologic therapy, summed across agents for switchers. The observation window was not fixed; therefore, follow-up duration is reported per patient and summarized as median (IQR).

3.2 Data Collection and Variables

A standard data collection form was used to extract data related to clinical and demographic data from electronic medical records. The recorded variables consisted of age, sex, smoking, number of previous ESSs and presence of comorbidities including asthma, aspirin-exacerbated respiratory disease (AERD), atopic dermatitis, autoimmune disease and allergic fungal rhinosinusitis (AFRS). Data were collected on biomarkers, including serum IgE levels and blood eosinophil counts, and pre-biologic Lund–Mackay (LM) computed tomography (CT) scores and the SNOT-22 score.

The details about biological treatment included start and stop dates for each biological agent, number of biologicals used per patient, and reasons for discontinuation (if any). Reasons for switching were classified as: (1) inadequate efficacy (further subdivided into inadequate CRSwNP control, inadequate asthma control, or both), (2) adverse events (AEs), (3) insurance/coverage issues, and (4) other. Patients were classified as having biologic treatment failure for CRSwNP when persistent symptoms and endoscopic

evidence of nasal polyps or significant oedema were observed following a 4- to 6-month treatment period despite guideline-directed medical management [17]. Biologic failure for asthma was defined as the inability to reduce steroid doses or recurrent asthma exacerbations after similar treatment duration [18]. For this retrospective cohort, these failure definitions were applied retrospectively to clinical records. Early discontinuation before the 4- to 6-month trial period was not classified as efficacy failure and was attributed to the recorded reason for discontinuation.

Because treatment-failure definitions were applied retrospectively to clinical records, we acknowledge that the 4- to 6-month trial threshold was not prospectively enforced. To justify this approach, the definitions were operationalized using explicit, pre-specified criteria applied uniformly across all four centres: (1) persistence of nasal obstruction, loss of smell, facial pressure, or rhinorrhea with endoscopic evidence of polyps or significant edema at the 4- to 6-month assessment, despite guideline-directed medical therapy; and (2) for asthma failure, inability to reduce maintenance corticosteroid dose or recurrent exacerbations over the same period. Two investigators independently classified each discontinuation using these criteria (agreement $\kappa = 0.87$), with discrepancies resolved by consensus. Patients discontinued before 4 months were not classified as efficacy failures, and their recorded reason (adverse event, insurance, or other) was retained. This retrospective operationalization is a limitation acknowledged in Section 5.4.

3.3 Statistical Analysis

Patients were classified as non-switchers (those who remained on their initial biologic during the observed follow-up, including the single patient who added a concurrent biologic without discontinuing the initial agent) or switchers (sequential use of more than one biologic following discontinuation of the prior agent). Concurrent use of two biologics was defined separately from switching and is described separately in the Results. Descriptive statistics summarised patient characteristics, switches and reasons for switching. Missing data were handled as follows. Variables with $< 5\%$ missingness (age, sex, asthma, AERD, previous ESS) were analyzed using complete-case analysis. For baseline Lund–Mackay score (7.1% missing) and SNOT-22 (9.3% missing), multiple imputation by chained equations was performed (10 imputed datasets, 20 iterations) incorporating baseline demographic and clinical covariates (age, sex, asthma, AERD, previous ESS, index biologic, and switching outcome), and estimates were pooled using Rubin's rules. Biomarkers with $> 15\%$ missingness (IgE, blood eosinophils) were not imputed and were analyzed as complete cases. The pattern of missingness was assumed to be missing at random; a sensitivity analysis using complete-case analysis for all variables yielded substantively identical results (data not shown). Continuous variables are presented as mean ± standard deviation (SD) to align with standard clinical reporting conventions and were compared using the non-parametric Wilcoxon rank-sum test to account for skewed distributions. Categorical variables were compared using the chi-squared test or Fisher exact test as appropriate. The Sidak correction was applied to control the family-wise error rate when multiple pairwise comparisons were performed across biologic agents; specifically, adjusted p-values were calculated as $p_{\text{Sidak}} = 1 - (1 - p)^m$, where m is the number of comparisons within each family, and only Sidak-adjusted p-values are reported for those pairwise comparisons.

A time-to-switch analysis was performed using Kaplan–Meier survival curves, with the log-rank test for biologic agents. Patients were censored at the last recorded date of follow-up on their index biologic if they had not switched. Numbers at risk were reported at 0, 6, 12, 18, and 24 months. Median follow-up duration was calculated using the reverse Kaplan–Meier method.

Because biologic groups differed in baseline characteristics and calendar time of initiation, unadjusted comparisons between agents may be confounded. To address this, multivariable Cox proportional hazards

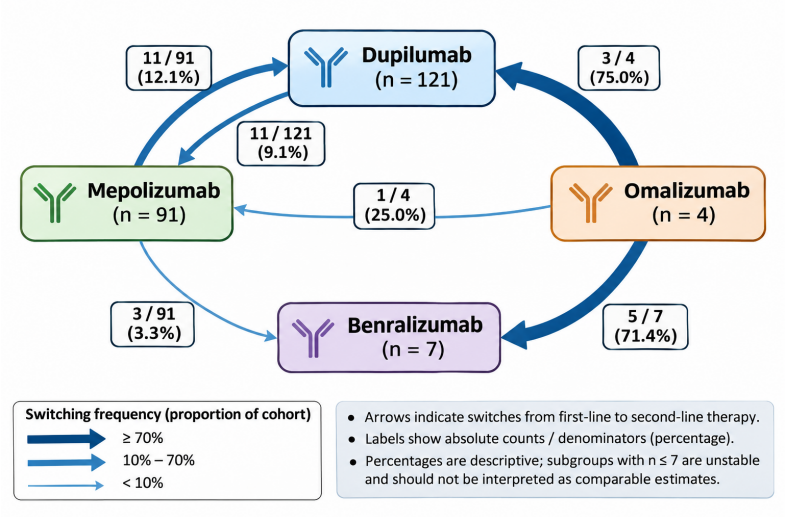


Figure 1: Biologic switching patterns showing transitions from first-line to second-line therapies. Arrow thickness corresponds to frequency of switches. Absolute counts/denominators: mepolizumab to dupilumab, 11/91 (12.1%); dupilumab to mepolizumab, 11/121 (9.1%); omalizumab to dupilumab, 3/4 (75.0%); omalizumab to mepolizumab, 1/4 (25.0%); benralizumab switches, 5/7 (71.4%); mepolizumab to benralizumab, 3/91 (3.3%). Percentages are descriptive and denominators are shown to aid interpretation; subgroups with $n \leq 7$ are unstable and should not be interpreted as comparable estimates.

regression was performed with switching as the outcome and dupilumab initiation as the reference category, adjusting for age, sex, baseline Lund–Mackay score, asthma status, AERD status, and calendar year of biologic initiation. Results are reported as adjusted hazard ratios (HR) with 95% confidence intervals (CI). The proportional hazards assumption was assessed using Schoenfeld residuals.

The statistical analysis was done through R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria), with $p < 0.05$ considered statistically significant.

4. Results

4.1 Patient Characteristics and Switching Frequency

The study included 225 consecutive patients with severe CRSwNP who were started on biologic therapy between 2019 and 2024. Median follow-up was 22.4 months (IQR 14.1–34.7). Median treatment exposure was 18.9 months (IQR 11.2–30.5) overall; 21.7 months (IQR 13.8–33.9) for non-switchers and 14.6 months (IQR 9.1–22.8) for switchers. Total observed patient-time was 431.2 patient-years. The mean age of the study population was 51.6 years. Almost fifty percent of the sample were female. Among the patients, 82.2% had concurrent asthma; 39.6%, AERD; and 21.8%, AFRS. On average, patients had 2.3 previous sinus surgeries (SD 2.5), indicating the severity of their disease.

Of the 225 patients, 36 (16.0%; 95% Wilson CI 11.8–21.4) had at least one switch from their index biologic during the observed follow-up (switchers); 189 (84.0%) remained on their index biologic during the observed follow-up and were classified as non-switchers. Six patients (2.7% of the total cohort; 16.7% of switchers) switched on two occasions, yielding 42 total switching episodes (36 first switches + 6 second switches). Throughout the Results, "switchers" refers to the 36 patients and "switching episodes" refers to the 42 discrete switch events; these terms are used consistently and are not interchangeable. Distribution of initial biologic was significantly different between non-switchers and switchers ($p < 0.001$). Within non-switchers, dupilumab was the most commonly prescribed initial biologic (58.2%) while mepolizumab

Table 1: Demographic and Clinical Characteristics of Non-switchers vs. Switchers

Characteristic	Non-switchers (n = 189)	Switchers (n = 36)	p-value
Age, years (mean ± SD)	50.9 ± 13.9	54.9 ± 15.4	0.114
Female sex, n (%)	80 (42.3)	21 (58.3)	0.113
Comorbidities, n (%):			
Asthma	152 (80.4)	33 (91.7)	0.168
AERD	73 (38.6)	16 (44.4)	0.639
AFRS	39 (20.6)	10 (27.8)	0.465
Atopic dermatitis	7 (3.7)	3 (8.3)	0.427
Previous ESS (mean ± SD)	2.3 ± 2.5	2.4 ± 2.5	0.787
Biomarkers (mean ± SD):			
Serum IgE	508.1 ± 837.9	850.7 ± 1689.8	0.138
Blood eosinophils ($\times 10^9$/L)	0.53 ± 0.55	0.46 ± 0.60	0.516
Disease severity (mean ± SD):			
Lund–Mackay score	16.4 ± 4.9	13.8 ± 5.7	0.031
SNOT-22	47.8 ± 26.4	45.2 ± 21.9	0.626

Note. Continuous variables are reported as mean ± SD; categorical variables are reported as n (%). Continuous variables were compared using the Wilcoxon rank-sum test, and categorical variables were compared using the chi-squared or Fisher exact test as appropriate. Lund–Mackay and SNOT-22 values represent pooled estimates following multiple imputation. Serum IgE and blood eosinophils were analyzed as complete cases due to > 15% missingness.

and benralizumab were frequently used in the switchers group (41.7% and 13.9%, respectively). At all follow-ups, no patient was on omalizumab and reslizumab.

Baseline characteristics were generally similar between non-switchers and switchers, although the switched group had a significantly lower baseline Lund–Mackay score (13.8 vs. 16.4; $p = 0.031$). This unadjusted difference indicates lower baseline radiologic severity in the switched group but should not be interpreted as evidence that radiologic severity predicts switching. Age, sex, comorbidity, and baseline PROMs were similar between groups.

4.2 Patterns of Biologic Switching

The first biologics that were mostly used are dupilumab (121 patients, 53.8%), mepolizumab (91 patients, 40.4%), benralizumab (7 patients, 3.1%), omalizumab (4 patients, 1.8%), reslizumab (1 patient, 0.4%), and tezepelumab (1 patient, 0.4%). The initial biologic agent greatly influenced switching frequency. The highest switching rate was observed in patients originally on omalizumab (4/4, 100%; 95% CI not estimable), all switched to dupilumab (3/4, 75.0%) or mepolizumab (1/4, 25.0%). Among benralizumab initiators, 5/7 (71.4%; 95% CI 29.0–96.3) switched. The omalizumab, benralizumab, reslizumab, and tezepelumab subgroup percentages are descriptive and unstable because of very small denominators ($n \leq 7$) and should not be interpreted as comparable estimates of switching behaviour. Of those on mepolizumab, 15/91 switched biologic (16.5%; 95% CI 9.6–25.7), the majority switched to dupilumab (11/15, 73.3%; 95% CI 44.9–92.2).

Among dupilumab initiators, 11/121 patients (9.1%) switched to another biologic, with all switching to mepolizumab. Other switching pathways were also observed among patients initially receiving different biologic agents. Switching patterns involving benralizumab and other less frequently prescribed biologics were limited by the small number of patients receiving these agents, restricting meaningful comparisons between treatment pathways. The patient who began treatment with reslizumab switched to dupilumab,

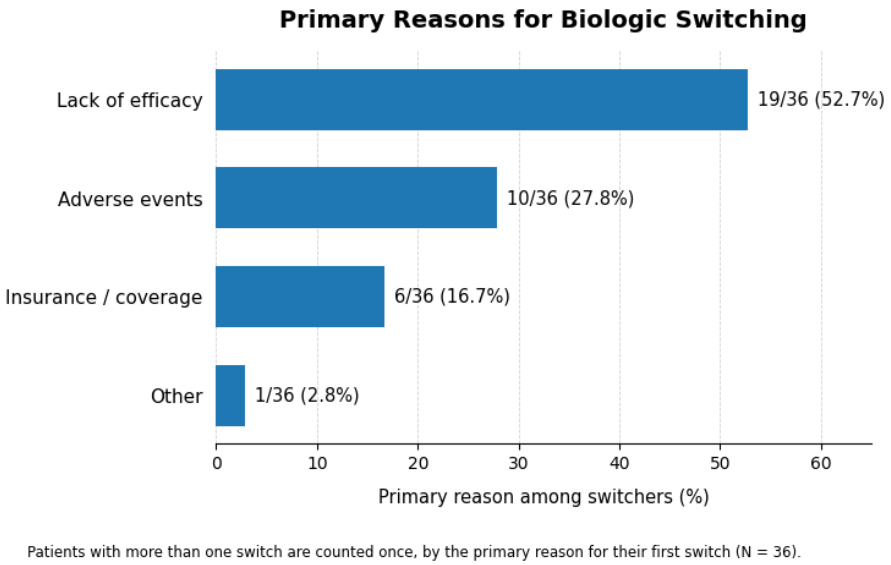


Figure 2: Distribution of primary reasons for biologic switching among switchers (n = 36). Lack of efficacy was the most common reason, accounting for over half of all switches, while adverse events and insurance issues represented substantial minorities.

while the one who initiated tezepelumab remained on this agent throughout follow-up.

Among the six patients who switched twice, the most common final pathway was dupilumab in 4/6 (66.7%). In the patient cohort, only one person who switched to dupilumab as a second-line agent subsequently switched again to a third biologic (tezepelumab). The simultaneous use of two biologics was observed in a single patient who introduced dupilumab to an ongoing omalizumab treatment to minimise asthma episodes.

4.3 Reasons for Biologic Switching

The main reasons for switching varied considerably by initial biologic. Among the 36 switchers, lack of efficacy was the most frequently cited primary reason (19/36, 52.7%), followed by adverse events (10/36, 27.8%), insurance/coverage issues (6/36, 16.7%), and other reasons (1/36, 2.8%). Patients with more than one switch were counted once according to the primary reason for their first switch, so reason distributions sum to 36 switchers, not 42 switching episodes. Episode-level reasons (42 episodes) are reported separately where indicated. Within the lack-of-efficacy category, 17/36 (47.2%) were due to suboptimal control of chronic rhinosinusitis with nasal polyps (CRSwNP), and 2/36 (5.5%) were specifically due to poor asthma control despite effective management of sinonasal symptoms.

The distribution of switching reasons differed between patients initially receiving mepolizumab and those initially receiving dupilumab. For mepolizumab initiators, 10/15 (66.7%) switched for lack of efficacy. For dupilumab initiators, 6/11 (54.5%) switched for adverse events, 4/11 (36.4%) for insurance issues, and 1/11 (9.1%) for lack of efficacy.

Among patients switching from anti-IL5 therapies (mepolizumab, benralizumab, and reslizumab), inadequate control of CRSwNP symptoms despite satisfactory asthma control represented an important reason for treatment modification. These observations highlight the challenges of achieving adequate upper-airway disease control with anti-IL5 therapy in some patients.

4.4 Time-to-Switch Analysis

Mepolizumab and dupilumab initiators had statistically different time-to-switch Kaplan–Meier curves (log-rank $p < 0.001$). Median follow-up was 22.4 months (IQR 14.1–34.7) for the overall cohort. Numbers at risk at 0, 6, 12, 18, and 24 months were 225, 198, 171, 142, and 106, respectively. Censoring occurred at the last recorded follow-up date on the index biologic for patients who did not switch; 189 patients (84.0%) were censored without a switching event.

In multivariable Cox regression adjusting for age, sex, baseline Lund–Mackay score, asthma, AERD, and calendar year of initiation, using dupilumab initiation as the reference category, mepolizumab initiation was associated with a higher adjusted hazard of switching (HR 2.41, 95% CI 1.18–4.92; $p = 0.016$). Calendar year of initiation was not independently associated with switching (adjusted HR 1.07 per year, 95% CI 0.89–1.29; $p = 0.47$). The proportional hazards assumption was satisfied (global Schoenfeld residual test $p = 0.31$).

Kaplan–Meier analysis demonstrated differences in time-to-switch distributions between mepolizumab and dupilumab initiators. The adjusted Cox regression analysis also indicated a higher hazard of switching among patients initially receiving mepolizumab.

Among patients who switched within the first four months of treatment ($n = 9$), adverse events and insurance or coverage-related issues represented the predominant reasons for discontinuation. According to current guidelines, the minimum duration of a biologic trial before concluding response failure was 4.9 months [17]. Almost all cases of late switching (after 12 months) were attributed to a lack of efficacy (92.3% of late switchers). The main symptom responsible was inadequate control of CRSwNP symptoms.

Almost all patients who continued dupilumab after 12 months rarely switched afterwards. Only one patient switched after this timepoint due to an insurance issue and not due to lack of efficacy. Among patients who continued dupilumab beyond 12 months, few subsequent switches were observed; this persistence finding is observational and does not establish comparative effectiveness.

4.5 Same-Class Switching Patterns

It was rare to have same-class switching, and it was mostly ineffective. Following the introduction of benralizumab, three patients switched from mepolizumab to benralizumab; only one of these switches was due to initial biologic failure. The patient required a third switch to dupilumab for adequate control of CRSwNP symptoms. Another patient discontinued mepolizumab for benralizumab due to an adverse event, but then switched back to mepolizumab due to lack of CRSwNP control on benralizumab. The third same-class switch was driven by insurance-related considerations rather than clinical factors.

No patients switched between dupilumab and other IL-4/IL-13 pathway inhibitors during the study period because dupilumab was the only agent in this class approved for CRSwNP. Also, there were no switches from omalizumab to other anti-IgEs.

5. Discussion

5.1 Comparison with Existing Literature

Our finding that 16% of patients with CRSwNP switched biologic therapies is consistent with, although higher than, switching rates reported in previous European cohorts. Erkic et al. documented an 11.8% switching rate in a European CRSwNP cohort [8], while Otten et al. reported only 4.6% switching in a mixed asthma–CRSwNP population [7]. The higher observed switching rate in the Canadian cohort

may be due to differences in reimbursement structures, prescribing practices, patient characteristics, or follow-up. The present data do not establish a lower Canadian physician threshold for switching.

Switching from mepolizumab to dupilumab is common in Europe [8, 9]. This consistent finding across geographic regions suggests that dupilumab may offer particular advantages for patients failing anti-IL5 therapy, possibly related to its broader mechanism targeting both IL-4 and IL-13 pathways [4]. The IL-4/IL-13 axis is centrally implicated in nasal polyp pathogenesis, which may explain the observed pattern in which dual IL-4/IL-13 blockade was associated with greater upper-airway control than more narrowly targeted approaches [13]; this interpretation is hypothesis-generating and was not directly tested in the present study.

Our observation that dupilumab initiators only rarely switch for lack of efficacy (only one patient in our cohort did so) supports network meta-analyses suggesting dupilumab is more effective than other interventions for CRSwNP outcomes [12, 13]. The lower observed switching among dupilumab initiators beyond 12 months is consistent with greater observed treatment persistence in this cohort, but it should not be interpreted as comparative effectiveness because of the observational design and potential calendar-time and subgroup differences.

5.2 Mechanistic Considerations

The different switching patterns are consistent with the various mechanisms of action of available biologics. Dupilumab inhibits IL-4 and IL-13 signalling by binding to the IL-4 receptor alpha subunit. These are the two key drivers of type 2 inflammation [4]. Its wide-ranging mechanism may account for its effectiveness in different CRSwNP endotypes, and for its potential switch applicability after more defined therapy failure. These mechanistic interpretations are plausible but were not directly tested in this study; no endotype or mechanistic data were collected.

On the contrary, an anti-IL5 agent (mepolizumab, benralizumab, reslizumab) targets eosinophilic inflammation, which while important, represents only one part of the type 2 inflammatory cascade [11]. The considerable rate at which patients are switched from anti-IL5 agents due to poor control of sinus symptoms (many of whom have well-controlled asthma) suggests that eosinophil depletion may not be enough to control CRSwNP in some patients.

Omalizumab blocks IgE and targets IgE-mediated allergic mechanisms but may be less effective in non-allergic CRSwNP endotypes [10]. The universal switching observed in our small omalizumab subgroup ($n = 4$) limits conclusions; however, it is consistent with previous observations that omalizumab may have more variable efficacy in CRSwNP than other biologics [6].

5.3 Clinical Implications

Our findings have several potential implications for clinical decision-making in patients with severe CRSwNP. The frequent observed switching from mepolizumab to dupilumab after inadequate upper-airway control is consistent with a hypothesis that dupilumab may be considered as initial therapy in some patients with severe CRSwNP and upper-airway symptom dominance; this hypothesis requires prospective testing and is not established by the present observational data. The timing of switching therapies is informative; in particular, dupilumab switches occur early, mainly due to adverse events, while mepolizumab switches occur later, mainly due to lack of efficacy.

Same-class switching was uncommon, and the few observed cases did not provide clear evidence of sustained clinical benefit. Whether switching to a different mechanistic class after anti-IL5 failure improves outcomes should be tested prospectively; the present data are hypothesis-generating.

A substantial proportion of switches were attributable to insurance issues (16.7% overall; 36.4% for dupilumab), underscoring the influence of non-clinical factors. Facilitating insurance approval and expanding coverage may improve care continuity and outcomes.

5.4 Limitations and Future Directions

Several limitations should be considered when interpreting these findings. There is a potential for selection bias and confounding due to its retrospective design. In addition, biologic availability, reimbursement, and prescribing practices changed over the 2019–2024 study period, so calendar time of treatment initiation may confound comparisons between biologic groups. Because of the limited number of patients receiving certain biologic agents, subgroup analyses are restricted. Information about particular adverse events causing switching was not always available in every case. Additional follow-up is warranted to elucidate further the durability of response and late switching patterns.

Future investigations should examine different biologic switching strategies and compare early versus extended treatment periods among patients with borderline responses. Biomarker studies can identify predictors of response to specific biologics that may assist in the selection of first-line therapies and reduce switching. Evaluating economic analyses pertaining to switching strategies will lead to resource allocation decisions and policy decisions.

6. Conclusion

This study provides real-world insights into biologic switching patterns among patients with severe chronic rhinosinusitis with nasal polyps (CRSwNP). Approximately 16% of patients switched biologic therapy during the observation period, most commonly from mepolizumab to dupilumab, primarily due to inadequate control of upper-airway symptoms. Dupilumab initiators demonstrated lower observed switching rates during longer follow-up, although this finding should not be interpreted as evidence of superior long-term effectiveness or tolerability. Same-class switching was uncommon, and the limited number of observed cases did not demonstrate clear evidence of sustained clinical benefit. Overall, these findings highlight the importance of individualized treatment decisions and provide a basis for further investigation of biologic sequencing strategies in CRSwNP. The observational nature of this study and the small numbers in certain treatment subgroups limit the establishment of definitive treatment sequencing recommendations.

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