The Laryngoscope

Influence of Prior Endoscopic Sinus Surgery Extent on Dupilumab Effectiveness in CRSwNP Patients

Matteo Alicandri-Ciufelli, MD, FEBORL, FACS; Daniele Marchioni, MD; Carlotta Pipolo, MD; Massimiliano Garzaro, MD; Letizia Nitro, MD; Valeria Dell'Era, MD; Francesco Ferrella, MD; Massimo Campagnoli, MD; Paolo Russo, MD; Costanza Galloni, MD; Angelo Ghidini, MD; Eugenio De Corso, MD; Daniela Lucidi, MD

Background: Guidelines recommend that the vast majority of patients with severe uncontrolled chronic rhinosinusitis with nasal polyps (CRSwNP) should have at least one endoscopic sinus surgery (ESS) prior to starting biologics. Because ESS can be performed with a variable extension, the aim of this study would be to evaluate the association between surgical extensiveness, as measured by ACCESS score, and outcomes collected in patients treated with Dupilumab.

Materials and Methods: This is a multicentric retrospective study; patients affected by CRSwNP who were subjected to Dupilumab therapy and who underwent at least one ESS prior to Dupilumab initiation were included. ACCESS score was assigned to each patient's pre-Dupilumab CT scan. Subjective and objective parameters (SNOT-22, NPS, VAS scores, Sniffin' Sticks) were collected before and during the administration of therapy. Statistical correlations between ACCESS scores and clinical outcomes were investigated.

Results: A total of 145 patients were included; mean time from last previous ESS was 68.6 months, and on average, patients were subjected to 2.2 surgeries. Many correlations with ACCESS scores were demonstrated: better NPS at all timepoints and subjective scores (30-days SNOT-22, VAS nasal obstruction, and rhinorrhea) were achieved in patients with low ACCESS score (more extensive ESS). On the other hand, significantly worse VAS loss of smell values were demonstrated in patients with lower ACCESS scores.

Conclusion: Dupilumab patients subjected to a prior extensive ESS may have reduced size of polyps and improved subjective indicators, together with a decreased chance to recover smell, when compared with patients who underwent a minimal excision.

Key Words: ACCESS score, biologic therapy, CRSwNP, Dupilumab, nasal polyps.

Level of Evidence: 3

***Laryngoscope*, 134:1556–1563, 2024**

INTRODUCTION

Chronic rhinosinusitis with nasal polyps (CRSwNP) represents a challenging disease entity with significant rates of recurrence following appropriate medical and surgical therapy. Several factors can influence its clinical course, as already reported in literature.[1] The advent of biologic drugs for therapy of CRSwNP has rapidly changed the management of this pathology among the ENT community. Dupilumab is an IgG4 human monoclonal antibody that targets the interleukin 4 (IL-4) receptor alpha subunit,[2] thus reducing the downstream effects of IL-4 and interleukin 13. At the time of data analysis, Dupilumab was the only monoclonal antibody approved for severe uncontrolled CRSwNP in the national setting, and few real-life reports on efficacy and safety were available.[3–9]

Although indications to biologic treatment can vary based on the guidelines, and regulatory administrations of each country can influence the prescriptions, it is generally accepted that a maximal pharmacological therapy and at least one surgical attempt (endoscopic sinus surgery or ESS) should be required before adding a biologic drug.[10] Actually, ESS can be performed with a variable degree of completeness and extent, depending on the attitude and experience of the surgeons, and settings of the performing centers. Many argue that more extensive surgery would allow better access of the sinus system to local

From the Department of Otolaryngology-Head and Neck Surgery (M.A.-C., D.M., C.G., D.L.), Azienda Ospedaliero-Universitaria di Modena, Modena, Italy; Otolaryngology Unit, Department of Health Sciences (C.P., L.N., F.F.), Santi Paolo e Carlo Hospital, Università degli Studi di Milano, Milan, Italy; ENT Division (M.G., V.D., M.C.), Eastern Piedmont University Hospital of Novara, Novara, Italy; ENT Department (P.R., A.G.), Azienda USL Reggio Emilia – IRCCS, Reggio Emilia, Italy; and the Department of Head, Neck and Sensory Organs (E.D.C.), A. Gemelli University Hospital IRCCS, Rome, Italy.

Editor's Note: This Manuscript was accepted for publication on July 31, 2023.

The following authors have performed lectures, meetings, and advisory boards with Sanofi, AstraZeneca, Novartis, and GSK: M.A.-C., C.P., M.G., A.G., E.D.C., and D.L.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Send correspondence to Dr. Costanza Galloni, Otorhinolaryngology-Head and Neck Surgery Department, University Hospital of Modena, Largo del Pozzo, 71, 41125 Modena, Italy. Email: costanza.galloni@gmail.com

DOI: 10.1002/lary.30983

medication, thus improving disease control.[11,12] Until some years ago, no validated tool existed to quantify the completeness of surgeries. In 2020, a postoperative grading system was introduced at this purpose, named ACCESS score (Amsterdam Classification of Completeness of Endoscopic Sinus Surgery).[13] In the authors' knowledge, no data are available at present describing the possible influence of previous surgery extent on the outcomes obtained in patients with severe uncontrolled CRSwNP undergoing biologic treatment.

The aim of this article was to evaluate the possible association between the degree of surgical extent, as measured by ACCESS score, and the main outcomes (both objective and subjective) collected in patients who were subjected to Dupilumab for recurrent severe uncontrolled CRSwNP, both as baseline and at different follow-up timepoints.

MATERIALS AND METHODS

Study Design

Patients treated at the Rhinology units of the following institutions: Modena University Hospital, Reggio Emilia Hospital, Novara University Hospital and Milano "Santi Paolo e Carlo" Hospital between November 2020 and October 2022 were considered for inclusion in the study and their clinical charts were retrospectively reviewed. The participating centers were chosen for having a similar rhinology unit in which patients undergoing biological therapy had analogous follow-up schedule, as follows: baseline (T0), 1 month (T1), 3 months (T2), 6 months (T3), and 12 months (T4). All the patients who completed the T4 follow-up have values for all the prior timepoints.

Study Population

Inclusion criteria were as follows: patients affected by severe uncontrolled CRSwNP who were subjected to subcutaneous 300 mg Dupilumab home self-administered every 2 weeks prescribed accordingly to the plan provided by Italian Agency of Drugs,[14] patients ≥18 years old, patients whose clinical data collected at the five above mentioned timepoints were available, patients who underwent at least one sinonasal surgical procedure (FESS or ESS) prior to Dupilumab initiation, and patients whose post-operative CT scan performed before the first administration of therapy was available.

The criteria observed for biological therapy candidacy were the following: severe disease stage (NPS ≥5 and/or SNOT-22 ≥50); inadequate symptom controls with intranasal corticosteroids (INCS); failure (or intolerance) of previous medical treatments (at least 2 cycles of oral corticosteroid or OCS over the last year); and/or previous ESS. All patients undergoing Dupilumab were indicated not to discontinue their previous intranasal corticosteroids during treatment. All the participating institutions routinely prescribe mometasone furoate nasal spray 200 μg/day for 12 to 24 consecutive weeks. A course of OCS has a duration of 7 to 21 days according to EPOS 2020 guidelines.[10]

Pregnant women, immunosuppressive therapy, radiochemotherapy treatments for cancer in the 12 months before starting therapy, and concomitant long-term corticosteroid therapy for chronic autoimmune disorders, intended as a daily low-dose systemic steroid administration, were exclusion criteria.

Outcomes

An anonymous database was created, retrospectively entering patients' data and outcome parameters (including SNOT-22 score, NPS score, smell identification test by Sniffin' Sticks, VAS related to nasal obstruction, loss of smell, sleeping disorders, rhinorrhea, and craniofacial pain) at the following timepoints: baseline (T0), 1 month (T1), 3 months (T2), 6 months (T3), and 12 months (T4). VAS score is a validated measurement for self-reporting the severity of a symptoms, ranging from 0 (no symptom) to 10 (the most intense symptom imaginable). VAS sleeping disorders refers to sleep disruption related to nocturnal exacerbation of CRSwNP symptoms.

Furthermore, four experienced rhinologists, one for each participating center, retrospectively reviewed all the last postoperative CT scans performed before starting biological therapy and assigned ACCESS score for each sinus, as follows: frontal sinus (FA), maxillary sinus (MA), osteo-meatal complex (OMCA), anterior ethmoid sinus (AEA), posterior ethmoid sinus (PEA), and sphenoid sinus (SA). An overall ACCESS score (OA) was calculated for each patient by adding those of the single sinuses. The structure of the scoring system is very similar to the Lund-Mackay system; per side, 6 anatomical sites are graded with a 0, 1, or 2. However, the ACCESS score does not focus on sinus opacification but only on access to the sinus based on bony boundaries. A score of 0 means that no additional surgery is needed to warrant access to this site ("functionally opened"). A score of 1 means that previous surgery did address this site but was inadequate to open it fully ("touched but not functional"). A score of 2 means that no previous surgery was performed to this sinus/site.

The study protocol and informed consent forms were approved by the Institutional Ethics Committee and conducted in accordance with the World Medical Association Declaration of Helsinki. Each patient signed informed consent to participate in the study.

Statistical Analysis

The statistical analysis of the results was performed using SPSS for Windows (IBM SPSS Statistics, Chicago, USA). Continuous variables were expressed as mean ± standard deviation (SD). Student's *t*-test was used for continuous variables with normal distribution, whereas Mann–Whitney *U* test was adopted for continuous variables without a normal distribution. Comparisons between groups were performed by Pearson's chi-square or Fischer exact test for discrete variables, as appropriate. The

TABLE I.
General Population Characteristics.

Feature	
Number of patients	145
Male	89 (61.3%)
Female	56 (38.7%)
Mean age	55.1 years (27–86)
Asthma	110 (75.8%)
NSAID-ERD	43 (29.6%)
Average duration of CRSwNP	15.6 years
Mean time from last prior ESS/FESS	68.6 mo (6–360)
Average number of prior surgeries	2.2 (1–13)

CRSwNP = chronic rhinosinusitis with nasal polyps; ESS = endoscopic sinus surgery; FESS = functional endoscopic sinus surgery; N-ERD = nonsteroidal anti-inflammatory drugs-exacerbated respiratory disease.

p values were obtained by one-way ANOVA test when the variable was normal or Kruskal–Wallis test when the variable was skewed. The strength of the correlation between the parameters was obtained by Pearson's correlation test. The results were considered as significant for p values <0.05 with a confidence interval of 95%.

RESULTS

General Characteristics

A total of 145 consecutive patients (89 males and 56 females; mean age: 55.1 years, range: 27–86) were included in the study. All the subjects completed the T1 and T2 follow-ups, whereas 111 (76.5%) of them the T3 and 65 (44.8%) the T4. As regards nasal identification test by Sniffin' Sticks, it was performed in a subset of patients: 72 patients (49.6%) at the baseline, 64 patients (44.1%) at T1, 21 patients (14.5%) at both T2 and T3, and 38 patients (26.2%) at T4. Although an NPS cutoff of 5 is indicated by the national prescription plan, four patients with NPS = 4 were included in the analysis, due to severe clinical condition and high personal motivation to undertake therapy. All the patients included were responders to Dupilumab.[15] General characteristics of the study population are reported in Table I.

Effectiveness of Dupilumab

Table II depicts baseline and in-treatment parameters registered over time. As far as NPS and SNOT-22 responses are concerned, a significant improvement was registered over time. NPS showed a significant decrease from baseline (median values: 6, IQR 5–6) until a median value of 1.0 (IQR 0.0–2.0) at 12 months ($p < 0.001$). Significant changes occurred throughout all timepoints. Also SNOT-22 values significantly decrease from a mean value of 56.1 at baseline to 12.5 at 12 months ($p < 0.001$), with significant changes throughout all timepoints. Figure 1 depicts the variation of all VAS scales at the different timepoints.

ACCESS Score

Mean overall ACCESS score at Dupilumab initiation was 8.48 (median: 8), mean FA was 2.4 (median: 2), mean MA was 0.4 (median: 0), mean OMCA was 0.19 (median: 0), mean AEA was 1.33 (median: 1), mean PEA was 1.97 (median: 2), and mean SA was 2.17 (median: 2). Mean Lund-Mackay score was 18.8.

When correlation between ACCESS scores and baseline parameters was investigated, statistically significant results were obtained between SNOT-22 and PEA (r coefficient: 0.185; $p < 0.05$), VAS nasal obstruction and AEA, PEA, SA, (r coefficient: 0.166, 0.195, 0.208 respectively; $p < 0.05$), VAS rhinorrhea and PEA (r coefficient: 0.191; $p < 0.05$), VAS craniofacial pain and AEA, PEA (r coefficient: 0.173 and 0.259 respectively; $p < 0.05$). All the other correlations between baseline parameters and ACCESS scores were not statistically significant.

TABLE II.
Overall Baseline and In-Treatment Scores.

Parameter	T0	*N*	T1	*N*	T2	*N*	T3	*N*	T4	*N*	*p*
NPS (0–8) (mean ± SD; median; range)	5.6 ± 1.3; 6; 4–8	145	2.7 ± 1.6; 3; 0–7	145	2.1 ± 1.7; 2; 0–7	145	2.2 ± 1.7; 2; 0–7	111	1.4 ± 1.6; 1; 0–6	65	0.0005
SNOT-22 (0–120) (mean ± SD; range)	56.1 ± 18.4; 32–101	145	27.4 ± 16.0; 0–88	145	19.4 ± 14.0; 0–87	145	14.4 ± 10.2; 0–51	111	12.5 ± 9.4; 0–48	65	0.0005
Sniffin' Sticks (smell identification score: mean ± SD; range)	5.7 ± 2.7; 0–15	72	10.7 ± 2.9; 2–16	64	10.1 ± 3.8; 3–16	21	9.7 ± 3.8; 0–16	21	11.1 ± 2.4; 3–14	38	0.0005
VAS loss of smell (0–10 cm) (mean ± SD; median; range)	7.4 ± 2.9; 8; 0–10	145	3.9 ± 2.4; 4; 0–10	145	3.2 ± 2.7; 3; 0–10	145	2.5 ± 2.8; 2; 0–10	111	2.4 ± 2.7; 2; 0–10	65	0.0005
VAS nasal obstruction (0–10 cm) (mean ± SD; median; range)	7.6 ± 2.1; 8; 0–10	145	3.0 ± 2.1; 2; 0–9	145	2.2 ± 2.0; 2; 0–10	145	1.5 ± 1.8; 1; 0–9	111	1.1 ± 1.5; 1; 0–8	65	0.0005
VAS rhinorrhea (0–10 cm) (mean ± SD; median; range)	6.6 ± 2.2; 7; 0–10	145	2.8 ± 2.2; 2; 0–9	145	1.9 ± 2.1; 2; 0–10	145	1.4 ± 1.8; 1; 0–9	111	1.5 ± 1.7; 1; 0–8	65	0.0005
VAS craniofacial pain (0–10 cm) (mean ± SD; median; range)	2.8 ± 3.1; 2; 0–10	145	1.7 ± 2.0; 1; 0–9	145	1.1 ± 1.7; 0; 0–9	145	0.7 ± 1.3; 0; 0–8	111	0.7 ± 1.3; 0; 0–6	65	0.001
VAS sleep disorders (0–10 cm) (mean ± SD; median; range)	5.7 ± 2.9; 6; 0–10	145	2.0 ± 2.0; 2; 0–8	145	1.3 ± 1.7; 0.5; 0–7	145	0.9 ± 1.7; 0; 0–10	111	1 ± 1.6; 0; 0–7	65	0.0005

T0 = baseline, T1 = 1 mo, T2 = 3 mo, T3 = 6 mo, T4 = 12 mo, *N* = number of evaluable participants.

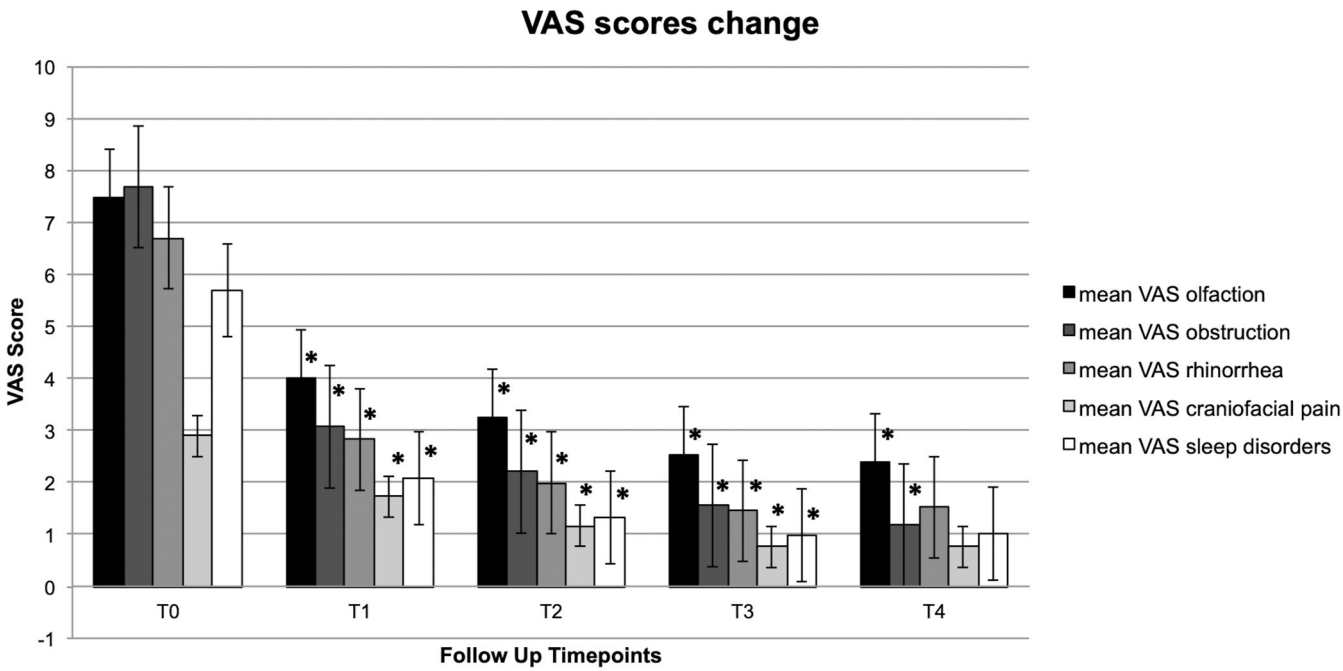

Fig. 1. VAS scores change at different timepoints. *Statistically significant timepoint changes.

Table III describes all correlations between ACCESS scores and parameters at baseline and all timepoints.

When correlation between ACCESS scores and NPS was investigated, statistically significant results were obtained between T1 NPS and AEA, PEA, OA (r coefficient: 0.381, 0.329, 0.191, respectively; $p < 0.000$ for AEA and PEA; $p < 0.05$ for OA), T2 NPS and AEA (r coefficient: 0.251; $p < 0.05$), T3 NPS and AEA (r coefficient: 0.353; $p < 0.05$). Regarding correlation between ACCESS scores and SNOT-22, statistically significant results were obtained between T1 SNOT-22 and MA, AEA, PEA, OA (r coefficient: 0.39, 0.212, 0.195, and 0.207, respectively; $p < 0.05$). Regarding correlation between ACCESS scores and VAS loss of smell, statistically significant correlation were obtained between T1 VAS loss of smell and AEA, PEA (r coefficient: −0.213 and −0.181, respectively; $p < 0.05$), T2 VAS loss of smell and AEA, PEA (r coefficient: −0.241 and −0.257, respectively; $p < 0.05$), T3 VAS loss of smell and MA (r coefficient: −0.216; $p < 0.05$), and T4 VAS loss of smell and PEA, SA, OA (r coefficient: −0.298, −0.276, −0.298 respectively, $p > 0.05$). To corroborate this result, a correlation between number of surgeries and VAS loss of smell at all timepoints was performed, and statistically significant correlations were demonstrated between number of surgeries and both T3 and T4 VAS loss of smell (r coefficient: 0.237 and 0.359, respectively; $p < 0.05$).

When correlation between ACCESS scores and VAS nasal obstruction was investigated, statistically significant results were obtained between T1 VAS nasal obstruction and SA (r coefficient: 0.186; $p < 0.05$) and between T3 VAS nasal obstruction and AEA (r coefficient: 0.302; $p < 0.000$). When correlation between ACCESS scores and VAS rhinorrhea was investigated, statistically significant results were obtained between T1 VAS rhinorrhea and SA (r coefficient: 0.221; $p < 0.05$) and T3 VAS rhinorrhea and AEA (r coefficient: 0.228; $p < 0.05$). No significant correlations were determined between ACCESS scores and VAS craniofacial pain and VAS sleeping disorders at any timepoints.

As far as correlation between ACCESS scores and Sniffin' Sticks was concerned, no significant correlations were recognized at any timepoints.

DISCUSSION

Our analysis confirms the efficacy of Dupilumab in reducing NPS and improving dramatically quality of life and sense of smell. Moreover, the highest reduction was detected at T1 to T2 especially for subjective parameters, such as SNOT-22 and VAS loss of smell and nasal obstruction. The subsequent months show further progressive improvement, although less pronounced. NPS, on the contrary, shows a progressive reduction along the entire follow-up duration, from a median of 6 at the baseline, to 1 at the 12 months follow up. This is consistent with other reports in the literature.[16]

The natural history of CRSwNP, before the advent of biologic drugs, was dictated by a high likelihood of undergoing a surgical intervention, often multiple times.[17] The polyps' recurrence rate after surgery ranged between 38% and 60%,[14,18] with many clinical factors predictive of high disease severity and recurrence rate (recalcitrant polyposis). Our results confirm previous series, as patients operated on 2.2 times on average were included, and 42 of them (29% of the total) underwent ≥3 surgeries. The issue whether to undergo extensive surgery of the paranasal sinuses before undertaking biological therapy is a matter of debate in the rhinological community. Several

TABLE III.
Correlations Between ACCESS Scores and Parameters at Baseline and at All Timepoints.

Parameter	T0	T1	T2	T3	T4
NPS (*p* value; *r* coefficient)	**NS for all comparisons** OA (0.645; 0.019), MA (0.833; 0.109), OMCA (0.246; 0.041), AEA (0.278; 0.045), PEA (0.072; 0.121), FA (0.077; 0.161), SA (0.698; −0.071)	**NS for all comparisons** OA (0.425; 0.032), MA (0.983; −0.023), OMCA (0.136; 0.152), AEA (0.768; 0.023), PEA (0.094; 0.082), FA (0.127; 0.154), SA (0.098; −0.135)	**OA (0.042; 0.191),** MA (0.813; 0.104), OMCA (0.256; 0.042), **AEA (0.0005; 0.381), PEA (0.0005; 0.329),** FA (0.427; 0.121), SA (0.124; 0.115)	OA (0.091; 0.102), MA (0.124; 0.187), OMCA (0.196; −0.024), **AEA (0.007; 0.251),** PEA (0.427; 0.081), FA (0.125; 0.014), SA (0.067; 0.105)	OA (0.081; 0.032), MA (0.754; 0.097), OMCA (0.192; −0.074), **AEA (0.004; 0.353),** PEA (0.351; 0.084), FA (0.083; 0.065), SA (0.234; 0.101)
SNOT-22 (*p* value; *r* coefficient)	OA (0.358; 0.015), MA (0.956; −0.076), OMCA (0.126; 0.059), AEA (0.217; 0.063), **PEA (0.027; 0.185),** FA (0.459; 0.038), SA (0.076; −0.112)	**OA (0.025; 0.207), MA (0.039; 0.394),** OMCA (0.135; 0.103), **AEA (0.022; 0.212), PEA (0.036; 0.195),** FA (0.356; 0.019), SA (0.082; −0.417)	**NS for all comparisons** OA (0.095; 0.122), MA (0.354; 0.087), OMCA (0.136; 0.069), AEA (0.087; −0.355), PEA (0.427; 0.082), FA (0.127; 0.054), SA (0.067; 0.133)	**NS for all comparisons** OA (0.695; 0.059), MA (0.755; 0.076), OMCA (0.426; −0.053), AEA (0.247; 0.073), PEA (0.297; 0.026), FA (0.382; −0.048), SA (0.084; 0.102)	**NS for all comparisons** OA (0.422; 0.113), MA (0.625; −0.089), OMCA (0.522; 0.134), AEA (0.279; 0.015), PEA (0.198; 0.023), FA (0.254; 0.054), SA (0.454; −0.083)
Sniffin' Sticks (*p* value; *r* coefficient)	**NS for all comparisons** OA (0.447; 0.134), MA (0.953; 0.083), OMCA (0.692; 0.171), AEA (0.291; −0.018), PEA (0.158; 0.054), FA (0.272; 0.041), SA (0.194; 0.033)	**NS for all comparisons** OA (0.821; 0.153), MA (0.722; 0.019), OMCA (0.582; 0.033), AEA (0.571; 0.010), PEA (0.138; −0.431), FA (0.458; 0.059), SA (0.114; 0.074)	**NS for all comparisons** OA (0.722; 0.117), MA (0.125; 0.049), OMCA (0.128; 0.130), AEA (0.249; 0.011), PEA (0.134; 0.083), FA (0.821; 0.122), SA (0.854; −0.013)	**NS for all comparisons** OA (0.128; 0.035), MA (0.634; 0.279), OMCA (0.522; 0.139), AEA (0.379; 0.085), PEA (0.258; −0.093), FA (0.564; 0.080), SA (0.156; 0.486)	**NS for all comparisons** OA (0.289; 0.102), MA (0.649; 0.012), OMCA (0.520; −0.132), AEA (0.865; 0.045), PEA (0.199; 0.043), FA (0.154; −0.298), SA (0.433; 0.120)
VAS loss of smell (*p* value; *r* coefficient)	**NS for all comparisons** OA (0.769; −0.072), MA (0.446; −0.092), OMCA (0.820; −0.107), AEA (0.867; −0.035), PEA (0.139; −0.085), FA (0.736; −0.072), SA (0.524; 0.127)	OA (0.722; −0.102), MA (0.124; −0.046), OMCA (0.348; −0.130), **AEA (0.010; −0.213), PEA (0.029; −0.181),** FA (0.821; −0.120), SA (0.855; −0.035)	OA (0.463; −0.101), MA (0.195; −0.026), OMCA (0.382; −0.021), **AEA (0.005; −0.241), PEA (0.003; −0.257),** FA (0.923; −0.023), SA (0.653; −0.053)	OA (0.748; −0.114), **MA (0.021; −0.216),** OMCA (0.322; −0.181), AEA (0.201; −0.029), PEA (0.658; 0.052), FA (0.357; −0.013), SA (0.190; −0.036)	OA (0.02; −0.293), MA (0.715; 0.086), OMCA (0.216; 0.023), AEA (0.345; 0.011), **PEA (0.018; −0.298),** FA (0.732; −0.076), **SA (0.028; −0.276)**
VAS nasal obstruction (*p* value; *r* coefficient)	OA (0.302; 0.041), MA (0.719; 0.016), OMCA (0.226; −0.069), **AEA (0.048; 0.166), PEA (0.020; 0.195),** FA (0.652; 0.011), **SA (0.013; 0.208)**	**OA (0.025; 0.186),** MA (0.875; 0.113), OMCA (0.751; 0.032), AEA (0.296; −0.274), PEA (0.617; 0.127), FA (0.075; 0.101), SA (0.482; 0.091)	**NS for all comparisons** OA (0.837; 0.104), MA (0.063; 0.088), OMCA (0.602; 0.074), AEA (0.561; 0.011), PEA (0.085; −0.094), FA (0.652; 0.031), SA (0.634; 0.073)	OA (0.769; −0.072), MA (0.446; −0.092), OMCA (0.820; −0.107), **AEA (0.001; 0.302),** PEA (0.134; 0.061), FA (0.461; 0.053), SA (0.211; −0.063)	**NS for all comparisons** OA (0.748; 0.124), MA (0.733; 0.075), OMCA (0.322; 0.181), AEA (0.201; 0.029), PEA (0.658; 0.052), FA (0.357; 0.013), SA (0.190; 0.036)
VAS rhinorrhea (*p* value; *r* coefficient)	OA (0.822; 0.043), MA (0.568; 0.067), OMCA (0.462; 0.454), AEA (0.872; 0.086), **PEA (0.023; 0.191),** FA (0.648; −0.021), SA (0.859; 0.071)	**OA (0.008; 0.221),** MA (0.061; 0.089), OMCA (0.612; 0.078), AEA (0.446; 0.011), PEA (0.485; 0.093), FA (0.651; 0.031), SA (0.634; 0.077)	**NS for all comparisons** OA (0.635; 0.049), MA (0.715; 0.096), OMCA (0.326; 0.029), AEA (0.347; 0.013), PEA (0.299; 0.061), FA (0.302; −0.078), SA (0.094; 0.139)	OA (0.649; 0.092), MA (0.926; 0.101), OMCA (0.538; 0.037), **AEA (0.026; 0.207), PEA (0.014; 0.228),** FA (0.263; 0.041), SA (0.648; 0.094)	**NS for all comparisons** OA (0.821; 0.153), MA (0.632; 0.087), OMCA (0.482; 0.036), AEA (0.871; 0.023), PEA (0.168; 0.091), FA (0.482; 0.058), SA (0.214; 0.063)
VAS craniofacial pain (*p* value; *r* coefficient)	OA (0.301; 0.041), MA (0.764; 0.094), OMCA (0.286; 0.061), **AEA (0.039; 0.173), PEA (0.002; 0.259)**, FA (0.174; 0.054), SA (0.433; 0.053)	**NS for all comparisons** OA (0.369; 0.023), MA (0.546; 0.082), OMCA (0.420; 0.114), AEA (0.167; 0.037), PEA (0.149; 0.086), FA (0.136; −0.063), SA (0.554; 0.117)	**NS for all comparisons** OA (0.197; 0.121), MA (0.304; 0.037), OMCA (0.196; −0.267), AEA (0.127; 0.053), PEA (0.437; 0.089), FA (0.418; 0.014), SA (0.066; 0.102)	**NS for all comparisons** OA (0.348; 0.164), MA (0.739; 0.025), OMCA (0.302; 0.087), AEA (0.211; 0.079), PEA (0.653; 0.055), FA (0.277; 0.043), SA (0.130; 0.057)	**NS for all comparisons** OA (0.681; 0.059), MA (0.876; 0.103), OMCA (0.766; 0.031), AEA (0.298; 0.034), PEA (0.097; 0.125), FA (0.072; 0.111), SA (0.682; 0.091)

(Continues)

TABLE III.
Continued

Parameter	T0	T1	T2	T3	T4
VAS sleep disorders (*p* value; *r* coefficient)	OA (0.628; 0.019), MA (0.782; 0.096), OMCA (0.136; 0.011), AEA (0.647; 0.063), PEA (0.299; −0.151), FA (0.362; 0.128), SA (0.031; 0.139)	OA (0.445; 0.024), MA (0.903; 0.033), OMCA (0.167; 0.146), AEA (0.758; 0.019), PEA (0.089; 0.022), FA (0.357; 0.155), SA (0.193; 0.133)	OA (0.237; 0.174), MA (0.163; 0.077), OMCA (0.609; 0.014), AEA (0.461; −0.064), PEA (0.086; 0.093), FA (0.362; 0.031), SA (0.674; 0.033)	OA (0.098; 0.032), MA (0.445; 0.097), OMCA (0.562; 0.095), AEA (0.067; 0.005), PEA (0.422; 0.052), FA (0.112; 0.164), SA (0.125; 0.108)	OA (0.348; 0.164), MA (0.719; 0.024), OMCA (0.362; 0.045), AEA (0.141; −0.075), PEA (0.673; 0.053), FA (0.377; 0.053), SA (0.430; 0.034)

Bold values signifies $p < 0.05$.
AEA = anterior ethmoid sinus ACCESS; FA = frontal sinus ACCESS; MA = maxillary sinus ACCESS; NS = nonsignificant; OA = overall ACCESS; OMCA = osteo-meatal complex ACCESS; PEA = posterior ethmoid sinus ACCESS; SA = sphenoid sinus ACCESS.

national and international societies have published updated CRSwNP treatment algorithms that include biologic therapy.[10,14,19,20] Many recommendations advocate for complete surgery prior to candidacy to biologic drugs. EPOS 2020 suggested the candidacy to biologic in patients affected by type-2 CRSwNP after the failure of surgical treatment.[10] On the other hand, EUFOREA has also extended its indication to naïve patients (those with no previous ESS) with type-2 CRSwNP[21,22] when four out of five severity criteria were met.

Recent studies compared primary ESS versus biologics in patients with severe uncontrolled CRSwNP, supporting the former's role as primary treatment when initial medications fail: Miglani et al., in a 111-patients cohort, demonstrated the superiority of ESS in terms of greater improvements in SNOT-22 and NPS as compared with both Dupilumab and Omalizumab trials, despite comparable improvements in smell identification.[23] These improvements persisted after a 52-week observation. A recent article by Scangas et al. took position against biologic therapy in comparison to ESS for primary therapy when taking into account quality-adjusted life-year and also reported that revision ESS is more cost-effective in case of recurrent CRSwNP.[24]

The discussion remains open regarding the concept of "complete" surgery. If, on one hand, the majority of clinical studies and guidelines agree on the need for at least one complete surgery, it is not clear what behavior should be adopted when a patient has already been operated on, but the CT scan reveals an incomplete opening of the paranasal sinuses (i.e., high ACCESS score). FESS/ESS is a common operative procedure done in both district general and tertiary centers and many studies testify the high prevalence of partial surgery limited up to the anterior ethmoid area or simple polypectomy/debridement,[11] as opposed to the use of "reboot" techniques aiming to completely remove all diseased sinus mucosa.[25,26] The reasons behind this trend may be the fear of increased complications, the higher operative time, and the attitude of the individual center and surgeon. Furthermore, until the advent of biologics, some clinicians used to manage the frequent recurrence of polyps in severe CRSwNP patients by repeated polypectomies, even under local anesthesia. As a result, even patients operated several times may have an incomplete opening of the paranasal sinuses. Our data confirm that, although the maxillary sinus, OMC, and anterior ethmoid were on average opened during previous surgery (median ACCESS score 0, 0, and 1, respectively), the frontal, posterior ethmoid and sphenoid sinus bony walls and openings were sometimes inadequate (median ACCESS Score 2 for all sinuses). The reasons supporting a reoperation in these patients could be to improve ventilation pathways to avoid superinfections and acute rhinosinusitis; the attempt to reach a long polyp-free interval before undertaking a lifelong therapy; and to gain a better access of the sinus system to local medication, thus improving disease control. At present, no data are available in the literature to guide this decision.

Our results demonstrated that some significant correlations exist between the extent of previous surgery (as measured by ACCESS score) and both baseline

parameters and in-treatment outcomes. As regards the formers, patients who were candidate to Dupilumab who showed lower ACCESS scores (i.e., who underwent a more extended surgery), especially regarding both anterior and posterior ethmoid sinus, presented with significantly lower SNOT-22 scores, VAS nasal obstruction, rhinorrhea, and craniofacial pain. In other terms, those patients, although affected by a recurrent CRSwNP (expression of severe type 2-pattern inflammation of the airways), experienced significantly lower subjective discomfort, compared with those who underwent incomplete surgery. Surprisingly, T0 NPS values did not correlate with ACCESS scores. NPS relies on landmarks such as the middle and inferior turbinates and the floor of the nasal cavity, which are not modified by a more or less extensive sinus opening. Therefore, a recurrence characterized by voluminous polyps, as measured by NPS, cannot be excluded even in patients extensively operated. Conversely, extensive surgery can improve the ventilation routes and the diffusion of topical therapy, positively influencing the subjective scores as a consequence. This difference is also evident at T1 and can be attributed to the relatively short time elapsed since the beginning of the therapy (especially NPS changes slowly over time).

Starting from T2, many significant results emerged: the most interesting one concerns NPS scores, which resulted as directly correlated to ACCESS scores, especially those measured in the anterior and posterior ethmoid sinus. At the 3-month evaluation, in fact, lower NPS scores correlated significantly with lower ACCESS scores (especially of the anterior and posterior ethmoid sinus). This difference was still significant at 6- and 12-month evaluations for anterior ethmoid ACCESS score only. Having intact ethmoid cells seems associated with higher nasal polyps volume, when Dupilumab is administered, and this may be due to an incomplete ventilation route or to a higher inflamed mucosa surface. One must keep in mind that this difference was not present at baseline; therefore, we can assume that, from a merely objective point of view, the pharmacological action is more effective in patients who underwent a more extensive ethmoidal dissection.

However, when subjective parameters such as SNOT-22 were considered, the only significant association was recognized at the first evaluation (30 days from the first injection), with patients characterized by more functionally open sinuses (namely maxillary, anteroposterior ethmoid sinuses) showing significantly lower SNOT-22 scores, starting from the 3-month evaluation up to the yearly evaluation no SNOT-22 differences were detected according to the extent of surgery. Better subjective results in those with lower ACCESS scores were confirmed at VAS nasal obstruction and VAS rhinorrhea, both at 1-month and 6-month evaluations, with the ethmoid sinus being the anatomical structure more significantly involved.

Analysis of VAS scores reveals a surprising result for what concerns the olfaction: a significant inverse relationship was determined between ACCESS scores and VAS loss of smell at all timepoints. Of note, no differences existed in terms of baseline olfaction impairment among varying degrees of ACCESS score, as subjectively assessed by VAS scale. However, when Dupilumab was initiated, those with higher ACCESS scores (subjected to more "partial" surgeries) showed better VAS loss of smell scores, as measured at 1 month up to 12 months. Sudden and remarkable improvement of smell has widely been described in all the Dupilumab cohorts analyzed so far in the literature.[18,27] However, no prognostic factors capable of influencing olfaction restoration were recognized, to the authors' knowledge. Our results seem to suggest that the more the patient was subjected to extensive surgeries, and the higher the number of surgeries performed, the worse the smell improved when the patient was subjected to Dupilumab. The olfactory mucosa is a challenging region to treat operatively given the risk for local trauma and scarring; surgical reduction of polyp burden, by respecting the olfactory region may be difficult to accomplish, especially in cases of multiple reoperations. We hypothesize that at baseline, when the nasal cavities are fully occupied by polyps and rhinorrhea, it may be difficult to detect if impaired smell is due merely to the mechanical bulk, to the scarred olfactory mucosa, or to sensorineural damage. When Dupilumab takes its action, the improvement was substantially lower in those who were operated in a radical way and multiple times, by sacrificing a larger amount of mucosa, and this difference remains significant over time. Unfortunately this assumption could not be confirmed by objective measurement: Sniffin' Sticks score did not correlate with any ACCESS scores but it is noteworthy that the sample size of those who underwent those measurements was too low to allow any conclusion.

This constitutes a major limitation of the study, together with the absence of a control group of non-operated patients and the retrospective nature of the study. Retrospective observational design in fact carries the risk of missing data; therefore, it is necessary to consider the possibility that overall Dupilumab outcomes could be worse than those reported, as among the data of missing patients, there may be some poor responders. However, the participating centers were chosen for having a dedicated rhinology out-patient clinic, in which patients had a precise follow-up schedule and systematic data collection; therefore, in the authors' opinion, the missing data effect may be considered minimal and comparable to all real-life studies. Another limitation of the study is the modest power of the statistical analysis, because the correlations are small and their predictive value (r2) is in most cases less than 5%. This may be due to large number of factors influencing the final outcome (severity of T2 inflammation, comorbidities, scoring severity, etc…), being previous surgery extent only one of them. The strength of the study is represented by the novelty of the topic: this is in fact the first article describing results of biologic drugs according to the extent of the previous sinonasal surgery.

CONCLUSION

Results from this multicentric study demonstrated that a previous extensive sinonasal surgery might significantly affect the outcomes of biologic treatment. On one

hand, some results are in favor of a prior extended surgery: in fact, NPS at all timepoints and subjective scores (30-days SNOT-22, VAS nasal obstruction and rhinorrhea) show better values in patients with low ACCESS scores. On the other hand, this study demonstrated that patients with prior extended surgery had a decreased chance to recover smell when in treatment with Dupilumab, and this is confirmed also at the 12-months observation. All these aspects must be weighted by the surgeon performing ESS in patients with severe CRSwNP and might be useful for the counseling of operated patients who undergo a biologic prescription.

BIBLIOGRAPHY

1. Vlaminck S, Acke F, Prokopakis E, et al. Surgery in nasal polyp patients: outcome after a minimum observation of 10 years. *Am J Rhinol Allergy*. 2021;35(4):449-457. https://doi.org/10.1177/1945892420961964.
2. Harb H, Chatila TA. Mechanisms of Dupilumab. *Clin Exp Allergy*. 2020; 50(1):5-14. https://doi.org/10.1111/cea.13491.
3. Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet*. 2019;394(10209):1638-1650. https://doi.org/10.1016/S0140-6736(19)31881-1.
4. Desrosiers M, Mannent LP, Amin N, et al. Dupilumab reduces systemic corticosteroid use and sinonasal surgery rate in CRSwNP. *Rhinology*. 2021; 59(3):301-311. https://doi.org/10.4193/Rhin20.415.
5. Lee SE, Hopkins C, Mullol J, et al. Dupilumab improves health related quality of life: results from the phase 3 SINUS studies. *Allergy*. 2022; 77(7):2211-2221. https://doi.org/10.1111/all.15222.
6. Mullol J, Azar A, Buchheit KM, Hopkins C, Bernstein JA. Chronic rhinosinusitis with nasal polyps: quality of life in the biologics era. *J Allergy Clin Immunol Pract*. 2022;10(6):1434-1453.e9. https://doi.org/10.1016/j.jaip.2022.03.002.
7. Ottaviano G, Saccardo T, Roccuzzo G, et al. Effectiveness of Dupilumab in the treatment of patients with uncontrolled severe CRSwNP: a "real-life" observational study in naïve and post-surgical patients. *J Pers Med*. 2022; 12(9):1526. https://doi.org/10.3390/jpm12091526.
8. Trimarchi M, Vinciguerra A, Rampi A, et al. A prospective study on the efficacy of dupilumab in chronic rhinosinusitis with type 2 inflammation. *Acta Otorhinolaryngol Ital*. 2022;42(6):538-544. https://doi.org/10.14639/0392-100X-N2156.
9. De Corso E, Settimi S, Montuori C, et al. Effectiveness of Dupilumab in the treatment of patients with severe uncontrolled CRSwNP: a "real-life" observational study in the first year of treatment. *J Clin Med*. 2022; 11(10):2684. https://doi.org/10.3390/jcm11102684.
10. Fokkens WJ, Lund VJ, Hopkins C, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinology*. 2020;58(Suppl S29):1-464. https://doi.org/10.4193/Rhin20.600.
11. Masterson L, Tanweer F, Bueser T, Leong P. Extensive endoscopic sinus surgery: does this reduce the revision rate for nasal polyposis? *Eur Arch Otorhinolaryngol: Official Journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : Affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery*. 2010;267: 1557-1561. https://doi.org/10.1007/s00405-010-1233-z.
12. Lilja MJ, Koskinen A, Virkkula P, et al. Factors affecting the control of chronic rhinosinusitis with nasal polyps: a comparison in patients with or without NERD. *Allergy Rhinol (Providence)*. 2021;12:21526567211003844. https://doi.org/10.1177/21526567211003844.
13. Reitsma S, Adriaensen GFJPM, Cornet ME, van Haastert RM, Raftopulos MH, Fokkens WJ. The Amsterdam Classification of Completeness of Endoscopic Sinus Surgery (ACCESS): a new CT-based scoring system grading the extent of surgery. *Rhinology*. 2020;58(6):538-543. https://doi.org/10.4193/Rhin20.165.
14. De Corso E, Bellocchi G, De Benedetto M, et al. Biologics for severe uncontrolled chronic rhinosinusitis with nasal polyps: a change management approach. Consensus of the Joint Committee of Italian Society of Otorhinolaryngology on biologics in rhinology. *Acta Otorhinolaryngol Ital*. 2022; 42(1):1-16. https://doi.org/10.14639/0392-100X-N1614.
15. Fokkens WJ, Viskens AS, Backer V, et al. EPOS/EUFOREA update on indication and evaluation of Biologics in Chronic Rhinosinusitis with Nasal Polyps 2023. *Rhinology*. 2023;61(3):194-202. https://doi.org/10.4193/Rhin22.489.
16. De Corso E, Pasquini E, Trimarchi M, et al. Dupilumab in the treatment of severe uncontrolled chronic rhinosinusitis with nasal polyps (CRSwNP): a multicentric observational Phase IV real-life study (DUPIREAL). *Allergy*. Published online May 18, 2023. https://doi.org/10.1111/all.15772.
17. Khan A, Huynh TMT, Vandeplas G, et al. The GALEN rhinosinusitis cohort: chronic rhinosinusitis with nasal polyps affects health-related quality of life. *Rhinology*. 2019;57(5):343-351. https://doi.org/10.4193/Rhin19.158.
18. Gevaert P, Lee SE, Settipane RA, et al. Dupilumab provides early and durable improvement of symptoms in patients with chronic rhinosinusitis with nasal polyps. *Clin Transl Immunology*. 2023;12(1):e1433. https://doi.org/10.1002/cti2.1433.
19. Roland LT, Smith TL, Schlosser RJ, et al. Guidance for contemporary use of biologics in management of chronic rhinosinusitis with nasal polyps: discussion from a National Institutes of Health-sponsored workshop. *Int Forum Allergy Rhinol*. 2020;10(9):1037-1042. https://doi.org/10.1002/alr.22633.
20. Thamboo A, Kilty S, Witterick I, et al. Canadian Rhinology Working Group consensus statement: biologic therapies for chronic rhinosinusitis. *J Otolaryngol Head Neck Surg*. 2021;50(1):15. https://doi.org/10.1186/s40463-021-00493-2.
21. Fokkens WJ, Lund V, Bachert C, et al. EUFOREA consensus on biologics for CRSwNP with or without asthma. *Allergy*. 2019;74(12):2312-2319. https://doi.org/10.1111/all.13875.
22. Bachert C, Han JK, Wagenmann M, et al. EUFOREA expert board meeting on uncontrolled severe chronic rhinosinusitis with nasal polyps (CRSwNP) and biologics: definitions and management. *J Allergy Clin Immunol*. 2021;147(1):29-36. https://doi.org/10.1016/j.jaci.2020.11.013.
23. Miglani A, Soler ZM, Smith TL, Mace JC, Schlosser RJ. A comparative analysis of endoscopic sinus surgery versus biologics for treatment of chronic rhinosinusitis with nasal polyposis. *Int Forum Allergy Rhinol*. 2023;13(2): 116-128. https://doi.org/10.1002/alr.23059.
24. Scangas GA, Wu AW, Ting JY, et al. Cost utility analysis of dupilumab versus endoscopic sinus surgery for chronic rhinosinusitis with nasal polyps. *Laryngoscope*. 2021;131(1):E26-E33. https://doi.org/10.1002/lary.28648.
25. Jankowski R, Pigret D, Decroocq F. Comparison of functional results after ethmoidectomy and nasalization for diffuse and severe nasal polyposis. *Acta Otolaryngol*. 1997;117(4):601-608. https://doi.org/10.3109/00016489709113445.
26. Alsharif S, Jonstam K, van Zele T, Gevaert P, Holtappels G, Bachert C. Endoscopic sinus surgery for type-2 CRS wNP: an endotype-based retrospective study. *Laryngoscope*. 2019;129(6):1286-1292. https://doi.org/10.1002/lary.27815.
27. Jansen F, Becker B, Eden JK, et al. Dupilumab (Dupixent®) tends to be an effective therapy for uncontrolled severe chronic rhinosinusitis with nasal polyps: real data of a single-centered, retrospective single-arm longitudinal study from a university hospital in Germany. *Eur Arch Otorhinolaryngol*. 2023;280(4):1741-1755. https://doi.org/10.1007/s00405-022-07679-y.