Real-world-effectiveness of biological treatment for severe chronic rhinosinusitis with nasal polyps*

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Rhinology 60: 6, 435 - 443, 2022

https://doi.org/10.4193/Rhin22.129

***Received for publication:**

April 5, 2022

Accepted: July 21, 2022

Abstract

Background: During the last two years, three different monoclonal antibodies have been approved in many countries for the treatment of patients suffering from severe chronic rhinosinusitis with nasal polyps (CRSwNP). Their efficacy has been demonstrated through large double-blind placebo-controlled clinical studies. Until now, only very limited reports on real-world data regarding this therapy have been published.

Methods: This per protocol analysis included patients with an indication for biological treatment because of uncontrolled CRSwNP, despite long-term nasal steroid treatment, systemic steroid use and/ or endonasal sinus surgery. Baseline data on demographics, medical history and comorbidities, polyp score, quality of life and sense of smell (using Sniffin´ Sticks) were assessed and a treatment with either dupilumab or omalizumab was started. The patients were followed up after three and six months. The changes in polyp score, quality-of-life measures and olfaction were noted.

Results: 70 consecutive patients were evaluated during the study. Of the patients, 49 were treated with dupilumab and 21 with omalizumab. The polyp score decreased significantly after three and six months, and the quality-of-life parameters and olfaction increased. More than 90% of patients showed a moderate to excellent response to the therapy and there was no difference in the overall response between the two treatments. Olfaction improved in two thirds of the patients, but one third was still anosmic after six months treatment.

Conclusions: This real-world study shows the effectiveness of the monoclonal antibodies dupilumab and omalizumab in the treatment of severe CRSwNP. Nasal polyp scores and quality-of-life parameters as well as measured olfactory function were improved after just three months. The response after guideline-based criteria was insufficient only in 5 patients of this cohort.

Key words: CRSwNP, monoclonal antibody, nasal polyps, quality of life, olfaction

Introduction

Up to 4% of the population in in the USA and Europe suffer from chronic rhinosinusitis with nasal polyps (CRSwNP) [1-4]. The disease is accompanied by a distinct reduction in quality of life, particularly nasal obstruction and discharge, as well as an impaired sense of smell. Olfaction is more often impaired in CRSwNP compared to chronic rhinosinusitis without nasal polyps (CRSsNP) [5,6]. As treatment with nasal steroids often has limited success in severe cases, systemic steroids and/ or endonasal sinus surgery (ESS) are generally used for second line treatment. Although these therapies have shown to be able to improve symptoms, quality of life and endoscopy scores [7,8], and despite the long-term use of nasal steroids after surgery, a recurrence of nasal polyps often occurs, causing the need for revision surgery or the administration of recurrent systemic steroids in these patients.

In about 80% of patients, CRSwNP is associated with a type II inflammatory disease [9] and comorbidities such as asthma or nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (NERD) are frequently found. The type II inflammatory diseases share a common attribute in that different effector cells, especially eosinophilic cells, interleukins (especially IL-4, IL-5 and IL-13) and immunoglobulin-E play an important role in the pathophysiology and disease progression [10,11].

Whereas in the past, patients, especially those with severe asthma, who were treated with monoclonal antibodies had an additional benefit in the course of their sinus disease (collateral efficacy) [12,13], three different biological therapies for the treatment of severe CRSwNP are now approved in the US and the EU, including Germany.
These are the IL-4Rα antibody dupilumab with dual blockade of IL-4 and IL-13 [14], the anti-IgE antibody omalizumab [15] and most recently the anti-IL-5 antibody mepolizumab [16].

For each of the above-mentioned antibodies, at least one international multicentre double-blind, placebo-controlled study preceded these approvals, with relatively high patient numbers and outcome measures [17-19]. Additionally, under CRSwNP-treatment with biologicals pulmonary symptoms improve, systemic steroid use is reduced as well and sinunasal surgery rates [20,21].
Although the primary and secondary criteria were reached for all studies with the three different antibodies, there is very limited experience in the treatment of patients with CRSwNP as the main diagnosis (and not asthma) outside the setting of clinical trials.

For clinical use, recommendations from different societies and expert groups for the biological treatment of severe CRSwNP patients are available [22-24]. But so far, there are no selection criteria available for making a choice between the different monoclonal antibody in CRSwNP, in contrast to the established endotyping in asthma patients [25].

The aim of this study was to obtain more data on the effectiveness of biological treatment in CRSwNP patients in a real-world setting at three centres in Germany and compare the results with the data of the clinical trials. Additionally, the criteria for responding and non-responding patients were evaluated.

Materials and methods

Study design

The research was conducted at the Department of Otorhinolaryngology of a maximum care hospital, a specialty practice and a university hospital in Germany. It was conducted in accordance with the Declaration of Helsinki on Biomedical Studies Involving Human Subjects and was approved by the local ethics committee in Baden Wurttemberg (approval number F-2021-139) and all participants gave written informed consent.

Setting

The cohort included patients who presented with severe complaints of chronic rhinosinusitis with nasal polyps in the Department of Otorhinolaryngology in one of the three participating facilities between January 2020 and January 2022. All patients had undergone prior conservative treatment, including long-term nasal steroids, ESS and/ or systemic steroids that did not resolve the complaints and fulfilled the inclusion and exclusion criteria for treatment with either dupilumab or omalizumab. The biological treatment is approved as an add-on therapy in addition to the continuing topical nasal steroid usage.

Participants

The inclusion criteria were based on the EPOS 2020 [22] / EUFOREA-2019 [23] criteria including the presence of bilateral chronic sinus disease with nasal polyps for more than three months despite conservative treatment and an age of 18 years or older. According to the nasal endoscopy score, a minimum polyp score of 2 on each side had to be documented. Depending on the label in the approval text for the medication, patients had to have been treated with either previous sinus surgery and/or systemic courses of steroid treatments (dupilumab) or long-term nasal steroid use (omalizumab) with the result that no sufficient disease control could be achieved. Therefore, patients without prior sinus surgery were also included.
The exclusion criteria included pregnancy, unilateral disease or signs of the presence of a mucocele, cystic fibrosis or an autoimmune driven disease. No patients were included that had received treatment with a monoclonal antibody in the last two years. Additionally, patients with a known hypersensitivity to either dupilumab or omalizumab were also excluded

Medical history of patients

Patients were inquired about the history of the sinus disease, including the number of surgical procedures or courses of systemic steroids patients had undergone. Information on the presence of comorbidities such as asthma or clinically reported NERD as well as allergies to inhalant allergens verified by allergy testing (skin prick testing and/or specific blood IgE in the past) were also collected.

Variables and measurements

Polyp score

The endonasal polyp score was determined by a modified classification of Lildholdt [26] like the classification used in the clinical trials for biological treatments. The polyp score was evaluated by an experienced specialist for each side by nasal endoscopy. In the used system, the absence of nasal polyps is noted as 0,

with small polyps not reaching the edge of the middle turbinate receiving 1. Polyps reaching below the lower edge of the middle turbinate are graded as 2. Larger polyps medially of the middle turbinates or polyps reaching the lower edge of the inferior turbinate are given a total of 3. Polyps that lead to a complete obstruction of the lower nasal meatus are classified as 4. The final number is calculated by adding up the two scores for each side, with a maximum of 8.

Assessment of the quality of life

As a disease-specific measure of the patients' quality of life, the sino-nasal outcome test (SNOT)-22 questionnaire [27,28] was used to quantify the sino-nasal symptoms. It consists of 22 questions of chronic rhinosinusitis (CRS)-related items scored from 0 to 5 (total range 0-110, with higher totals representing worse symptoms), which evaluates the severity of complaints that patients have been experiencing over the past weeks due to CRS. Results of 40 or more are considered to show a severe impairment [22] and the minimal clinically important difference (MCID) is considered to be 8.9 points [29].

Visual analogue scale (VAS)

A recommended method for the subjective assessment of the severity of nasal symptoms in CRS is the use of a visual analogue scale (VAS) recorded by the patient on a 10cm line giving a score on a measurable continuum of 0 to 10cm [30]. A range of 0-3cm would indicate mild, >3-7cm moderate and >7cm severe symptoms.

Olfactory testing

Olfactory function was quantified using an established clinical test ("Sniffin' Sticks", Burghart Instruments, Wedel, Germany) [31-33], in which the standardized, forced-choice 16-item odour identification test was carried out. The olfactory functional diagnosis was obtained from the correct answers. Normal olfactory function is presumed for scores of 13 and above and hyposmia between 8 and 12, while scores below 8 are considered "functionally anosmic" [34].

Blood parameter

Before the start of the treatment and during follow-up, total serum IgE and a differential blood count including eosinophils (total count and percentage of white blood cells) were assessed.

Initiation of therapy

After the indication for the antibody treatment was ascertained, the therapy was explained to the patients and they gave written informed consent. In the beginning of the study period, only dupilumab was available as a treatment option and all the patients received this medication. After omalizumab was approved for severe CRSwNP in August 2020, both antibodies were used. The type of treatment was chosen without any specific preferences. The first two or three applications were administered by the doctor in the office and the patients were observed for at least 45 minutes. Usually, after these injections the patients used the self-administration option for the medication after instruction. All the patients continued the usage of nasal steroids throughout the treatment.

Table 1. Response criteria for biologicals after EPOS2020 [22].

Evaluating 5 criteria	Excellent response
	5 criteria
• Reduced nasal poly size	Moderate response
• Improved quality of life	3-4 criteria
• Improved sense of smell	Poor response
• Reduced need for systemic corticosteroids	1-2 criteria
• Reduced impact of co-morbidities	No response
	0 criteria

As a primary outcome criterion, the impact of the biological treatment on different parameters such as the polyp score, Sniffin' Sticks result, VAS- and SNOT-22 score after three and six months was determined. The secondary outcome was a response analysis after six months following the EPOS 2020 criteria (Table 1) and the determination of the influence of different co-factors [22].

Statistics

All analyses were performed using the IBM SPSS Statistics, Version 28.0 software system (IBM, Germany). Histograms and skewness were used to evaluate normal distribution. Mean values were computed ± standard deviations. In abnormally distributed values, a Wilcoxon test was used for statistical analysis. Spearman correlations were computed. The significance level was set at $p<0.05$. Other explorative analyses were performed wherever deemed appropriate. In these cases, p values are given for descriptive reasons only. Changes in the efficacy of the two investigated biological treatments on the different outcome measures were evaluated using the Mann-Whitney U test. Multivariate regression analysis was used to identify influencing factors for baseline measures and the overall response of the therapy.

Results

Demographics

Initially, 72 patients were started on the treatment with monoclonal antibodies. There were two dropouts. One patient was lost to follow-up because he moved to the northern part of Germany and another patient stopped the medication because of unclarified infection. The latter patient started the medication with the same monoclonal antibody after he overcame this condition. The time of the start of the antibody-therapy and the

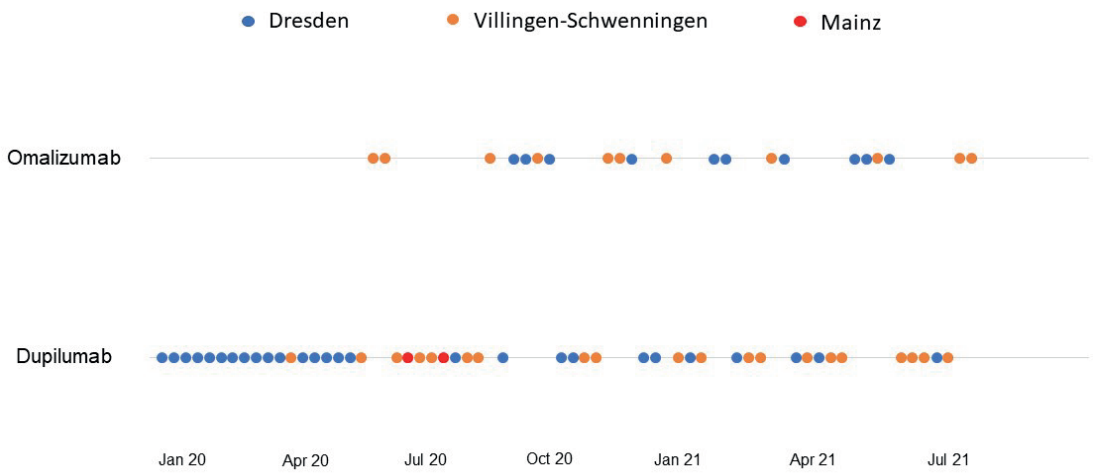

Figure 1. Timeline of the start of the treatment with either dupilumab or omalizumab. Each dot represents one patient and the colours represent the participating centre.

Table 2. Demographic baseline data of all CRSwNP-patients included for treatment with dupilumab or omalizumab.

	Dupilumab group	Omalizumab group
n	49	21
Age (years)	51.3	53.3
female	35%	34%
male	65%	66%
atopy	64%	50%
asthma	86%	80 %
NERD	55%	44%
previous sinus surgery	94%	91%
previous systemic steroids	92%	80%
Polyp-Score	6.1	5.2
SNOT-22	59.2	53.1
VAS	8.4	8.1
total serum IgE	183.6	126.5
Eosinophiles count	525.0	511.8
Sniffin´ Sticks Identification-Score	4.17	4.35
Normosmia	0%	5%
Hyposmia	11.9%	10.0%
Anosmia	88.1%	85.0%

Differences between groups all p > 0.17, except for polyp score (p=0.005).

distribution of the patients among the different centers can be seen in Figure 1.

For the analysis, 70 patients (46 men, 24 women; aged 19-83 years, 51.9 ± 14.1 years) were evaluated in a per protocol analysis. Many patients had known type II comorbidities like asthma (84%), history of allergic reaction to inhalant allergies (59%) or NERD (50%). Almost every patient had undergone previous endonasal sinus surgery (93%) and most patients had more than two surgical interventions in the past (56%). A treatment with systemic steroids of different dosages and duration of courses was reported by 88% of the patients.

Primary outcome parameter

The mean pre-treatment polyp score was 5.8 ± 1.2 (median 6.0, IQR 2). The mean SNOT-22 score was 57.3 ± 19.9 (median 60.5, IQR 30) points and mean VAS score 8.3 ± 1.3 (median 8.55, IQR 2). The evaluation of the sense of smell revealed a mean dentification score of 4.2 points ± 3.0 (median 4.0, IQR 2).

Of the patients, 49 started a treatment with dupilumab and 21 with omalizumab. Baseline parameter of the two specific antibody treatments can be seen in Table 2. There were no statistical differences of these measures between the two treatment groups (all p > 0.17), except that the polyp score was lower in the Omalizumab treated group (p=0.005).

No severe side effects occurred during the initiation of the monoclonal antibody therapy. During the whole six-month follow-up period in one case an increased local reaction occurred that led to a discontinuation of the therapy with dupilumab after 6 months and switch to another monoclonal antibody. Of the patients, one received oral steroids due to an increase in blood eosinophils over 10.000 /µl without any clinical signs in the dupilumab group. Almost all the patients started self-administration after two or three initial injections of the antibody and every patient continued the use of the nasal steroids throug-

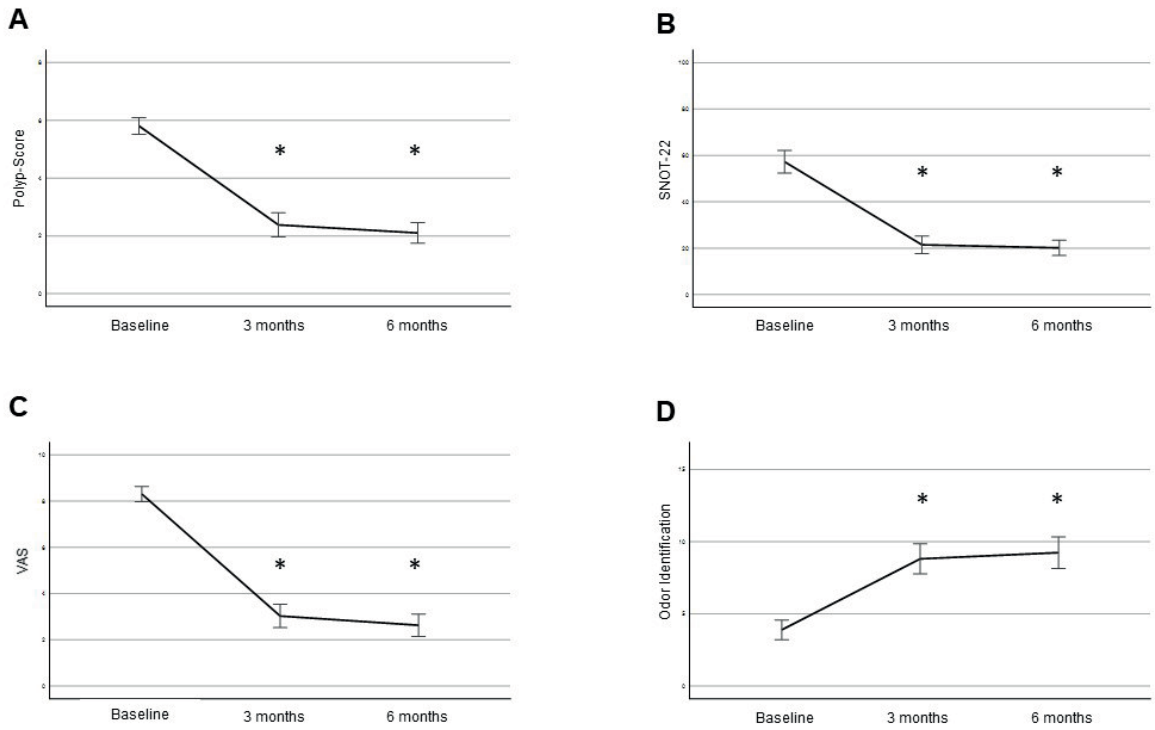

Figure 2. Mean values (including 95% confident interval) at baseline, 3 and 6 months after start of monoclonal antibody treatment for CRSwNP for a) endonasal polyp score (0-8), b) SNOT-22-score (0-110), c) VAS score of nasal health rating (0-10); d) Sniffin´ Sticks 16-Item Identification Score (0-16). Significant changes are marked by *.

hout the study period.

The mean change between baseline and 6 after months in the polyp score of the included 70 patients was -3.7 ± 1.5 ($p \leq 0.001$), median 4, IQR 2. The mean decrease vs. baseline in the SNOT-22 score was 31.1 ± 21.6 ($p \leq 0.001$), median 38.5, IQR 36 and 5.7 ± 2.3 points in VAS ($p \leq 0.001$), (median 6.05, IQR 3). The mean increase vs. baseline in the Sniffin' Sticks identification score was 5.2 ± 4.6 points ($p \leq 0.001$), (median 4.5, IQR 7). The changes were all already present after three months of therapy (Figure 2).

The response according to the EPOS 2020 criteria after six months was poor (response in 1-2 criteria) in one patient, moderate (response in 3-4 criteria) in 30 patients and excellent (response in all criteria) in 39 patients.

In one patient the indication for a revision sinus surgery was made due to insufficient efficacy of the monoclonal antibody therapy. After the follow-up period of six months, three patients were switched (two from dupilumab, one from omalizumab), two because of an insufficient response, one due to a strong local reaction at the injection site.

Concerning the aspect of olfaction data was available for the baseline evaluation in 62 patients and for the six-month results in 67 patients (missing data due to reduced feasibility because of the SARS-CoV-2 pandemic). Before the start of the biological treatment, 87% of patients showed anomia, 11% hyposmia and 2% normosmia. After six months of treatment 30% were anosmic, 43% were hyposmic and 27% were normosmic (Figure 3). Overall, this resulted in a recovery of at least some sense of smell in 38 of 60 patients. The change in olfaction correlated with the response after six months (-0.54, $p \leq 0.001$, Spearman), age (0.38, p=0.02) and the SNOT-22 change (-0.40, $p = 0.02$, Pearson), but not with the change in polyp score (0.20; $p = 0.12$, Spearman), asthma (p=0.064) or the initial Sniffin' Sticks result (p=0.14), supplementary Table 1.

By trying to detect certain parameters to predict the response, a multivariate regression analysis was used with the response (1-5) as the dependent variable and age, gender, asthma, the presence of NERD, allergy and prior sinus surgery as the independent variables. Here, only asthma was identified as a prognostic parameter with a regression-coefficient β of 1.079 (p=0.014). The corrected r^2 is 0.145.

Comparison of the two monoclonal antibodies

Since numbers of patients were limited for the two treatment groups, the following statistical analysis only has a descriptive character and the changes in the different parameters can be

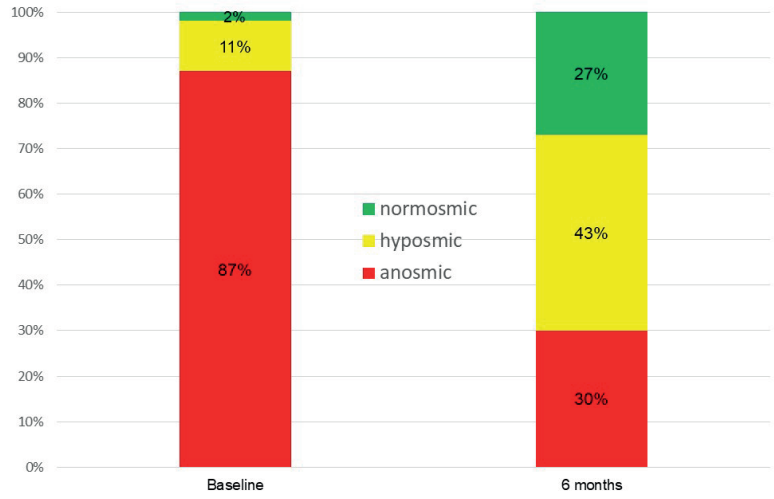

Figure 3. Percentual proportion of patients in the different classifications of olfaction (normosmic, hyposmic or anosmic) at baseline and 6 months after therapy with monoclonal antibodies for CRSwNP.

seen in Figure 4.

A difference in the outcome criteria after six months of treatment with the two monoclonal antibodies was found for the polyp score (p=0.012), SNOT-22 (p=0.015) and VAS (p=0.013) with a pronounced effect of dupilumab. Scores for the Sniffin' Sticks tended to be better for dupilumab (p=0.094). No difference could be seen between the two antibodies in the overall response after six months (p=0.57). The best response of 5 points was seen in 52% of the patients with omalizumab and in 57% with dupilumab, with a response of 4 points in 33% of patients with omalizumab and in 37% with dupilumab. A response of 3 points or less was seen in 14% of patients with omalizumab and 6% with the dupilumab treatment.

Discussion

This description of a cohort of 70 patients is one of the first reports on the efficacy of monoclonal antibody treatment in patients with CRSwNP outside of controlled clinical studies and with chronic rhinosinusitis as primary diagnosis. It is very important to collect the experiences of treatment of patients in a real-world environment, as the inclusion and exclusion criteria in clinical studies often do not match the real clinical setting. Data collection in the context of this research was performed by experienced specialists in the field who are also very well trained in the use of measures of symptoms and surgical approaches in chronic rhinosinusitis. Therefore, one can assume that more severe cases of patients with CRSwNP would have been included, and indeed, compared to the phase 3 studies for dupilumab [17] and omalizumab [18] the rate of included patients with comorbid asthma or NERD and the number of patients who had undergone at least one surgical intervention for CRSwNP were higher in this cohort. On the other hand, the mean polyp, SNOT-22 or VAS scores were quite similar to the randomized controlled clinical trials. Additionally, most of the patients in the present examination were anosmic, which is comparable to the included subjects in phase 3 studies. However, the UPSIT test was not used for evaluation, but rather the Sniffin' Sticks test, which is more commonly used in Europe.

After six months of treatment, the included subjects showed impressive improvements in all clinical parameters. Interestingly, these changes were already present after three months. The amount of improvement after six months was more apparent than the mean changes in the phase 3 studies of the two biological treatments patients were treated with in the present study. This might be due to the non-randomized uncontrolled design of this study or the fact that included patients of this investigation probably had more serious disease in terms of other typically type II associated co-morbidities, such as asthma and NERD. Therefore, a better selection of type II inflammatory disease cases might lead to a better response. However, there were also cases in which a limited effect was noted or patients who had no response at all. Here, the further course of the disease after the switch to another antibody or surgery under biological treatment will give us new insights into the handling of non-responders.

We have identified comorbid asthma as having a significant effect on the response, which is consistent with previous reports [18,19]. The task in the future will be to find more special conditions or biomarkers to forecast the efficacy of monoclonal antibodies in general or a specific antibody in single patient cases.

The safety of the monoclonal antibody therapy proved to be good beyond clinical trials and the side effects were comparable

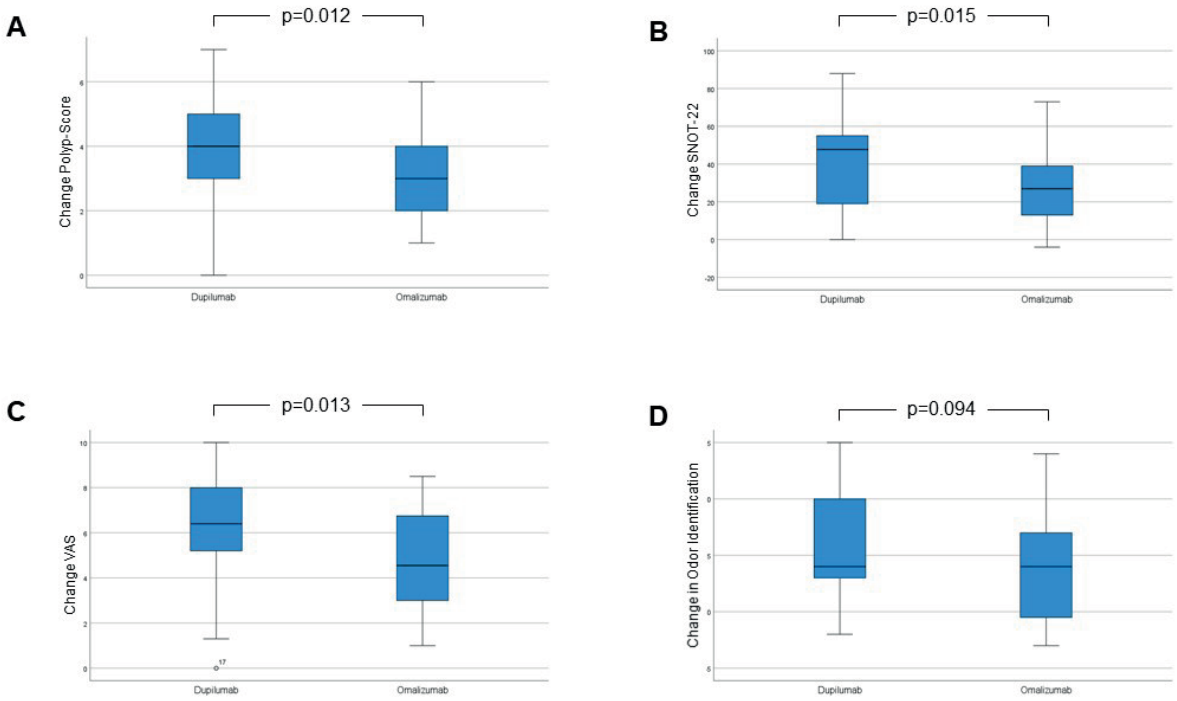

Figure 4. Boxplots of changes of a) nasal polyp score; b) SNOT-22 score; c) VAS-score; d) Sniffin´ Sticks 16-Item Identification score 6 month after start of therapy in the dupilumab (n=49) and omalizumab (n=21) treatment group. The lines represent the medians; the boxes include 75% of the results; the whiskers include 95% of the results. The circles demonstrate outliers. Significant differences are indicated.

in severity and frequency to the reports in the clinical studies [17-19]. The dropout rate was also very low.

In particular, the impaired sense of smell as a main reason behind the reduced quality of life in those suffering from CRSwNP also showed recovery during the study period. After six months, two thirds of the patients showed improvement, although only one third were classified as normosmic. Still, the fact that another third were anosmic after this period, which is comparable to the results of surgical interventions for CRSwNP, is important [35,36]. Further investigations are needed to assess changes after a longer period of treatment or identifying factors that result in a limited outcome for olfaction. One could speculate if the chronic inflammation might have led to an irreversible damage of olfactory cells. Specifically, future studies should involve the assessment of odour thresholds to address changes more specifically at the level of the olfactory epithelium [37].

The more pronounced numerical effect of dupilumab on polyp score, SNOT-22 score and VAS observed in our study compared to omalizumab has been published before [38,39]. However, this did not result in a significant higher overall response according to the EPOS 2020 recommendations [22] in our research. Nonetheless comparing results from two monoclonal antibodies must be done with caution based on the study design. Furthermore, no randomized, controlled head-to-head clinical study has been published to date.

Before the availability of monoclonal antibodies for the treatment of CRSwNP, aspirin desensitization therapy was considered as a possible supportive option in patients with a co-morbidity of NERD [40]. The first reports have been published that biological treatment is outperforming this procedure (41,42). Some of our patients had undergone aspirin desensitization therapy in the past, which turned out to be insufficient to control the disease. The monoclonal antibody treatment also proved its effectiveness in these patients.
The results of the present research are difficult to compare with the outcomes of the one other study using real-world data in patients that received monoclonal antibodies because they included patients with asthma with a comorbid CRSwNP [43]. The present study exclusively examined patients who received a monoclonal antibody treatment for the indication severe uncontrolled CRSwNP. In the investigation of Meier et al. [43], the treatment of 28 patients with either mepolizumab, omalizumab or benralizumab was described and many therapy switches were necessary due to an insufficient response. In addition, 22 patients also received at least one course of systemic steroids and some patients had to undergo revision sinus surgery, because a successful therapy was reported in only 31%, which is much less than our findings with dupilumab and omalizumab.

One other report exclusively for dupilumab treatment in CRSwNP patients showed the 24 weeks results in 98 patients [44]. Similar improvement of SNOT-22 scores and reduction in polyp scores were described. Another very recently published real world analysis from Canada [45] confirms the efficacy of the treatment with dupilumab in severe CRSwNP in a real-world setting in terms of improvement of SNOT-22 scores. Interestingly, in their cohort only 42 of 85 patients who were considered for treatment received coverage from the insurance company.

This gives an insight on the discussion about cost-efficacy of antibody-treatment for CRSwNP-patients especially in comparison to surgical approaches. There are many reports that sinus surgery improves disease-specific quality of life outcomes even over 10 years [46]. A recent meta-analysis on rates of revision surgery in CRSwNP [47] reported a mean revision rate of 16% in a mean follow-up of 90 months. Co-morbid asthma and NERD were identified as factors that significantly increased the revision rates to more than 25%. Algorithms were proposed for the therapeutic work-up of patients before starting biological treatment [48].

Besides the cost of the therapy, variances of the efficacy of the different monoclonal antibodies need to be evaluated in the future in further real-world studies. It needs to be proven if tendencies of recent comparative analysis [49] can be verified.

Limitations of the study

This research has some limitations: Because it was designed as a real-world study, this was a non-randomized, uncontrolled study. The patients selected for biological treatment were included consecutively without any randomization to either of the two treatment options, dupilumab and omalizumab. Therefore, a bias cannot be ruled out. Additionally, the third monoclonal antibody mepolizumab which is permitted for the same indication could not be taken into account, as the certification of approval was only recent.

Conclusions

This study delivers real-world evidence for the efficacy of treatment of CRSwNP, with the monoclonal antibodies dupilumab and omalizumab showing a safety profile as previously described. Patient selection, handling of the therapy and follow up for evaluating the effectiveness of the therapy is uncomplicated. A decrease in polyp score and increase of quality of life as well as olfaction could be demonstrated. Although the response to the therapy was moderate to excellent in most cases, few patients show a poor response. Until now no special comorbidities or biomarkers could be identified for an individual treatment stratification.

Authorship contribution

All authors were involved in the design, delivery, and analysis of the study, and have written and edited this manuscript.

Conflict of interest

Medical writing assistance of this manuscript was supported by Novartis Pharma GmbH, Nuremberg, Germany

Funding

None.

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This manuscript contains online supplementary material

		Re-sponse	Change Sniffin´ Sticks	Change Polyp Score.	Asthma	gender	age	NERD	Sinus Surger-ies	Base-line Polyp Score	Baseline Sniffin´_ Sticks	Change of olfac-tory class	Change VAS	Change SNOT-22
Response	Correlation-Coefficient	1.000	.576**	.442**	.198	.008	-.326**	.074	-.156	.053	.138	-.543**	.148	.346**
	Sig. (2-sided)		<.001	<.001	.103	.945	.006	.650	.197	.664	.286	<.001	.248	.004
	N	70	60	70	69	70	70	40	70	70	62	60	63	67
Change Sniffin´Sticks	Correlation-Coefficient	.576**	1.000	.365**	.188	.068	-.429**	.254	-.034	.173	-.413**	-.881**	.310*	.386**
	Sig. (2-sided)	<.001		.004	.154	.608	<.001	.113	.798	.187	.001	<.001	.022	.002
	N	60	60	60	59	60	60	40	60	60	60	60	54	60
Change Polyp Score	Correlation-Coefficient	.442**	.365**	1.000	.119	-.241*	-.036	.369*	.087	.420**	-.069	-.203	.340**	.248*
	Sig. (2-sided)	<.001	.004		.331	.044	.767	.019	.473	<.001	.593	.120	.006	.043
	N	70	60	70	69	70	70	40	70	70	62	60	63	67
Asthma	Correlation-Coefficient	.198	.188	.119	1.000	.235	-.064	.267	.243*	-.084	.064	-.242	.230	.177
	Sig. (2-sided)	.103	.154	.331		.052	.603	.100	.044	.494	.622	.064	.070	.154
	N	69	59	69	69	69	69	39	69	69	61	59	63	66
gender	Correlation-Coefficient	.008	.068	-.241*	.235	1.000	-.016	.180	.140	-.018	.064	-.116	.217	.142
	Sig. (2-sided)	.945	.608	.044	.052		.898	.267	.248	.884	.624	.376	.088	.251
	N	70	60	70	69	70	70	40	70	70	62	60	63	67
age	Correlation-Coefficient	-.326**	-.429**	-.036	-.064	-.016	1.000	-.327*	.002	.154	.123	.384**	-.093	-.232
	Sig. (2-sided)	.006	<.001	.767	.603	.898		.039	.986	.204	.341	.002	.467	.059
	N	70	60	70	69	70	70	40	70	70	62	60	63	67
NERD	Correlation-Coefficient	.074	.254	.369*	.267	.180	-.327*	1.000	.433**	.275	-.174	-.191	.074	-.011
	Sig. (2-sided)	.650	.113	.019	.100	.267	.039		.005	.086	.284	.238	.673	.947
	N	40	40	40	39	40	40	40	40	40	40	40	35	40
Sinus surgeries	Correlation-Coefficient	-.156	-.034	.087	.243*	.140	.002	.433**	1.000	.067	-.078	.109	.157	-.093
	Sig. (2-sided)	.197	.798	.473	.044	.248	.986	.005		.584	.546	.409	.218	.453
	N	70	60	70	69	70	70	40	70	70	62	60	63	67
Baseline Polyp Score	Correlation-Coefficient	.053	.173	.420**	-.084	-.018	.154	.275	.067	1.000	-.004	-.087	.373**	.178
	Sig. (2-sided)	.664	.187	<.001	.494	.884	.204	.086	.584		.975	.506	.003	.150
	N	70	60	70	69	70	70	40	70	70	62	60	63	67
Baseline Sniffin´_Sticks	Correlation-Coefficient	.138	-.413**	-.069	.064	.064	.123	-.174	-.078	-.004	1.000	.192	-.058	.016
	Sig. (2-sided)	.286	.001	.593	.622	.624	.341	.284	.546	.975		.141	.673	.903
	N	62	60	62	61	62	62	40	62	62	62	60	56	62

		Re-sponse	Change Sniffin´ Sticks	Change Polyp Score.	Asthma	gender	age	NERD	Sinus Surger-ies	Base-line Polyp Score	Baseline Sniffin´_ Sticks	Change of olfac-tory class	Change VAS	Change SNOT-22
Change of olfactory class	Correlation-Coefficient	-.543**	-.881**	-.203	-.242	-.116	.384**	-.191	.109	-.087	.192	1.000	-.254	-.396**
	Sig. (2-sided)	<.001	<.001	.120	.064	.376	.002	.238	.409	.506	.141		.063	.002
	N	60	60	60	59	60	60	40	60	60	60	60	54	60
Change VAS	Correlation-Coefficient	.148	.310*	.340**	.230	.217	-.093	.074	.157	.373**	-.058	-.254	1.000	.415**
	Sig. (2-sided)	.248	.022	.006	.070	.088	.467	.673	.218	.003	.673	.063		<.001
	N	63	54	63	63	63	63	35	63	63	56	54	63	61
Change SNOT-22	Correlation-Coefficient	.346**	.386**	.248*	.177	.142	-.232	-.011	-.093	.178	.016	-.396**	.415**	1.000
	Sig. (2-sided)	.004	.002	.043	.154	.251	.059	.947	.453	.150	.903	.002	<.001	
		67	60	67	66	67	67	40	67	67	62	60	61	67

Supplementary Table 1. Correlation (Pearson) of different parameter examined during the study (baseline and changes after 6 months). Significant correlations are pointed out in green. N=number of patients included.