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Subgroups in the treatment of nasal polyposis with dupilumab

A retrospective study

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Abstract

Dupilumab has been shown to be safe and effective in treating chronic rhinosinusitis with polyposis (CRSwNP). There is to this date no published data whether subgroups like patients with aspirin exacerbated respiratory disease (AERD), increased histologic eosinophilia or elevated blood eosinophil or IgE-levels benefit greater from dupilumab therapy. Moreover, there is no data comparing the efficacy of functional endoscopic sinus surgery (FESS) with dupilumab therapy. We conducted a retrospective chart review of all patients that were treated at a tertiary referral center for CRswNP with dupilumab. We also contacted the patients with a questionnaire to evaluate the efficacy of previous surgeries and dupilumab therapy by visual analogue scale (VAS) and the glasgow benefit inventory (GBI) as well as report on side effects. Overall, 75 patients were included in the study at hand that reported back 138 times. While dupilumab treatment was efficient, we found no systematic evidence of greater efficacy of dupilumab in patients with AERD, histologic eosinophilia or increased blood eosinophil or IgE-levels. All patients showed a considerable decrease in subjective burden of disease, objective smell tests and endoscopic findings. From the patients point of view, dupilumab therapy showed greater efficacy both in the VAS and the GBI overall and all subcategories but "social support." Dupilumab is efficient in treating CRSwNP; this effect is independent from disease characteristics like AERD, histologic eosinophilia, serum IgE-levels or eosinophil counts. There seems to be a group of patients that benefit greater from dupilumab therapy compared to FESS.

Abbreviations: AERD = aspirin exacerbated respiratory disease, BSIT = brief smell identification test, CRS = chronic rhinosinusitis, CRSwNP = chronic rhinosinusitis with nasal polyposis, FESS = functional endoscopic sinus surgery, GBI = Glasgow benefit inventory, HPF = high power field, IL = interleukin, SNOT-22 = sinu-nasal outcome score, VAS = visual analogue scale.

Keywords: chronic rhinosinusitis, CRSwNP, dupilumab, nasal polyps, type II inflammation

1. Introduction

Chronic rhinosinusitis (CRS) commonly presents with nasal congestion, impaired sense of smell and often considerable impairment of the Quality of Life. It may present with (CRSwNP, Chronic Rhinosinusitis with Nasal Polyposis) or without (Chronic Rhinosinusitis sine [without] Nasal Polyposis) nasal polyposis. While the latter is more common, management is regularly straightforward as functional endoscopic sinus surgery (FESS) is a safe and effective method of achieving long-term control the disease.[1] CRSwNP on the other hand is characterized by a strong tendency for relapses, even after FESS.[2]

It is commonly believed that one of the main factors for the chronic course of the disease in CRSwNP is an underlying predisposition for type II inflammation, causing frequent relapses of mucosal inflammation. Patients with CRSwNP regularly exhibit a typical type II inflammatory signature, consisting of interleukins (IL) 4, 5, and 13 as well as infiltration of the nasal mucosa by eosinophils.[3,4] The underlying predisposition in these patients

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

The study at hand was registered with the appropriate authorities (Ethikkommission der Ludwig-Maximilians Universität München) under the file no. 20-842.

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makes them more susceptible to similar diseases like atopic dermatitis and bronchial asthma. Aspirin exacerbated respiratory disease (AERD), that is also called M. Widal or Samter's Triad, is a specific phenotype of CRSwNP characterized by sensitivity to nonsteroidal anti-inflammatory drugs like Aspirin, Ibuprofen or Diclofenac as well as bronchial asthma. AERD patients make up at least 15% of CRSwNP patients[5,6] and tend to show a greater burden of disease, requiring more extensive and costly therapies.[7]

Taking this into account, another approach at CRSwNP aims at managing a predisposition rather than a chronified, previously acute inflammation: Intranasal steroids have long been considered as a first-line treatment, particularly after FESS. However, those applied as a nasal spray regularly fail to provide long-term symptom relief. If intranasal steroids do not provide sufficient relief, systemic steroids may be considered as these usually provide rapid relief of symptoms.[8] While being very effective in providing quick relief, long-term use of systemic steroids is associated with numerous side effects, limiting their use to very few times annually. Consequently, systemic steroids are not suitable for long-term management of CRswNP. Intralesional injections may provide aid in control of some symptoms of CRswNP with little systemic side effects.[9] However, there are few studies addressing this topic, and there is little scientific data in respect to smell function and overall burden of disease. Acetylsalicylic acid-Desensitization may provide prevention of CRSwNP relapse of sinus surgery. However, these therapies show - depending on their respective dosage - either relatively low efficacy,[10] may be rich in side effects[11] and occasionally even both.[12]

Another, relatively new approach is the regular systemic application of dupilumab (DUPIXENT®), humanized monoclonal antibodies that target the IL-4 and IL-13 receptors. The advantage of this approach is that it specifically targets the mediators of the regularly underlying type II inflammation.[13] Dupilumab has shown to be safe and effective in controlling both atopic dermatitis[14] as well as bronchial asthma.[15] Moreover, it has proven a similarly effective treatment in CRSwNP in the prospective LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52 trials.[16]

While these trials outlined the advantage of managing patients with CRSwNP, we found that there is little information on several subgroups of dupilumab treatment in CRSwNP. As treatment with dupilumab is associated with considerable costs, accurate knowledge of the expected efficacy is crucial. We therefore conducted a retrospective chart review on the efficacy of dupilumab treatment in CRSwNP in respect to blood eosinophil and IgE levels, histologic presence of eosinophils in the mucosa and an underlying AERD. Moreover, we systematically investigated side effects of dupilumab treatment and asked patients to rate the success of dupilumab therapy and previous FESS. Finally, we evaluated the efficacy of dupilumab after switching to 4 Weeks intervals compared to 2-week intervals.

2. Materials and methods

The study was registered with the responsible ethics committee at the Ludwig-Maximilians University of Munich under the File No. 20-842. The need for informed consent was waived since the nature of the study was in its entirety retrospective.

2.1. Clinical approach

Patients that were diagnosed with CRS as laid out by the American Academy of Otolaryngology–Head and Neck Surgery,[17] had endoscopically confirmed nasal polyposis and fulfilled the European Forum for Research and Education in Allergy and Airway Diseases criteria, yet still suffered a short-term relapse of CRS complaints were considered for treatment with biologics. Only interventions that included at least the maxillary sinus as well as the ethmoidal cells were considered as FESS. Patients then underwent routine screenings that included bloodwork (particularly IgE and eosinophil count), nasal endoscopy, a smell test (the brief identification smell test [BSIT], a short version of the University of Pennsylvania Smell Test[18]), histology and completion of the Sinus Nasal Outcome Test (SNOT-22). If no written histology could be produced by the patient from previous surgeries, a histology was obtained in local anesthesia. To obtain quantitative tissue eosinophil levels, we had all specimens that were stored with our department of pathology reexamined by a board-certified pathologist and obtained 5 eosinophil counts per high power field (HPF) and patient. These were then averaged to get a patient individual eosinophil count per HPF. Patients that indicated insufficient disease control despite conventional treatments (continuous use of nasal steroids and/or FESS with rapid onset of CRSwNP symptoms post-surgery) as well as considerable subjective burden of disease (Visual Analogue Scales [VAS] >7 and/or SNOT-22 > 50) were offered treatment either with dupilumab or other biologics. If treatment with dupilumab was commenced, patients were prescribed 6 300 mg ready-to-use dupilumab pens for self-administration. Initially, patients were asked to administer 1 pen every 2 weeks. The patients were then seen every 3 months (the duration of 6 pens, the largest dose that could be prescribed in Germany) and subsequently reevaluated. Once patients had reached a subjectively adequate disease control (VAS and/or SNOT-22 had improved by at least 1/3), injection intervals were switched from 2 to 4 weeks. Re-consultations were then only every 6 months. During late March 2021, patients were contacted and asked to report on any side effects they had noticed and medication before and during dupilumab therapy. Moreover, patients were asked to judge the success of the therapy as well as previous FESS using the Glasgow Benefit Inventory (GBI)[19] as well as a VAS, where 10 was the greatest possible success of the therapy and 1 the lowest.

2.1.1. Data collection All patients that underwent treatment of CRSwNP were collected in a database of the local ENT clinic. Only those patients that were treated for dupilumab were included in the study at hand. Exclusion criteria were an age of <18 years, insufficient documentation and a treatment period that was lower than 3 months. Individual datasets were obtained from the individual patient files; these included age, gender, number of previous FESS, duration of dupilumab treatment, and individual datasets at baseline and individual follow-ups. Baseline datasets included histologic features (presence of eosinophils in the nasal polyps), presence of AERD, bloodwork including IgE and eosinophil count and the state of the disease (endoscopy score, BSIT values, VAS and SNOT-22). Patients that suffered from bronchial asthma but did not exacerbate upon exposure to nonsteroid anti-inflammatory drugs were few (n = 4) and counted to the AERD group. Histologic eosinophilia was defined if more than 5 eosinphils per HPF were present. At follow-up visits, the latter 4 were regularly recorded. Endoscopy score was calculated by adding the degree of nasal polyposis as described by Rasp et al[20] from each side. Patients that showed subjectively adequate (VAS and/or SNOT-22 had improved by at least 1/3) control of the disease with s.c. dupilumab every 2 weeks were then prescribed dupilumab every 4 weeks, as has been done in the LIBERTY-52 study.

2.1.2. Statistics Statistical analysis was carried out using project R for Windows (Build 4.0.2 for Mac, The R Project for Statistical Computing, http://www.r-project.org/). In order to detect significant differences between the groups, wilcoxon-signed rank test, student's t-test or chi-squared tests were used, as applicable. A *P* value smaller than .05 was considered to be significant.

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3. Results

Overall, 112 patients were treated with biologics for CRSwNP. Three patients were excluded due to treatment with omalizumab, 2 were excluded due to insufficient documentation and 32 patients were excluded since they had not yet shown up for the first follow-up visit. Out of these 75 patients, 55 (73.3%) reported back on a separate question are concerning their side effects and therapy success during March 2021.

The general characteristics of the collective at hand can be found in Table 1. When treatment with dupilumab was commenced, average endoscopic score was 5.9 ± 1.7 (n = 76), average VAS was 8.3 ± 1.7 (n = 74), SNOT-22 was 66.9 ± 15.2 (n = 75) and BSIT was 3.7 ± 2.5 (n = 75). At the first follow up, endoscopy scores dropped to 1.7 ± 1.8 (n = 76), VAS to 2.9 ± 1.6 (n = 72), SNOT-22 to 24.4 ± 15.7 (n = 74) and BSIT rose to 7.6 ± 3.4 (n = 75). At subsequent follow ups, endoscopy scores remained steady (1.3 ± 1.8, n = 44 and 1.1 ± 1.9, n = 18) as did VAS (2.7 ± 1.8, n = 40 and 2.0 ± 1.0, n = 16), SNOT-22 (20.7 ± 13.5, n = 43 and 16.6 ± 10.9, n = 18) and BSIT (7.6 ± 3.4, n = 43 and 7.4 ± 3.7, n = 17) (Fig. 1).

Histological specimens were available in 29 cases; average eosinophil count was 70.7 ± 21.9 eosinophils per HPF (range 57.8–95.2). The exact values can be found in the supplementary materials (Supplement "Tissue Eosinophilia", http://links.lww.com/MD/H571).

In brief, we found very little significant differences in treatment success between different patient groups. In terms of AERD, there were no significant differences in any respect or at

Table 1

General cohort characteristics.

General cohort characteristics		n =
Gender (ratio male/female)	49/26	75
Number of previous surgeries	2.9 ± 1.5 [1–8]	74
Patients suffering from AERD	49 (65.3%)	75
Presence of histologic eosinophilia	54 (85.7%)	63
Serum eosinophil levels (×10³/µL)	0.46 ± 0.32 [0.06–1.78]	58

AERD = aspirin exacerbated respiratory disease.

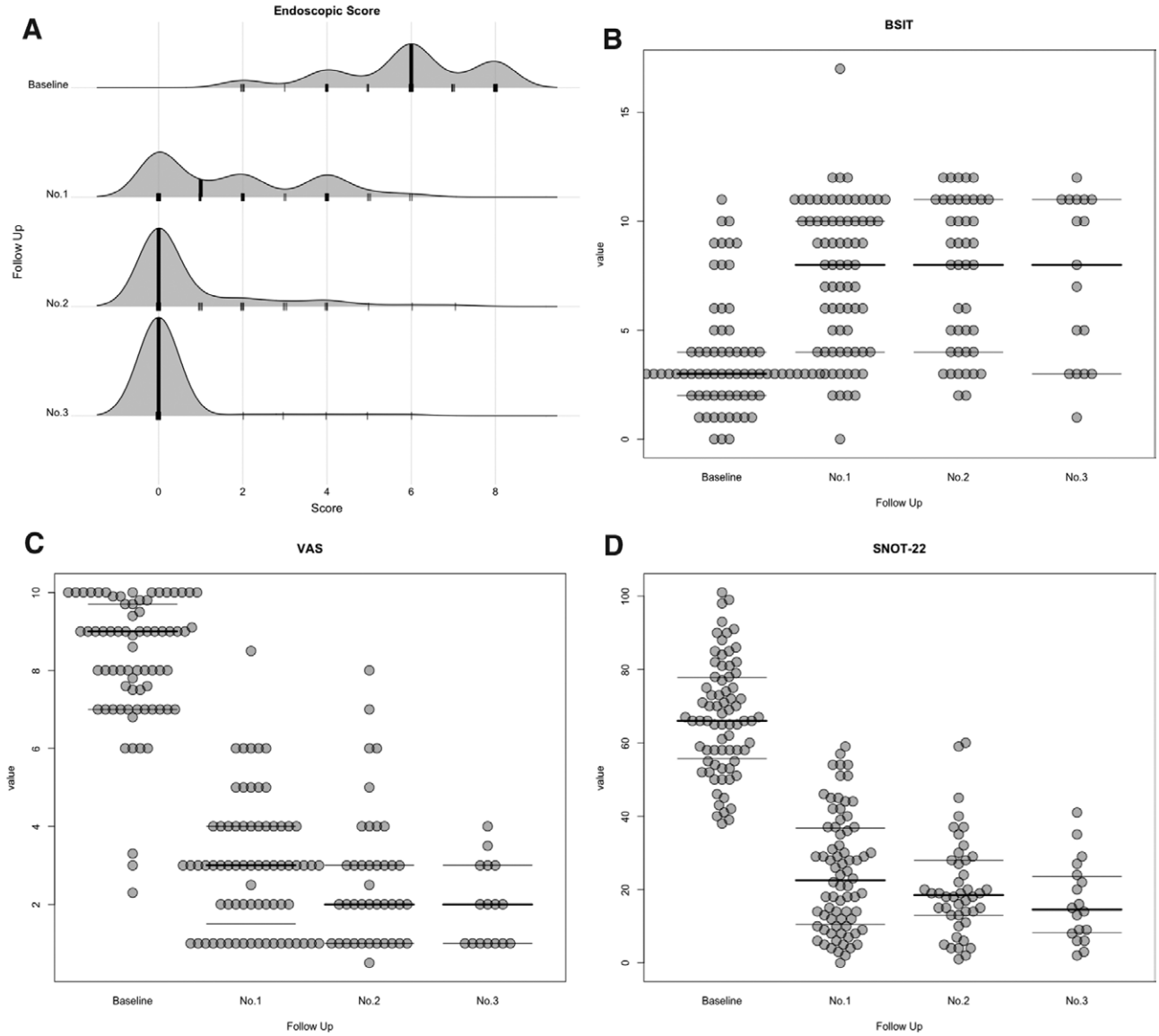

Figure 1. Graphic displays of dupilumab efficacy for the endoscopy score (A), the BSIT (B), the VAS (C) and the SNOT-22 (D). The thick black line represents the median and the thin black lines represent the standard deviation. BSIT = brief smell identification test, SNOT-22 = Sinu-nasal outcome score, VAS = visual analogue scale.

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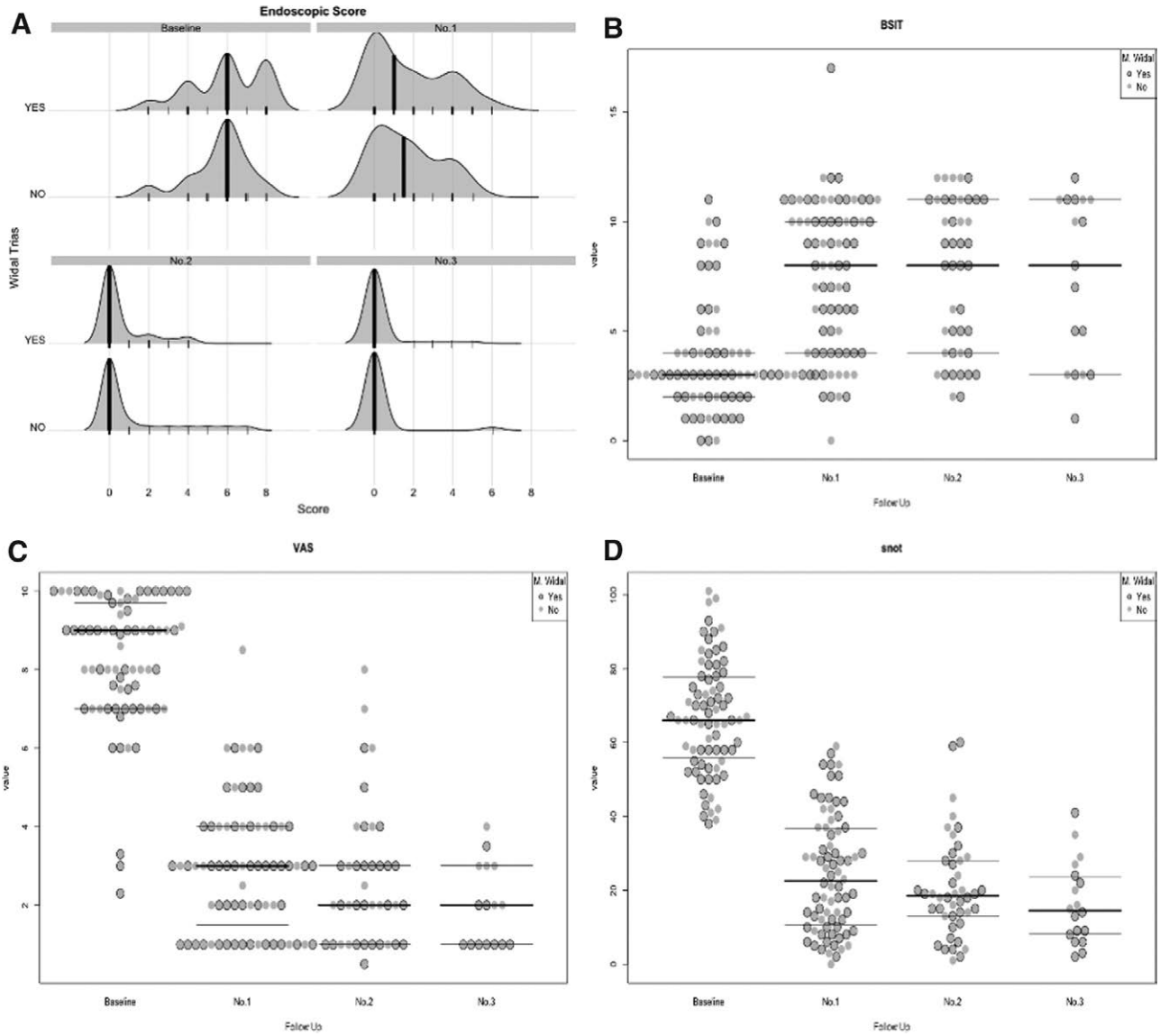

Figure 2. Graphic displays of dupilumab efficacy with and without AERD for the endoscopy score (A), the BSIT (B), the VAS (C) and the SNOT-22 (D). The thick black line represents the median and the thin black lines represent the standard deviation. AERD = aspirin exacerbated respiratory disease, BSIT = brief smell identification test, SNOT-22 = Sinu-nasal outcome score, VAS = visual analogue scale.

any timepoint (Fig. 2). In terms of histologic eosinophilia, only the SNOT-22 showed a significant difference before treatment was commenced (81.8 ± 12.3 vs 65.4 ± 14.8 $P = .010$, n = 62) and at the first follow up (24.3 ± 14.5 vs 26.6 ± 16.2, $P = .028$, n = 62), while differences at follow ups no. 2 and 3 were not significant (Fig. 3). Exact values as well as *P* values can be found in the supplement (supplementary Tables No. 1 & 2, http://links.lww.com/MD/H571). Initial Eosinophil counts showed a significant influence on the SNOT-22 upon the first follow up, while initial serum IgE-levels showed a significant influence on the BSIT upon the first and third follow up (Supplementary Tables No. 3 & 4, http://links.lww.com/MD/H572). Patients with more or less than 3 previous FESS had no significant differences at any timepoint whatsoever (supplementary Table No. 5, http://links.lww.com/MD/H573). Gender revealed no effect whatsoever on any aspect of the disease (supplementary Table No. 6, http://links.lww.com/MD/H574) while age > 60 years showed significant differences in terms of SNOT-22 at baseline as well as VAS at follow-up No. 2 (supplementary Table No. 7, http://links.lww.com/MD/H575).

Moreover, in total, 41 patients were prescribed dupilumab every 4 weeks after an initially successful initiation of therapy. Out of those, 27 were seen again and included in the analysis at hand. From these patients, 15 reported a considerable worsening of the condition compared to 2-week intervals and asked for the intervals between injections to be lowered again. 12 patients on the other hand experienced a steady disease control under 4-week intervals of dupilumab injections. The exact individual values can be found in Table 2.

In respect to the side effects, the most common one reported was weight gain (12, 21.8%) followed by myalgias (11, 20.0%) and migraines (8, 14.5%) as well as arthralgias (8, 14.5%), tiredness (7, 12.7%) and conjunctivitis (6, 10.9%). Concomitant medication significantly decreased under dupilumab therapy; the exact values can be found in Table 3. GBI indicated a considerable benefit of dupilumab therapy in terms of overall use, general and physical wellbeing, but not in terms of social support. GBI did not indicate any subjective benefit of FESS while dupilumab therapy was considered beneficial in overall score, general and physical wellbeing. A comparison between FESS

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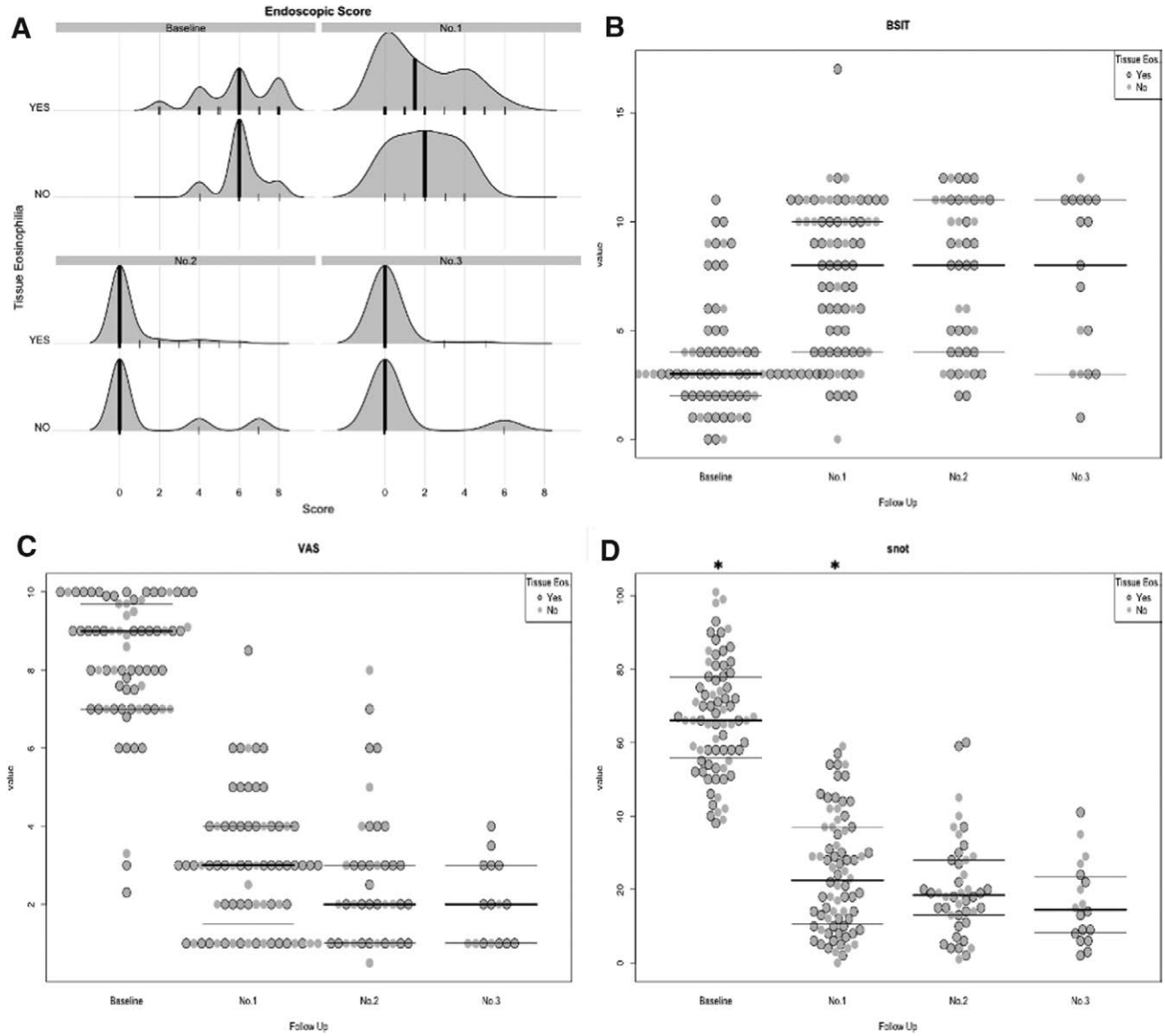

Figure 3. Graphic displays of dupilumab efficacy with and without histologic eosinophilia for the endoscopy score (A), the BSIT (B), the VAS (C) and the SNOT-22 (D). The thick black line represents the median and the thin black lines represent the standard deviation. BSIT = brief smell identification test, SNOT-22 = Sinu-nasal outcome score, VAS = visual analogue scale.

and dupilumab therapy in terms of the GBI as well as the VAS showed significant differences in terms of overall score, general and physical wellbeing as well as the VAS (Fig. 4). The exact values can be found in the supplement (supplementary Table No. 8, http://links.lww.com/MD/H576).

4. Discussion

Firstly, the collective at hand showed a relevant effect of dupilumab on the overall burden of symptoms of CRSwNP. This was not the primary objective of the study at hand, as has been proven by the prospective LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52 studies.[16] Nonetheless, the overall congruence with prospective, placebo-controlled, double-blind multicenter studies underlines the validity of the collective presented in this manuscript.

However, when comparing the exact results of the aforementioned, prospective studies with the results at hand, it seems that the collective at hand may demonstrate an even greater benefit from dupilumab therapy than shown in said studies. This may be due to the fact that a considerable proportion of the patients suffered from substantial type-II inflammation, as is vividly displayed by the extensive eosinophil tissue counts. Fittingly, similar results have been reported for very minor collectives of patients that suffer from AERD and have previously failed oral acetylsalicylic acid (aspirin)-desensitization.[21]

However, a new aspect is that when considering dupilumab therapy in patients with CRSwNP is that all patients in the collective, regardless of their status concerning AERD, histologic eosinophilia or serum IgE or eosinophilic levels seem to benefit from dupilumab therapy. While this had always been assumed in previous studies,[16] the hypothesis has not been explicitly tested. It is our conviction that the very few statistically significant differences observed in various aspects of the therapy's success, variables and timepoints are not so much indicated of an underlying systematic effect but bound to occur, considering the great number of statistical tests performed. Quite the contrary, the dataset at hand supports the viewpoint that any patient suffering from CRSwNP may benefit from dupilumab therapy.

Moreover, another aspect that is worth mentioning are the side effects. While the most side effects are in line with the

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Table 2

Interval switches.

	Overall (n = 27)			
	SNOT-22	VAS	Endoscopy score	B-SIT
Baseline	69.0 ± 15.8 (n = 27)	8.5 ± 1.2 (n = 27)	5.5 ± 1.7 (n = 27)	3.3 ± 2.0 (n = 26)
Before	18.3 ± 13.3 (n = 27)	2.0 ± 1.1 (n = 26)	0.7 ± 1.1 (n = 27)	8.3 ± 2.9 (n = 27)
After	22.9 ± 14.5 (n = 27)	2.8 ± 1.7 (n = 25)	1.1 ± 1.6 (n = 27)	8.0 ± 3.3 (n = 25)
Successfull interval switch (n = 12)				
Baseline	67.9 ± 15.7 (n = 12)	8.4 ± 1.2 (n = 12)	5.9 ± 1.2 (n = 12)	3.3 ± 0.7 (n = 11)
Before	21.8 ± 13.8 (n = 12)	2.0 ± 1.1 (n = 12)	0.6 ± 0.8 (n = 12)	8.3 ± 2.8 (n = 12)
After	21.8 ± 13.6 (n = 12)	1.9 ± 0.9 (n = 12)	0.3 ± 0.7 (n = 12)	9.0 ± 3.6 (n = 11)
Unsuccessful interval switch (n = 15)				
Baseline	69.9 ± 15.9 (n = 15)	8.6 ± 1.1 (n = 15)	5.2 ± 2.0 (n = 15)	3.3 ± 2.5 (n = 15)
Before	15.5 ± 12.1 (n = 15)	1.9 ± 1.0 (n = 14)	0.8 ± 1.4 (n = 15)	8.3 ± 3.0 (n = 15)
After	23.9 ± 15.2 (n = 15)	3.6 ± 1.8 (n = 13)	1.7 ± 1.9 (n = 15)	7.2 ± 2.9 (n = 14)

BSIT = brief smell identification test, SNOT-22 = Sinu-nasal outcome score, VAS = visual analogue scale.

Table 3

Concomitant medication before and under dupilumab therapy.

Concomitant medication	Before dupilumab therapy	Undergoing dupilumab therapy	
Topical steroids	55	44	***P* = .001**#
Inhalative steroids (PariSINUS)	18	7	
Oral steroids	32	2	
Intralesional steroids	2	1	
Antileukotrienes	8	2	
ASS desensitization	14	1	

ASA = acetylsalicylic acid.
#Pearsons chi-squared test.

frequency in relevant literature,[22] the most common side effect that was reported was weight gain. Not only was this reported in a considerable proportion of patients, but this is - to the best of our knowledge - the first report of this side effect in CRSwNP treatment by dupilumab. Initially, believed that the weight gain might be explained by the increased sense of smell and subsequent pleasure in food consumption.[23] However, there are reports of considerable weight gain of dupilumab in atopic dermatitis,[24] so an underlying systemic effect might be considered as well.

Finally, there are some limitations that need to be considered when interpreting the results. Obviously, the limitations of a retrospective study apply. This is in particular a systematic lack of data and various types of bias. One aspect that should be lined out in the collective at hand is that the study population was almost exclusively of caucasian descent. This potential bias has been pointed out extensively, but should, from our experience, be considered particularly when it comes to type-II inflammation. Moreover, clinical decisions, like exclusion criteria for dupilumab therapy cannot be deducted from the approach that was used in this manuscript. Moreover, 1 major limitation should be explicitly pointed out - patients that were treated with dupilumab exclusively underwent previous FESS without longer-lasting disease control, potentially causing a considerable bias.

Still, taking all this into account, there seems to be a proportion of CRSwNP patients that not only benefited greatly from dupilumab therapy. Moreover, this population seemed to benefit greater even than FESS, at least from the subjective, retrospective viewpoint. Fittingly, there is evidence that CRswNP patients have a strong tendency for relapses after FESS, even with adequate postoperative care, and subsequent need for additional treatment and revision-FESS.[25,26] While exact conclusions about the prevalence of this - potentially very circumscript - group of patients cannot be drawn from the collective at hand, given the studies limitations, its mere existence should warrant further, prospective research into that matter.

Taking into account the considerable costs of dupilumab therapy as well as the relative novelty of the medication together with unknown long-term effects, clinical dosage should be as low as possible. As the LIBERTY NP SINUS-52 study did show, 4 week intervals might well suffice for control of the disease.[16] However, a majority of patients that changed from 2 to 4 week intervals complained from subjective worsening of symptoms. At the same time, over 40% of patients were satisfied with 4-week intervals. So, in conclusion, while a stretching of injection intervals is not always successful, as has been reported in the LIBERTY SINUS NP 52 study, there is still a considerable proportion of patients that still show major benefit under 4 week intervals.

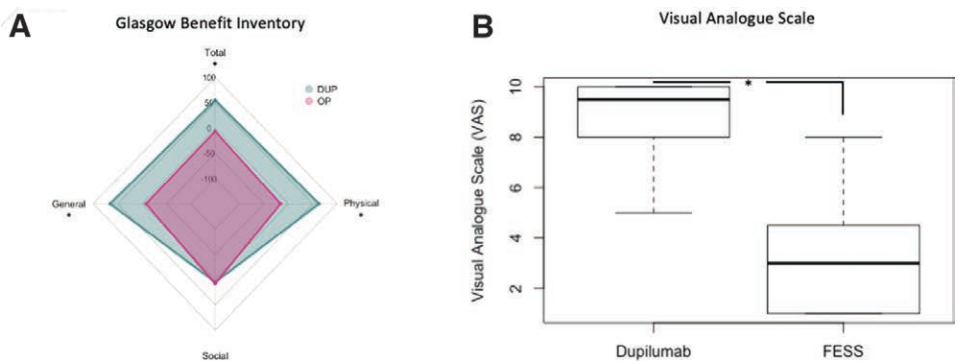

Figure 4. Graphic displays of subjective ratings of the individual success of FESS and dupilumab therapy in the GBI (A) and VAS (B). The thick black line represents the median and the thin black lines represent the standard deviation. FESS = functional endoscopic sinus surgery, GBI = Glasgow benefit inventory, VAS = visual analogue scale.

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5. Conclusion

Dupilumab shows great efficacy in treating CRSwNP in paramount aspects of the disease: endoscopic findings, objective smell tests and subjective findings. There seems to be no systematic difference between patients with or without AERD, histologic eosinophilia or elevated blood eosinophil or IgE-levels; all patients seem to benefit from dupilumab therapy. Moreover, there may exist a distinct group of patients that benefit greater from dupilumab therapy compared to FESS. Finally, we found that a major side effect of dupilumab therapy is weight gain.

Author contributions

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