

ORIGINAL RESEARCH ARTICLE

Benefits of biologic therapy administered for asthma on co-existent chronic rhinosinusitis: A real-world study

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Background: Asthma and some chronic rhinosinusitis (CRS) subtypes are mediated by similar pathophysiologic mechanisms. The purpose of this study was to evaluate the effects of biologic therapy for asthma on co-existent CRS in the “real-world” setting.

Methods: A review of electronic health records (2016–2019) at Mayo Clinic was conducted to identify asthma patients treated with biologics who had co-existent CRS. Matched-pair analyses compared pretherapy and posttherapy Lund-Mackay computed tomography (CT) scores and 22-item Sino-Nasal Outcome Test (SNOT-22) scores. Performance of endoscopic sinus surgery (ESS) after initiating biologics was studied.

Results: We identified 247 patients who received anti-asthma biologic therapy and had co-existent CRS. Of these, 181 patients (73.3%) had CRS with nasal polyposis (CRSwNP) and 66 (26.7%) had CRS without nasal polyposis (CRSsNP). The biologics utilized were omalizumab (51.0%), mepolizumab (46.6%), benralizumab (10.5%), reslizumab (1.6%), and dupilumab (2.4%). Anti-interleukin-5 (anti-IL-5) intervention was associated with significant improvement in CT scores (CRS overall, CRSwNP subgroup, CRSsNP subgroup) and SNOT-22 scores (CRS overall, CRSwNP subgroup). Patients on omalizumab had a decrease in CT scores, but not SNOT-22 scores. ESS was performed in 206 patients (84.1%); 55 (22.3%) underwent surgery post-biologic intervention (anti-IL-5: 16.5%; omalizumab 27.8% of patients).

Conclusion: Anti-IL-5 agents were associated with improved CT and SNOT-22 scores in the overall CRS group and in CRSwNP subgroup; CRSsNP patients showed improved CT scores only. Omalizumab improved CT but not SNOT-22 scores. ESS was performed in 22% of patients after initiating biologics. These real-world results may influence future trial designs and clinical applications of biologics for CRS. ©2021 ARSAAOA, LLC.

KEYWORDS

asthma, benralizumab, biologic, chronic rhinosinusitis, dupilumab, machine learning, mepolizumab, omalizumab, reslizumab, sinusitis, therapy

Chronic rhinosinusitis (CRS) and asthma are inflammatory disorders of the airway that often co-exist.¹ Asthma and some CRS subtypes are mediated by similar pathophysiologic mechanisms that involve type 2 inflammatory pathways via eosinophils and pro-eosinophilic cytokine mediators such as interleukin-5 (IL-5), IL-4, IL-13, and immunoglobulin E (IgE). Biologic therapy targeted toward these mediators is currently U.S. Food and Drug Administration (FDA)-approved for use in some subtypes of poorly controlled asthma.¹⁻³ These drugs include anti-IgE (omalizumab), anti-IL-5 (mepolizumab, benralizumab, reslizumab), and anti-IL-4, 13 (dupilumab) monoclonal antibodies.⁴ Dupilumab has just recently been approved for use in CRS with nasal polyps (CRSwNP).^{5,6} In a recent 2-part phase III randomized clinical trial, omalizumab was noted to improve nasal polyp and nasal congestion scores compared to placebo,⁷ and was approved for use in the treatment of CRSwNP in December 2020. The other biologics (mepolizumab, benralizumab, reslizumab) have been assessed for CRS in small trials, with some studies reporting benefit.⁸⁻¹⁰ These trials have mostly been limited to CRSwNP. Additionally, the studies on dupilumab and omalizumab were limited to CRSwNP with select inclusion and exclusion criteria. The goals of our study were therefore to study the effect of biologics administered for asthma on co-existent CRS in the “real-world” environment outside the enrollment limitations of clinical trials.

1 | PATIENTS AND METHODS

Patient consent was waived by the Mayo Clinic Institutional Review Board for this retrospective study. The study cohort was identified by scanning the electronic medical record (EMR) using the “Advanced Text Explorer (ATE),” a natural language processing search tool developed and hosted by the Mayo Clinic. Patients undergoing therapy for asthma with biologics (anti-IL-5, anti-IgE, and anti-IL-4/13) at any site at the Mayo Clinic between January 1, 2016 and April 30, 2019 were identified. Ten total searches were performed with the ATE using generic and brand names: “asthma + omalizumab”/“asthma + Xolair®”, “asthma + mepolizumab”/“asthma + Nucala®”, “asthma + benralizumab”/“asthma + Fasenra®”, “asthma + reslizumab”/“asthma + Cinqair®”, “asthma + dupilumab”/“asthma + Dupixent®”. The search yielded patient notes and correspondences containing the selected search words. The documents were then reviewed to confirm asthma diagnosis and the administration of the biologic agent. Subsequently, a further detailed review of each patient’s EMR was performed to confirm the findings of the preliminary review and to identify the subset of patients who also had a concurrent CRS diagnosis made by an otolaryngologist at our institution. Next, focusing

on the patients with asthma and CRS only, characteristics of CRS were studied. Data collection was concluded on July 18, 2019, and this date was defined as the conclusion of the study period. The following clinical data was collected and entered into a secure institutionally-hosted database (Research Electronic Data Capture [REDCap®], Vanderbilt University, Nashville, TN)¹¹:

1. Demographic data including age and sex
2. Clinical data (asthma severity, otolaryngology consultation, CRS subtype diagnosis, previous sinus/nasal surgery and number of procedures). Diagnosis of CRS and subtype was based on evaluation of notes by the treating otolaryngologist.
3. Laboratory tests results before and after first use of biologic: serum eosinophil count (reference range, 0.03 to $0.48 \times 10^9/L$) and total serum IgE (reference range ≤ 214 kU/L). If there was more than 1 test value after initiation of therapy, then the test performed later in the course of biologic therapy was collected and used for analysis.
4. Any systemic corticosteroid prescription after the initiation of biologic therapy
5. Performance of endoscopic sinus surgery (ESS) prior to or after administration of biologic therapy
6. Sinus computed tomography (CT) scans before and after initiation of biologic therapy; the CT scan was scored using the Lund-Mackay system (range, 0 to 24 points; higher scores reflect worse disease).¹² Scoring was performed and recorded by S.B. after training and validation (with D.L. and M.J.M.). If there was more than 1 posttreatment CT, then the CT scan performed later in the course of biologic therapy was used for analysis.
7. Patient-reported Sino-Nasal Outcome Test (SNOT-22) scores were recorded pretreatment, 6 months and 12 months posttreatment with biologic therapy, as well as at the last recorded follow-up when available in the EMR. The last follow-up was variable for each patient but needed to be at least 3 months for inclusion in the study of SNOT-22 scores. The total SNOT-22 scores range from 0 to 110; higher scores reflect higher symptom burden.¹³ A change in the total score ≥ 8.9 (minimal clinically important difference [MCID]) is considered clinically significant.¹³

2 | DATA ANALYSIS

Data was analyzed to study the impact of biologic therapy on CRS outcomes. The primary outcomes of interest included changes in SNOT-22 scores, Lund-Mackay CT scores, performance of ESS after the initiation of biologic

TABLE 1 Demographic and baseline clinical characteristics of study population

Demographic and clinical characteristics	Total	Omalizumab	Anti-IL-5
Total patients, n (%)	247 (100)	126 (51.0)	139 (56.3)
Age (years), mean $\pm$ SD	54.4 $\pm$ 14.1	54.2 $\pm$ 14.8	54.8 $\pm$ 14.2
Male, n (%)	114 (46.2)	60 (52.4)	62 (44.6)
Female, n (%)	133 (53.8)	66 (47.6)	77 (55.4)
CRSwNP, n (%)	181 (73.3)	88 (69.8)	103 (74.1)
CRSsNP, n (%)	66 (22.3)	38 (30.2)	36 (25.9)
AFRS, n (%)	14 (5.7)	7 (5.6)	9 (6.5)
AERD, n (%)	49 (19.8)	23 (18.3)	26 (18.7)
Previous ESS, n (%)	206 (84.1)	96 (77.4)	120 (87.0)
Number of previous ESS, mean (range) ^a	2.46 (1–13)	2.53 (1–13)	2.36 (1–11)
Pretreatment SNOT-22 score, mean $\pm$ SD	42.6 $\pm$ 22.6	42.5 $\pm$ 25.1	42.6 $\pm$ 22.5
Pretreatment Lund-Mackay score, mean $\pm$ SD	14.4 $\pm$ 4.3	13.9 $\pm$ 4.9	14.9 $\pm$ 3.7
Pretreatment serum eosinophil count ($\times 10^9$ /L), mean (range)	1.23 (0–17.68)	0.98 (0–7.76)	1.34 (0–17.68)
Pretreatment total serum IgE (kU/L), mean (range)	604.8 (4.2–11960)	670.1 (8.3–8450)	538.7 (4.2–11960)

^aAmong patients having ESS prior to starting biologic therapy.

AERD = aspirin exacerbated respiratory disease; AFRS = allergic fungal rhinosinusitis; CRSsNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyps; ESS = endoscopic sinus surgery; IgE = immunoglobulin E; IL-5 = interleukin 5; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test.

therapy use, and trends in serum eosinophil counts and serum IgE levels. If patients were treated with multiple biologic agents, then they were included in the analysis for each agent.

Statistical analyses, including descriptive statistics where applicable, were conducted using JMP Pro software (version 14.1.0; SAS Institute, Inc., Cary, NC). Continuous variables were compared with the Student *t* test. Matched-pair analyses with Wilcoxon signed-rank test was conducted to study changes in SNOT-22 scores, Lund-Mackay CT scores, serum eosinophil counts, and serum IgE levels before and after initiating treatment. Patients with data both before and after treatment were selected to be studied in these matched-pair analyses.

3 | RESULTS

3.1 | Study population and demographics

An initial cohort of 845 patients was identified as having an asthma diagnosis and being treated with at least 1 biologic drug (omalizumab, mepolizumab, benralizumab, reslizumab, dupilumab). Of these 845 patients, 36.3% (307 patients) were identified as having concurrent CRS diagnosis. Approximately 80% (247/307) of the patients with CRS had formal Otolaryngology evaluation and diagnosis of CRS at Mayo Clinic and are the focus of this study.

Of the 247 CRS patients, 114 (46.2%) were male-identifying and 133 (53.8%) were female-identifying. Classified by subtype, 181 (73.3%) had CRSwNP and 66

TABLE 2 Distribution of biologics used in the study population

Biologic	n	%
Omalizumab	126	51.0
Mepolizumab	115	46.6
Benralizumab	26	10.5
Reslizumab	4	1.6
Dupilumab	6	2.4
Omalizumab + mepolizumab	17	6.9
Omalizumab + benralizumab	4	1.6
Omalizumab + dupilumab	1	0.4
Mepolizumab + benralizumab	4	1.6
Mepolizumab + reslizumab	1	0.4
Mepolizumab + dupilumab	2	0.8
Reslizumab + dupilumab	2	0.8

(26.7%) had CRS without nasal polyps (CRSsNP). Allergic fungal rhinosinusitis (AFRS) were diagnosed in 14 patients (5.7%), and 49 patients (19.85%) had a diagnosis of aspirin-exacerbated respiratory disease (AERD). The demographic and baseline clinical characteristics of the study group are demonstrated in Table 1. The most frequently administered biologics in the study were omalizumab (n = 126 patients; 51.0%) and mepolizumab (n = 115; 46.6%). During the study period, only 6 (2.4%) patients were prescribed dupilumab. Because of the small sample size, patients who were prescribed only dupilumab were excluded from further subgroup analysis. Thirty-one (12.6%) patients were administered more than 1 biologic during the study period. These details are presented in Table 2.

TABLE 3 SNOT-22 scores from pretherapy to 12 months posttherapy

Interval	All biologics	Omalizumab	Anti-IL-5 ^a
Pretreatment	42.6 (3–85); n = 63	42.5 (7–79); n = 15	42.6 (73–85); n = 50
3 Months	25.1 (3–68); n = 21	35 (33–38); n = 3	23.5 (3–68); n = 18
6 Months	23.8 (4–45); n = 16	15.5 (6–25); n = 2	23.7 (4–45); n = 15
12 Months	21.5 (3–59); n = 7	18.3 (14–27); n = 3	22.8 (3–59); n = 8
Longest follow-up period	24 (3–68); n = 38	23.7 (6–38); n = 7	23.5 (3–68); n = 32

^aValues are presented as mean (range); n = number of subjects.

IL-5 = interleukin 5; SNOT-22 = 22-item Sino-Nasal Outcome Test.

TABLE 4 Change in outcome measures for matched pairs within the overall study population

Matched-pair analyses of patients pre vs post-treatment	n	Mean difference (95% CI)	p
SNOT-22 pretreatment vs 3 months posttreatment all CRS	21	–15.6 (–25.6 to –5.5)	0.005
SNOT-22 pretreatment vs 6 months posttreatment all CRS	16	–17.6 (–29.1 to –6.1)	0.006
SNOT-22 pretreatment vs 12 months posttreatment all CRS	11	–29.1 (–44.5 to –13.7)	0.005
SNOT-22 pretreatment vs longest follow-up all CRS	38	–17.8 (–25.1 to –10.5)	<0.001
SNOT-22 pretreatment vs longest follow-up (CRSwNP)	34	–18.1 (–25.6 to –10.6)	<0.001
SNOT-22 pretreatment vs longest follow-up (CRSsNP)	4	N/A	N/A
Lund-Mackay CT score pretreatment vs posttreatment all CRS	67	–3.0 (–4.0 to –2.1)	<0.001
Lund-Mackay CT score pretreatment vs posttreatment (CRSwNP)	51	–2.9 (–4.1 to –1.7)	<0.001
Lund-Mackay CT score pretreatment vs posttreatment (CRSsNP)	16	–3.4 (–5.0 to –1.9)	<0.001
Serum eosinophil pretreatment vs posttreatment ($\times 10^9/L$) all CRS	131	–1.2 (–1.6 to –0.8)	<0.001
Serum eosinophil pretreatment vs posttreatment ($\times 10^9/L$) CRSwNP	98	–1.2 (–1.6 to –0.8)	<.0001
Serum eosinophil pretreatment vs posttreatment ($\times 10^9/L$) CRSsNP	33	–1.8 (–2.3 to –0.1)	<0.001
IgE pretreatment vs posttreatment (kU/L)	35	–589.7 (–1230.6 to 51.2)	<0.001
IgE pretreatment vs posttreatment (CRSwNP) (kU/L)	22	–188.1 (–339.9 to –36.4)	0.015
IgE pretreatment vs posttreatment (CRSsNP) (kU/L)	13	–1269.2 (–3068.1 to 529.7)	0.021

CI = confidence interval; CRS = chronic rhinosinusitis; CRSsNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyps; CT = computed tomography; IgE = immunoglobulin E; N/A = could not be analyzed; SNOT-22 = 22-item Sino-Nasal Outcome Test.

3.2 | Performance of ESS

ESS was performed in 206 (84.1%) patients, and the average number of surgeries performed per patient was 2.46 (95% confidence interval [CI], 2.17 to 2.75), with a range of 1 to 13 surgeries. Of these 206 patients, 189 (91.7%) had surgery prior to initiation of biologic therapy and 55 (10.7%) had surgery after having been administered a biologic agent. Only 58 subjects had not had prior ESS before being given biologic therapy, and 16 of these patients eventually underwent ESS within the study period. For patients on omalizumab, 35 patients (27.8%) underwent ESS after initiation of the drug, whereas 23 (16.5%) on anti-IL5 biologics (mepolizumab, benralizumab, reslizumab) underwent ESS after intervention with any of the anti-IL-5 agents.

3.3 | SNOT-22 score

Baseline SNOT-22 data was available for 63 of 247 patients. The average SNOT-22 pretreatment score (Table 1) was 42.6 (95% CI, 36.9 to 43.8) with a range of 3 to 85 points. Table 3 details the SNOT-22 scores pretherapy and posttherapy by the type of biologic agent. The interval changes in matched-pair analyses in total SNOT-22 scores for the entire study population are depicted in Table 4. For the overall study population, the average drop in SNOT-22 scores at 6-month and 12-month follow-up as well as longest follow-up was statistically and clinically significant (Table 4). At their longest follow-up interval, CRSwNP patients (n = 34) were noted to have an average total SNOT-22 score reduction of 18.1 points ($p < 0.001$; 95% CI, –25.6

to -10.6). For CRSsNP, the sample size of 4 was not a large enough to conduct meaningful analysis.

3.3.1 | Matched-pair analyses

Pre-biologic and post-biologic intervention analyses of patients at 6 months (16 patients), 12 months (11 patients), and at the longest follow-up (38 patients) also showed a drop in total SNOT-22 scores that was clinically and statistically significant (Table 4); no significant difference at the 3-month follow-up period could be detected. Some patients had multiple SNOT-22 scores recorded post-therapy throughout their follow-up care. Therefore, if a patient had a SNOT-22 score at 3 months, 6 months, and/or 12 months posttherapy, all scores were recorded accordingly.

Thirty of 38 patients did not require surgery after biologic treatment and had an average reduction of 15.6 points from pretreatment scores ($p < 0.001$; 95% CI, -23.6 to -7.6). Fourteen patients did not undergo any post-treatment surgery or systemic corticosteroid therapy; they showed an average reduction of 19.1 points from pretreatment SNOT-22 scores ($p = 0.014$; 95% CI, -32.8 to -5.3).

3.4 | CT scan scores

Pretreatment CT scans were available for 183 of 247 patients (omalizumab: 82; all anti-IL-5: 113 [benralizumab 22; mepolizumab: 92; reslizumab: 3] and dupilumab: 4). CT scans after initiation of biologic therapy were available for 106 patients, some of whom may have been treated with different biologic agent at different time periods (omalizumab 67, anti-IL-5: 49 and dupilumab: 3). Overall, the average pretreatment Lund-Mackay CT score was 14.4 (95% CI, 13.7 to 15.2) with a range of 3 to 24, and the average post-treatment score was 10 (95% CI, 8.9 to 11.0) with a range of 2 to 24 (Table 1).

3.4.1 | Matched-pair analyses

Pre-biologic and post-biologic intervention analyses could be conducted for 67 patients and these patients showed a significant reduction in Lund-Mackay CT score (CRS overall, as well as CRSwNP and CRSsNP subgroups) (Table 4). Twenty-one patients who did not undergo either surgery or systemic corticosteroid after initiating biologics also showed reduction in Lund-Mackay CT score by 2.6 points ($p = 0.002$; 95% CI, -4.3 to -0.8).

3.5 | Serum eosinophil levels

Average serum eosinophil count prior to initiating biologic therapy (178 patients) was $1.23 \times 10^9/L$ (95% CI, 0.93 to 1.53) with a range of 0 to $17.68 \times 10^9/L$ (Table 1). Average post-treatment eosinophil count (191 patients) was $0.23 \times 10^9/L$ (95% CI, 0.19 to 0.26) with a range of 0 to $1.54 \times 10^9/L$.

3.5.1 | Matched-pair analyses

Pre-biologic and post-biologic study of 131 patients showed a significant decrease in serum eosinophil levels post-treatment ($p < 0.0001$; 95% CI, -1.6 to -0.8) in both CRSwNP (98 patients) and CRSsNP (33 patients) subgroups (Table 4).

3.6 | Serum IgE levels

The average IgE pretreatment level (154 patients) was 604.8 kU/L (95% CI, 403.4 to 806.2) with a range of 4.2 to 11960 kU/L. The average IgE posttreatment level (67 patients) was 339.6 kU/L (95% CI, 202.8 to 476.4) with a range of 0.2 to 3128 kU/L. Matched-pair analyses for 35 patients pre-biologic and post-biologic therapy showed significant reduction in serum IgE levels for both CRSwNP (22 patients) and CRSsNP (13 patients) subgroups (Table 4).

3.7 | Analysis by type of biologic agent

3.7.1 | Omalizumab

Omalizumab was prescribed to 126 patients. Of these, 22 subjects were prescribed an additional biologic agent. Overall, omalizumab was not associated with any significant change in SNOT-22 scores at 6, 9, and 12 months and the longest period of follow up (Table 5).

Matched-pair analyses

Pre-omalizumab and post-omalizumab therapy matched-pair analyses showed average reduction of 3.4 points in CT score (38 patients; $p < 0.001$; 95% CI, -4.7 to -2.2); average reduction of 387.2 kU/L in IgE levels (15 patients; $p = 0.008$; 95% CI, -937.2 to 162.9) and average reduction of $0.75 \times 10^9/L$ in serum eosinophil counts (55 patients; $p < 0.001$; 95% CI, -1.09 to -0.41). Twenty-two patients did not undergo any ESS after starting omalizumab treatment and showed an average reduction of 3.5 points on their CT score ($p < 0.001$; 95% CI, -5.2 to -1.8).

TABLE 5 Baseline demographics and outcomes for patients treated with omalizumab

All patients on omalizumab	Values	Range	
Total subjects, n (%)	126 (100)		
Male, n (%)	60 (52.4)		
Female, n (%)	66 (47.6)		
CRSwNP, n (%)	88 (69.8)		
CRSsNP, n (%)	38 (30.2)		
AFRS, n (%)	7 (5.6)		
AERD, n (%)	23 (18.3)		
History of ESS, n (%)	96 (77.4)		
ESS before anti-IL-5 biologic treatment, n (%)	87 (69.0)		
ESS after anti-IL-5 biologic treatment, n (%)	35 (27.8)		
Number of ESS (patients with prior surgery), mean (95% CI)	2.53 (2.02–3.04)	1–13	
Pretreatment serum eosinophil count (×10 ⁹ /L), mean (95% CI)	0.98 (0.71–1.24)	0.03–7.76	
Posttreatment serum eosinophil count (×10 ⁹ /L), mean (95% CI)	0.33 (0.27–0.39)	0.03–1.54	
Highest serum IgE pretreatment (kU/L), mean (95% CI)	670.1 (394.5–945.6)	8.3–8450	
Highest serum IgE posttreatment (kU/L), mean (95% CI)	394.7 (215.1–574.4)	0.2–3128	
Pretreatment SNOT-22, mean (95% CI)	42.5 (28.5–56.4)	7–79	
3-month SNOT-22 posttreatment, mean (95% CI)	35 (41.6–28.4)	33–38	
6-month SNOT-22 posttreatment, mean (95% CI)	15.5 (–105.2 to 136.2)	6–25	
12-month SNOT-22 posttreatment, mean (95% CI)	18.3 (–0.3 to 37)	14–27	
SNOT-22 longest follow-up, mean (95% CI)	23.7 (12.3–35.1)	6–38	
Pretreatment Lund-Mackay CT score, mean (95% CI)	13.9 (12.5–15.2)	1–24	
Posttreatment Lund-Mackay CT score, mean (95% CI)	9.3 (8.0–10.6)	2–20	
	Mean difference (95% CI)	p	
Wilcoxon signed rank test for matched pairs	n		
SNOT-22 pretreatment vs 3 months posttreatment	3	–2.7 (–44.9, 39.6)	0.750
SNOT-22 pretreatment vs 6 months posttreatment	2	0 (–50.8, 50.8)	1.000
SNOT-22 pretreatment vs 12 months posttreatment	3	–38.3 (–105.9, 29.3)	0.250
SNOT-22 pretreatment vs longest follow-up	7	–18.1 (–42.6, 6.3)	0.109
Lund-Mackay CT score pretreatment vs posttreatment	38	–3.4 (–4.7, –2.2)	<0.001
Serum eosinophil count pretreatment vs posttreatment (×10 ⁹ /L)	55	–0.75 (–1.09, –0.41)	<0.001
Serum IgE pretreatment vs posttreatment (kU/L)	15	–387.2 (–937.2, 162.9)	0.008

AERD = aspirin exacerbated respiratory disease; AFRS = allergic fungal rhinosinusitis; CRSSNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyps; CT = computed tomography; CI = confidence interval; ESS = endoscopic sinus surgery; IgE = immunoglobulin E; IL-5 = interleukin 5; SNOT-22 = 22-item Sino-Nasal Outcome Test.

3.7.2 | Anti-IL-5 biologics

The summary of baseline demographics and outcomes of interest is presented in Table 6. A total of 145 subjects were treated with anti-IL-5 biologic agents. Of these, 21 patients were also treated with omalizumab, 4 with dupilumab, and 5 with another anti-IL agent (Table 2).

Matched-pair analyses

Pre-biologic and post-biologic intervention analyses of patients on anti-IL-5 biologics (mepolizumab, benralizumab, reslizumab) showed a clinically important reduc-

tion in SNOT-22 scores at 3 months ($n = 18$), 6 months ($n = 15$), 12 months ($n = 8$), and the longest follow-up ($n = 32$) period (Table 6). There was average reduction of 2.3 points on CT score (35 patients; $p = 0.002$; 95% CI, –3.6 to –0.9), average reduction of serum eosinophil count by $1.47 \times 10^9/L$ (83 patients; $p < 0.001$; 95% CI, –2.07 to –0.87) and average serum IgE reduction by 724.1 kU/L (19 patients; $p = 0.01$; 95% CI, –1811.5 to 363.4). Average Lund-Mackay CT score reduction of 2.7 points ($p = 0.002$; 95% CI, –4.2, –1.1) was seen in patients that did not undergo ESS after anti-IL-5 biologic intervention.

TABLE 6 Baseline demographics and outcomes for patients treated with anti-IL-5 biologics

All anti-IL-5 patients	Values	Range	
Total subjects, n (%)	139 (100)		
Male, n (%)	62 (44.6)		
Female, n (%)	77 (55.4)		
CRSwNP, n (%)	103 (74.1)		
CRSSNP, n (%)	36 (25.9)		
AFRS, n (%)	9 (6.5)		
AERD, n (%)	26 (18.7)		
History of ESS, n (%)	120 (87.0)		
ESS before anti-IL-5 biologic treatment, n (%)	111 (79.9)		
ESS after anti-IL-5 biologic treatment, n (%)	23 (16.5)		
Number of ESS (patients with prior surgery), mean (95% CI)	2.36 (2.07–2.66)	1–11	
Pretreatment serum eosinophil count (×10 ⁹ /L), mean (95% CI)	1.34 (0.90–1.79)	0–17.68	
Posttreatment serum eosinophil count (×10 ⁹ /L), mean (95% CI)	0.14 (0.10–0.18)	0–1.23	
Highest serum IgE pretreatment (kU/L), mean (95% CI)	538.7 (273.0–804.4)	4.2–11960	
Highest serum IgE posttreatment (kU/L), mean (95% CI)	255.4 (91.6–419.2)	0.2–2036	
Pretreatment SNOT-22, mean (95% CI)	42.6 (36.2–49.0)	3–85	
3-month SNOT-22 posttreatment, mean (95% CI)	23.5 (15.2–31.8)	3–68	
6-month SNOT-22 posttreatment, mean (95% CI)	23.7 (17.1–30.4)	4–45	
12-month SNOT-22 posttreatment, mean (95% CI)	22.8 (8.2–37.3)	3–59	
SNOT-22 longest follow-up, mean (95% CI)	23.5 (17.6–29.5)	3–68	
Pretreatment Lund-Mackay CT score, mean (95% CI)	14.9 (14.0–15.7)	6–24	
Posttreatment Lund-Mackay CT score, mean (95% CI)	11.3 (9.8–12.8)	2–24	
	Mean difference (95% CI)	p	
Wilcoxon signed rank test for matched pairs	n		
SNOT-22 pretreatment vs 3 months posttreatment	18	−17.7 (−28.9 to −6.5)	0.006
SNOT-22 pretreatment vs 6 months posttreatment	15	−19.1 (−31.0 to −7.1)	0.004
SNOT-22 pretreatment vs 12 months posttreatment	8	−25.6 (−44.1 to −7.2)	0.023
SNOT-22 pretreatment vs longest follow-up	32	−17.3 (−25.0 to −9.6)	<0.001
Lund-Mackay CT score pretreatment vs posttreatment	35	−2.3 (−3.6 to −0.9)	0.002
Serum eosinophil count pretreatment vs posttreatment (×10 ⁹ /L)	83	−1.47 (−2.07 to −0.87)	<0.001
Serum IgE pretreatment vs post-treatment (kU/L)	19	−724.1 (−1811.5 to 363.4)	0.010

AERD = aspirin exacerbated respiratory disease; AFRS = allergic fungal rhinosinusitis; CRSSNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyps; CT = computed tomography; CI = confidence interval; ESS = endoscopic sinus surgery; IgE = immunoglobulin E; IL-5 = interleukin 5; SNOT-22 = 22-item Sino-Nasal Outcome Test.

4 | DISCUSSION

With the exclusion of a small, early trial on omalizumab,¹⁴ trials of biologic agents in CRS have been conducted in patients of CRSwNP exclusively. In our real-world study, we were able to review the effect of biologics used against asthma in their impact on co-existent CRS. These patients included both CRSwNP and CRSSNP subgroups. Overall, we noted that use of a biologic for asthma resulted in a significant improvement in CRS symptoms reported by patients. We found a significant decrease in the total SNOT-22 scores that was well over the MCID

level of 8.9 (Table 4) in the overall CRS group as well as the CRSwNP subgroup. This decrease was largest at the 12-month follow-up period. In our study, one-fourth of the patients (26.7%) were noted to have CRSSNP. Because only a small number of CRSSNP patients had both pre-biologic and post-biologic SNOT-22 scores available, we were unable to analyze the impact in this subgroup specifically.

Although we did not have histopathological data on the type of inflammation in these CRS patients, the association with asthma may point to a type 2 eosinophilic pathophysiology. We noted a significant reduction in objective

disease burden by Lund-Mackay CT scores for the overall CRS group as well as in CRSwNP and CRSsNP subgroups post-biologic intervention. We also noted a decrease in serum IgE and serum eosinophil counts in the overall CRS group as well as CRSwNP and CRSsNP subgroups. The benefit of anti-IL-5 biologics observed in CRS was significant in both patient-reported outcomes as well as objective CT-based data in CRS overall and CRSwNP. The small number of CRSsNP matched-pair data limits comment on impact in this subgroup. The presence of IL-5, however, has been previously reported as prognostic marker for improved response to mepolizumab.¹⁵

On analysis by type of biologic therapy, anti-IL-5 agents were associated with significant improvement in postintervention CT scores as well as SNOT-22 scores for the overall CRS group. Further subanalyses for individual anti-IL-5 agents were not meaningful because of the small samples in each group. Patients on omalizumab had a meaningful improvement in SNOT-22 scores. Omalizumab was associated with a significant 3.4-point reduction in Lund-Mackay CT score but the clinical impact of this change is unclear as there is no defined MCID for Lund-Mackay CT scores. Recently, in a 2-part randomized clinical trial, omalizumab was found to be effective in improving endoscopic, clinical, and patient-reported outcomes in severe CRS patient with inadequate response to intranasal corticosteroids.⁷ That trial showed a drop of 1.08 points in nasal polyp score (maximum 8) and a drop of 24.7 points on the SNOT-22 score. However, as opposed to our study, that study was restricted to patients with CRSwNP.

Data has increasingly emerged that phenotypic classification of CRS into those with and without nasal polyps is inadequate.^{1,16–18} Phenotypes of CRS do not necessarily conform to presumed histopathologic and endotypic characteristics. Many patients with CRSsNP have eosinophilic infiltration and likely have type 2 driven immunopathology.^{2,17,19} Unfortunately, all recent trials on biologic therapy have excluded CRSsNP patients within their study criteria. Conversely, many patients with CRSwNP may not have the presumed type 2 inflammation and therefore may respond poorly to biologic therapy.^{20,21} Recent trials of dupilumab and omalizumab report a polyp size decrease of about 2 points on an 8-point total nasal polyp score in CRSwNP patients.^{5,7} It is possible that the higher the disease burden, the more likely that therapy will have impact, even in type 2 eosinophilic patients. CRSsNP patients with eosinophilic inflammation may potentially be at an advantage in the response to such anti-IL-5 treatment. This hypothesis needs to be further studied in a trial setting.

Our study highlights the need to further direct therapy based on the biological characteristics of CRS, not just the endoscopic visualization of the presence or absence of

polyps. Trials should utilize criteria beyond the CRSwNP phenotype, using biomarkers and other clinical data. These could include histopathology data, tissue eosinophil count,^{17,19,22} urinary LTE4,^{23,24} or other biomarkers under investigation.²³ As with the current study, our recent study showed that about one-third of CRSsNP patients have eosinophilic inflammation.¹⁷ Certain inclusion criteria have been perhaps too stringent in prior trials of biologics and do not reflect real-world scenarios. Biologic therapy could be an option for all eosinophilic CRS, especially if using for a labeled condition of uncontrolled asthma. Clinicians can potentially use the diagnosis of asthma, IgE, and serum peripheral eosinophil counts in recalcitrant CRS patients as clues to further identify subsets of patients that are candidates for biologic therapy. We believe that while specific biomarkers are being developed, studying patients by tissue eosinophil counts is a practicable strategy.^{17,19,25} The more precise emerging route will be likely through use of specific biomarkers (peripheral eosinophil count, urinary leukotriene E4 [LTE4]) or with a combination of other biomarkers under investigation such as eosinophil peroxidase, which has been studied by our group.²⁶

We also found that about 85% of our study patients had previous sinonasal surgery with the number ranging from 1 to 13 (average 2.46 per patient). However, 16.5% of patients on anti-IL-5 therapy and 27.8% on omalizumab underwent surgery after initiating biologics. It is also therefore important to conduct trials to identify patients who respond better to biologics vs ESS. We also observed that from our initial cohort of 845 patients placed on biologic therapy for asthma control, over one-third (36.3%) were identified to have concurrent CRS diagnosis. Our results support previously published literature on the co-existence of CRS in patients with severe asthma.¹

Our study has several weaknesses. We studied the patient characteristics and outcomes through a retrospective review of electronic charts. Endoscopic appearance and endoscopic scoring in the standardized fashion was not available. For the number of biological agents studied, 247 patients may not be an adequate sample. The matched-pair numbers for CRSsNP was too small to analyze meaningfully. Additionally, there was no control group in this study. The study population is heterogeneous. The wide 95% CI in some of the metrics reflects that the dataset was not normally distributed. The Wilcoxon signed-rank (nonparametric) test was used, because it is resistant to the outlier data. We also did not have histopathological data for most of the study patients because data on tissue eosinophilia and structured histopathological reports²⁵ are only generated at our Arizona site. Therefore, analysis of the subtypes of CRS based on tissue eosinophilia could not be conducted.¹⁹ Additionally, only a limited number of patients were treated with dupilumab, precluding

further analysis. Because this was a retrospective review, we also had to rely on the otolaryngologist of record to diagnose CRS and CRS subtypes. We cannot comment on criteria used for CRS diagnosis and diagnosis of subtype. We are also not able to assess the differential impact of a biologic agent vs these other therapies given during the study. Additionally, if patients were treated with multiple biologic agents, they were included in the analysis for each agent because we had a relatively small sample size. Although we believe it is rare to adjust dose and frequency of anti-asthma biologics, we did not record dosage and cannot account for differences from variations in dosage. Data collection was concluded on July 18, 2019. Therefore, subsequent effects of biologic therapy on CT, SNOT-22, and other tests, as well as further surgical intervention is not known. Finally, we present an uncontrolled study with a relatively small data set. We should be careful not to generalize and over-interpret the data. Rather, this study highlights the need to conduct a prospective study on use of biologic therapy on CRS patients in a real-world setting that also includes patients that have not met past enrollment criteria for clinical trials.

5 | CONCLUSION

In a real-world retrospective review of biologics used for asthma in patients who had co-existent CRS, we found that uncontrolled/severe asthma was associated with CRSsNP in 27% of patients. Anti-IL-5 therapeutic agents were associated with improved CRS control as measured by both SNOT-22 and Lund-Mackay CT scores in the overall CRS group and CRSwNP patients, and improved CT scores for the CRSsNP subgroup. Omalizumab was associated with benefit in Lund-Mackay CT scores, but not in the patient reported SNOT-22 scores. The data suggest that treatment decisions for biologics for recalcitrant CRS should consider patient characteristics other than presence or absence of nasal polyps. Our study highlights that biologics might have impact on CRS subgroups such as patients with CRSsNP who have previously not been included in trials of biologics. Our study results may have implications that can influence future trial designs, as well as the clinical applications of biologic therapy in CRS patients.

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