Efficacy and safety of switching between biologics in chronic rhinosinusitis with nasal polyps or N-ERD*

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Abstract

Background and objective: The effectiveness of biologics in chronic rhinosinusitis with nasal polyps (CRSwNP) is well-established. However, real-world experience on the effectiveness of transitioning between two monoclonal antibodies is scarce. Therefore, we aimed to analyze the safety and efficacy of antibody switching in treatment of chronic rhinosinusitis.

Methods: All patients with CRSwNP or nonsteroidal anti-inflammatory drugs-exacerbated respiratory disease (N-ERD) requiring a switch between biologics were retrospectively studied. Analysis included changes in polyp size, quality of life parameters, asthma control, and side effects.

Results: Out of 195 patients treated with biologics for CRSwNP or N-ERD in our center, 23 (11.8%) required transition to a different monoclonal antibody. The majority switched from omalizumab to dupilumab (17/23, 73.9%), mostly due to inadequate symptom control. Nine out of these 17 patients (52.9%) were switched without a washout period. All patients showed significant improvement in nasal polyp score, asthma control test and sino-nasal outcome test-22 after changing to dupilumab. Keratoconjunctivitis sicca was the side-effect (4.3%) reported after the switch from omalizumab to dupilumab, which lead to termination of therapy in one patient. Due to limited sample size, other antibody transitions were reported in a descriptive manner.

Conclusion: The transition to dupilumab is an effective option in patients with inadequate treatment response or side-effects of omalizumab in nasal polyposis. Our preliminary results indicate that a wash-out period may not be necessary when switching between biologics, however, these findings require further investigations. Other monoclonal antibody transitions also show promising results, but warrant validations in larger cohorts due to small patient samples in our study.

Key words: biologics, CRSwNP, N-ERD, omalizumab, dupilumab

Introduction

The significant global burden of chronic rhinosinusitis (CRS), particularly CRS with nasal polyps (CRSwNP), is well established. In particular, 1.95-4% of the population are affected by CRSwNP [1-3]. Surgery, as well as local or systemic corticosteroids were the main therapeutic options for several decades. In the western world, CRSwNP is dominated by a type 2 inflammation pattern with elevated IL-4, IL-5, and IL-13 levels along with eosinophil infiltration [4]. CRSwNP is associated with comorbidities such as asthma and hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) in a syndrome called NSAID-exacerbated respiratory disease (N-ERD) [5]. For the treatment of type 2 disease, a variety of monoclonal antibodies has been developed and successfully used to manage asthma as well as atopic dermatitis and particularly dupilumab, omalizumab, and mepolizumab, targeting interleukin (IL)-4Rα, IgE, and IL-5 respectively, were recently approved for the treatment of severe CRSwNP [1]. Biologic medications have broadened therapeutic options for difficult to treat CRSwNP and N-ERD patients and, in recent years, guidelines for prescription and treatment evaluation of biologics have been established [1]. For assessment of treatment response of individual patients, the following criteria have been defined [6]: reduced nasal polyp size, reduced need for systemic

corticosteroids, improved quality of life, improved sense of smell and reduced impact of co-morbidities. Nevertheless, there is still limited guidance on which antibody to choose and, more importantly, on the procedure of switching between biologics in CRSwNP if the first choice leads to unsatisfactory disease management or side effects [7-9]. In this context, effectiveness of switching from IL-5 or IL-5Rα targeting biologics (mepolizumab, reslizumab, or benralizumab) to dupilumab (against IL-4Rα) was reported in a retrospective study involving 27 patients [7], but so far there is only one case report on switching from omalizumab (targeting IgE) to mepolizumab (targeting IL-5) due to insufficient CRS control [10]. Furthermore, the necessity of a wash-out period prior to starting the second biologic remains questionable. A washout time of at least 5-10 half-lives or 3-months is recommended in the current literature, but as biologics are prescribed for severely suffering and standard therapy refractory patients, rapid change of biologic medication would be desirable if safe [8]. In this regard, recent data from Papaioannou et al. suggest that switching between biologics in type 2 high asthma was well tolerated and did not cause any adverse events even without a wash-out period [9]. Whether this also applies to switching in CRS patients remains to be investigated.

In the current study, we conducted a retrospective chart review of physician-diagnosed CRSwNP and N-ERD patients treated at the Department of Otorhinolaryngology at the Medical University of Vienna who were switched between two different monoclonal antibody treatments. Firstly, as the primary and objective outcome, polyp size reduction was assessed by endoscopy. Secondly, disease specific quality of life (QoL) scores regarding sino-nasal and asthma symptoms were analyzed. Additionally, we investigated indications for transitioning of biologics, if a washout was adhered to and side-effects of the preceding and current monoclonal antibody therapy. Based on this, novel insights were gained into the safety and efficacy of switching between monoclonal antibodies in CRSwNP and N-ERD patients with inadequately controlled upper respiratory tract symptoms or side-effects under the first-choice biological antibody.

Patients and methods

A retrospective chart review of all patients with physician diagnosed CRSwNP or N-ERD who received at least two biologic treatments at the Department of Otorhinolaryngology, Head and Neck Surgery, Medical University Vienna, from January 1st 2020 to September 30th 2021 was performed. During this period, dupilumab (300 mg biweekly) and omalizumab (dosage according to weight and IgE levels [10]) were offered as therapy for CRSwNP. Furthermore, patients initially started on mepolizumab (100 mg every 4 weeks) or benralizumab (30 mg every 4 to 8 weeks) for severe asthma by a pulmonologist and later switched to dupilumab at our department based on their CRSwNP or N-ERD symptoms, after consultation with the pulmonologist, were included as well. Due to the severe symptom burden of most of the patients at the outpatient clinic, it was planned to start therapy with the second antibody within 1-2 weeks after stopping the first. However due to the COVID pandemic, severely restricted access to the hospital and multiple canceled appointments due to disease of patient/doctor/nursing staff or lockdown, washout periods occurred in some patients. Those who were switched to another monoclonal antibody due to side-effects or self-reported inadequately controlled upper respiratory tract symptoms were included in the analysis. Clinical and subjective assessments were conducted prior to starting the course of monoclonal antibody and 1, 2, and 6 months after starting treatment. Timepoint for outcome measures was defined as the 6-month follow-up visit or alternatively, the last visit, if the switch occurred earlier.

Clinical evaluations at our department included endonasal examination with a 0- or 30-degrees rigid endoscopes. Polyp size was assessed and documented according to the nasal polyp score (NPS, 0-4 for each side, total NPS 0-8, as previously published) [11]. Patient-reported outcome measures were evaluated by sino-nasal outcome test (SNOT) and asthma control test (ACT). Due to the lack of availability of a German SNOT-22 in patients included early in the study and treated with omalizumab as a first antibody, the SNOT-20 German adapted version values of these patient are reported for their first antibody treatment. At all other timepoints and patients, SNOT-22 data were available. The type of SNOT used has clearly been marked in figure legends and text.

Self-reported data on comorbidities (asthma, allergy) as well as previous endoscopic sinus surgery (ESS) were retrieved from medical records. Moreover, the duration of the first and second monoclonal antibody treatment, indication for switching between individual agents, side effects and data on washouts or immediate switches were reported. Four out of the 5 EUFOREA criteria [6, 12, 13] were retrospectively assessed (yes/no) in the patients and graded as follows: Reduced nasal polyp size: yes - if NPS reduction >1, no - if NPS reduction ≤1; improved quality of life: yes - if SNOT-20/22 reduction ≥8.9 points, no - if SNOT-20/22 reduction <8.9 points; improved sense of smell: yes - if SNOT-20/22 item "Impaired smell" reduction >1 point, no - if SNOT-20/22 item "Impaired smell" reduction ≤ 1 point; reduced impact of comorbidities: yes - if ACT improved by 3 points, no - if ACT improved by less than 3 points. The fifth criteria, reduced need for corticosteroids, could not be assessed as this item was not recorded in the files.

Datasets from first- and second-choice treatments were available for patients switching from omalizumab to dupilumab or dupilumab to omalizumab of patients as indicated in the figure legends. Patients treated with mepolizumab or benralizumab were started on the first antibody by a pulmonologist outside an academic setting and thus NPS, SNOT-22, and ACT scores are

Table 1. Detailed characteristics of patients with indications for switching between biologics for each group.

	Oma - Dupi	Mepo - Dupi	Benra - Dupi	Dupi - Oma	Total
Total [%]	17 [73.9%]	3 [13.0%]	2 [8.7%]	1 [4.3%]	23 [100%]
Male [%]	7 [41.2%]	2 [66.7%]	2 [100%]	0 [0%]	11 [47.8%]
Female [%]	10 [58.8%]	1 [33.3%]	0 [0%]	1 [100%]	12 [52.2%]
Age [min. - max.]	47.4 [18.1 - 72.5]	52.2 [24.6 - 62.4]	49.1 [48.5 - 49.6]	48.0 [48.0 - 48.0]	48.3 [18.1 - 72.5]
No. ESS [min. - max.]	2 [0 - 7]	1 [1 -4]	2 [1 - 3]	1 [1 - 1]	2 [0 - 7]
Asthma [%]	16 [94.1%]	3 [100%]	2 [100%]	1 [100%]	22 [95.7%]
Allergy [%]	10 [58.8%]	1 [33.3%]	2 [100%]	1 [100%]	14 [60.9%]
N-ERD [%]	16 [94.1%]	1 [33.3%]	0 [0%]	1 [100%]	18 [78.3%]
Indications for biologics switch	**Oma - Dupi**	**Mepo - Dupi**	**Benra - Dupi**	**Dupi - Oma**	**Total**
Progressive nasal congestion [%]	12 [70.6%]	3 [100%]	2 [100%]	0 [0%]	17 [73.9%]
Anosmia or Hyposmia [%]	4 [23.5%]	0 [0%]	0 [0%]	0 [0%]	4 [17.4%]
Psoriasis [%]	0 [0%]	0 [0%]	0 [0%]	1 [100%]	1 [4.3%]
Joint pain [%]	1 [5.9%]	0 [0%]	0 [0%]	0 [0%]	1 [4.3%]

Oma: omalizumab; Dupi: dupilumab, Mepo: mepolizumab; Benra: benralizumab; N-ERD: nonsteroidal anti-inflammatory drug-exacerbated respiratory disease; ESS; endoscopic sinus surgery; %: percentage. Median, minimum, and maximum values are presented.

only available from baseline and post-therapeutic 2nd biologic. Therefore, these patients are described as case reports.

Statistics

The statistical package for the social sciences (SPSS, IBM Corp. released 2016. IBM SPSS statistics for windows, Version 24.0. IBM Corp., Armonk, NY, USA) was used for all statistical analyses. Due to small patient sample size, non-normal data distribution was assumed. Therefore, we presented all descriptive data using median, minimum, and maximum values.

To compare NPS, SNOT-20 (pre- and during omalizumab) and SNOT-22 (pre- and during dupilumab) and ACT scores at baseline and at the 6-month time-point, we utilized the Wilcoxon Signed-Ranked Test. The level of statistical significance was set at 0.05, two-tailed. As the study is of a descriptive and hypothesis-generating character, multiple testing correction was omitted.

The group transitioning from omalizumab to dupilumab was statistically analyzed. Scores at four visits: "pre-omalizumab" (immediately prior to omalizumab start) and "pre-dupilumab" (immediately prior to dupilumab start) were compared to measurements at visits "during omalizumab" (6 months after omalizumab start (n=14), or last available visit in patients that were switched earlier (n=3)) and "during dupilumab" (6 months after dupilumab start), were compared for statistical significance, respectively. Other therapy transition groups were merely descriptively analyzed due to small patient samples.

The graphical presentation was performed with GraphPad Prism (GraphPad Prism version 8.0.0, GraphPad Software, San Diego, CA, USA).

Ethical statement

The ethical committee of the Medical University of Vienna approved data collection and analysis (EK number 2222/2021). Due to the retrospective character of the study, patient informed consent was not required.

Results

Patients

Between January 1st 2020 and September 30th 2021, 195 patients at our department were treated with a monoclonal antibody for CRSwNP. Dupilumab was used as primary therapy in 169 out of 195 patients (86.7%). Omalizumab was the first-choice biologic treatment in 20/195 patients (10.3%). Whilst the 189 patients (96.9%) received the biologics for CRSwNP as a primary indication, three (1.5%) and three (1.5%) patients primarily received mepolizumab and benralizumab for severe asthma but were followed in the otolaryngology department due to their comorbid severe nasal polyposis and thus included in the study. Twenty-three out of 195 patients (11.8%) included in the analysis required a switch to another biologic agent due to self-reported inadequate symptom control or therapy side-effects (table 1). Of these, 52.2% (n=12) were female, and the median age of the cohort at the time of transition to the second monoclonal antibody was 48.3 years (18.1 - 72.5 years). Eighteen patients (78.3%) had N-ERD. With regards to comorbidities, 22 (95.7%) and 14 (60.9%) had asthma and allergy, respectively. Four patients (17.4%) did not undergo an ESS prior to initial biologic treatment. The median number of previous ESS was 2 (0 - 7). The mean, minimum, and maximum duration of the second biologic was 12.9, 5.3, and 31.6 months, respectively.

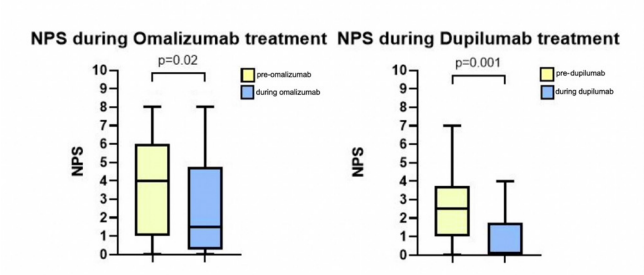

Figure 1. Changes in nasal polyp score (NPS) during treatment periods in patients switching from omalizumab to dupilumab treatment. The line within each box represents the median, bottom border represents the 25th percentile and top border the 75th percentile of the data. Whiskers show minimum and maximum values. Pre-omalizumab (n=16/17); visit immediately prior to omalizumab start, during omalizumab (n=17/17); visit after 6 months of omalizumab treatment, or last available if therapy was terminated or switched earlier, pre-dupilumab (n=16/17); visit immediately prior to dupilumab start, during dupilumab (n=17/17); visit after 6 months of dupilumab treatment.

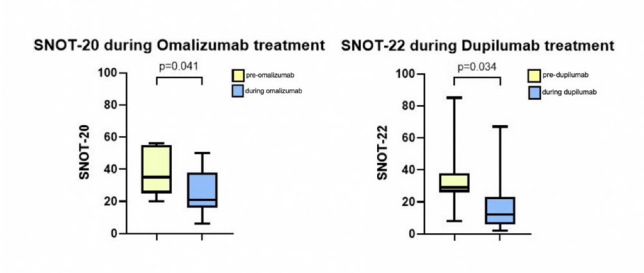

Figure 2. Changes in sino-nasal outcome test 20 and 22 (SNOT-20 and SNOT-22) during treatment periods in patients switching from omalizumab to dupilumab treatment. The line within each box represents the median, bottom border represents the 25th percentile and top border the 75th percentile of the data. Whiskers show minimum and maximum values. Pre-omalizumab (n=15/17); visit immediately prior to omalizumab start, during omalizumab (n=15/17); visit after 6 months of omalizumab treatment, or last available if therapy was terminated or switched earlier, pre-dupilumab (n=13/17); visit immediately prior to dupilumab start, during dupilumab (n=13/17); visit after 6 months of dupilumab treatment.

As the majority of patients (n=17/23; 73.9%) switched from omalizumab to dupilumab treatment, statistical analysis was performed in this group only. Due to small patient sample size, other switch patients are presented using descriptive methods. Detailed patient characteristics of the whole cohort, including comorbidities and indications for switching between biologics, are shown in Table 1. Furthermore, the characteristics of the individual patients, including duration of each treatment, side-effects, and pre- and post-therapeutic eosinophil counts, are shown in the supplementary Table 1.

Patients switch from omalizumab to dupilumab mainly due to lack of improvement of nasal congestion or olfactory function

As aforementioned, 17 patients were identified who switched from omalizumab to dupilumab. Most patients required the switch due to subjectively nasal congestion (70.6%, n=12/17). Subjective worsening or no improvement of olfactory function was self-reported by four patients (23.5%, n=4/17). Last, one patient experienced new-onset of joint pain and was therefore switched to dupilumab (5.9%, n=1/17). The median time of omalizumab treatment was 11.4 months (3.3 – 47.4 months). Nine out of 17 patients (52.9%) were switched to dupilumab without washout time followed by a median treatment time of 11.7 months (5.3 – 31.6 months) within our observation period. Only two out of 17 patients switching to dupilumab (11.8%) stopped treatment thereafter for the following reasons: one patient experienced worsening of allergic symptoms including rhinorrhea after six months of dupilumab treatment and, thus, switched back to omalizumab at his own request. The other patient developed keratoconjunctivitis sicca after six months of dupilumab treatment and declined to receive further biological treatment. Thus, out of 23 patients receiving biologicals, only one patient stopped treatment with monoclonal antibodies during our observation period. No further side-effects were reported during dupilumab therapy.

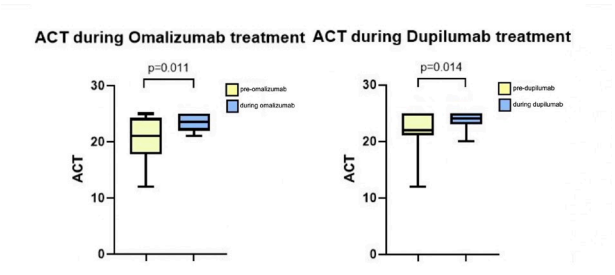

Figure 3. Changes in asthma control test (ACT) during treatment periods in patients switching from omalizumab to dupilumab. The line within each box represents the median, bottom border represents the 25th percentile and top border the 75th percentile of the data. Whiskers show minimum and maximum values. Pre-omalizumab (n=15/17) visit immediately prior to omalizumab start, during omalizumab (n=14/17); visit after 6 months of omalizumab treatment, or last available if therapy was terminated or switched earlier, pre-dupilumab (n=13/17); visit immediately prior to dupilumab start, during dupilumab (n=14/17); visit after 6 months of dupilumab treatment.

Improvement in total NPS during omalizumab and dupilumab therapy

Median pre- and post-omalizumab therapy NPS scores were 4 (0 – 8) and 1 (0 – 8), and this improvement tested as statistically significant (p=0.020). After switching to dupilumab, the median NPS score of 2.5 (0 – 7) significantly improved to 0 (0 – 4) after

six months of treatment (p=0.001) (Figure 1).

Improvement in sino-nasal symptom burden as measured by SNOT-20 or SNOT-22 during omalizumab and dupilumab treatment

During omalizumab treatment, patients experienced an improvement in sino-nasal symptom burden as quantified by SNOT-20 scores. The median pre-treatment SNOT-20 score was 35 (20 – 56) and significantly improved to 21 (6 – 50) (p=0.041, Figure 2). Subsequent dupilumab treatment improved the SNOT-22 significantly by a median of 13 points (p=0.034).

Asthma symptom score (ACT) improvement

Patients with comorbid asthma were asked to complete the ACT questionnaire. The median pre- and post-omalizumab scores were 21 (12 – 25) and 23.5 (21 – 25) (p=0.011, Figure 3). Prior to starting dupilumab therapy, the median ACT was 22 (12 – 25) and improved to 24.5 (20 – 25) after six months. After dupilumab treatment ACT scores improved significantly (p=0.014).

EUFOREA criteria

With regards to EUFOREA criteria, 15.4% (n=2 of 13 patients where all 4 criteria could be retrospectively assessed) of patients fulfilled 3 out of 4 criteria prior to the transition from omalizumab to dupilumab whilst 69.2% of patients (n=9/13) scored positive in two or less assessed criteria (supplementary Table 2) at the time of switching. After dupilumab therapy, 45.5% of patients (n=5 of 11 where all 4 criteria could be retrospectively assessed) fulfilled 3 out of the 4 criteria and 54.5% (n=6/11) fulfilled at two or less of the above-mentioned criteria (supplementary Table 3).

Transition to other biologics – case reports

As mentioned, other transitions between biologics included changes from mepolizumab (13.0%, n=3/23) and benralizumab (8.7%, n=2/23) to dupilumab, and from dupilumab to omalizumab (4.3%, n=1/23). Importantly, all of these transitions were performed without a washout period. As treatments with mepolizumab and benralizumab were initiated at the clinical division of pulmology, NPS, ACT and SNOT-22 from baseline and post-therapeutic of the first biologic were not available and thus are described here briefly as case reports.

Patients were treated with mepolizumab (n=3) for on average 29.5 (0.8 - 32.5) months before switching to dupilumab. Their NPS of 4 (2 - 4) and their SNOT-22 score of 75 (69 - 81) dropped to 0 (0 - 2) and 13.5 (8 - 19) respectively, after receiving dupilumab. Benralizumab (n=2) was administered for 8.0 (6.9 - 9.2) months before the transition to dupilumab. The NPS decreased from 6.5 (6 - 7) before starting dupilumab to 2 (0 - 4) under dupilumab treatment and the SNOT-22 score from 42.5 (31 - 54) to 6 (3 - 9).

Only one patient switched from dupilumab to omalizumab due to the worsening of his allergic symptoms. During dupilumab therapy, his NPS dropped from 4 to 1 and remained at 1 during omalizumab treatment, also the drop in SNOT-22 score from 29 to 3 remained at 2 after switching to omalizumab.

Discussion

Dupilumab, omalizumab, and mepolizumab are monoclonal antibodies used for treatment of CRSwNP with their safety, efficacy and side effects being already well-established [14]. In this retrospective analysis of real-life data, we report on switching between biologics in 23 patients suffering from CRSwNP or N-ERD. Most patients (91.4%) were switched due to inadequate symptom control with the first-choice biologic, only 2 patients had to be switched to another antibody due to side effects. Switching was well tolerated, relatively safe with no unknown side effects observed and led to efficient symptom control in the majority of patients also without maintaining a wash-out period. Although three different monoclonal antibodies are currently licensed for treatment of CRSwNP, literature on the effect of switching between these antibodies is scarce. To the best of our knowledge, so far only two studies reported on switching between biologics in more than 20 patients with N-ERD [7, 14]. Our results support the findings of Wangberg et al. that anti-IL-4Rα treatment led to significantly higher symptom improvement in N-ERD as compared to other biologics [14]. Their observation that over 40% of patients trialed more than one biologic underlines the need for defining switching algorithms and/or biomarkers for predicting and monitoring treatment success. As there are currently no guidelines available, the decision for transition of biologics in our patient cohort was mainly based on the patients perceived symptom changes, requests, as well as polyp burden. To objectively assess efficacy of the respective antibodies in the patients, we have retrospectively applied 4 of the 5 EUFOREA criteria to our cohort [6]. Although patients subjectively reported great improvements during dupilumab therapy, 50% of patients fulfilled only half of the criteria. However, it needs to be mentioned that for the purpose of this study and due to the retrospective nature of the analysis, we have based our definitions on previously reported clinically meaningful differences in established scores, and that e.g. ACT improvement does not fully cover the item "improved comorbidities". Furthermore, smell perception could certainly be more objectively assessed by testing. Though the EUFOREA criteria provide a level of guidance, they still need to be further elaborated on as the terms "reduced" and "improved" are not yet defined quantitatively and are currently left to the physician's discretion. Furthermore, up to now, there are no standardized test suggested for quality of life assessment or impact of comorbidities.

Here we report on both CRSwNP or N-ERD patients switching from omalizumab to dupilumab. During omalizumab therapy,

we observed an NPS improvement with a median of 2 and SNOT-20 by 7 points in accordance with previous reports [15, 16]. During subsequent treatment with dupilumab, NPS dropped to a median of 0 and SNOT-22 improved by 14 points. This was accompanied by significantly better asthma control, supporting the notion that dupilumab has a stronger effect on polyp burden as compared to anti-IgE therapy or anti-IL5/IL-5Rα [17-20]. Of note, in 50% of patients no washout period was performed, thus these patients may have started with lower baseline pre-treatment values for the second antibody due to the prevailing effect of the first antibody. Apart from omalizumab, we also describe case reports on other transitions (mepolizumab and benralizumab to dupilumab and dupilumab to omalizumab), which also led to improvement in CRSwNP burden in line with previous case reports of severe asthma with nasal polyposis [9, 21]. However, these observations were only descriptively analyzed, need to be interpreted with caution due to small sample size and warrant further validation. Importantly, the heterogeneous reasons for switching between groups with progressive nasal congestion being the primary reason in those receiving primarily benralizumab or mepolizumab as opposed to the omalizumab group, where persisting anosmia was an important motive for 23.5%, may have been observed due to the small sample size.

Our CRSwNP patient cohort requiring switching was suffering from multiple comorbidities such as asthma, N-ERD or allergy, which also need to be considered for optimal therapy. In this respect, omalizumab targeting the IgE pathway may be beneficial in patients suffering from concomitant severe allergy, as it may alleviate allergic symptoms faster and more efficiently than dupilumab due to its different mode of action [22, 23]. In line with this, out of 17 patients switching from omalizumab to dupilumab, one switched back to omalizumab after six months due to inadequate control of his allergic symptoms, despite improvement in polyp scores. The choice of antibody in patients suffering from multiple type 2 diseases should also be based on the patient's most burdensome symptoms. These patients should be discussed by an expert board involving pulmonologists, immunologists, and otolaryngology specialists. In future, eventually a combination of monoclonal antibodies may also be carefully considered to achieve optimal treatment success for both asthma and CRSwNP symptoms. Recent case reports have shown improved results using a combination of anti-IgE and anti-IL-5 treatment in difficult to treat severely asthmatic patients [24, 25].

Out of 195 patients treated with monoclonal antibodies at our department, only one patient required switching from dupilumab to another biologic due to developing psoriasis, a suspected rare effect of dupilumab therapy [27, 28]. After switching to dupilumab, only one patient stopped treatment due to keratoconjunctivitis sicca, a side-effect that has previously been observed with regards to dupilumab treatment [28]. Importantly, no novel side effects were observed due to switching even in absence of a wash-out period. Thus, our data confirm that therapy with biologics and switching is relatively safe and no previously unidentified side effects were observed.

It remains a matter of debate, whether washout periods of five to ten elimination half-life periods should be maintained as previously recommended [8]. As half-lives for biologics used for treating CRSwNP are reported between 15 to 26 days [9], a washout period could potentially lead to considerable and life quality-impairing symptom worsening, and, thus, switching without delay would be beneficial for patient wellbeing. Due to the heavy symptom burden of the patients attending the outpatient clinic, the authors initially intended to switch without washout time within 1-2 weeks, however during the COVID pandemic this was often not feasible resulting in approximately 50% of patients experiencing a washout period. After treatment change, patients experienced a comparable reduction in symptom burden and no additional side effects regardless of whether a washout period took place or not. Thus, as our observations confirm findings in antibody transitioning in asthma [9], it can be hypothesized that transitions from omalizumab to dupilumab without a washout period might not increase the risk for side-effects.

Limitations of this study include its retrospective character and the relatively small study sample and a heterogenic cohort. However, it needs to be kept in mind that this study was conducted in a real-world setting where monoclonal antibodies for treatment of CRSwNP only became available recently. A certain bias towards preferred prescription of dupilumab cannot be excluded due to several reasons: Firstly, evidence for the superior real-world effectiveness of dupilumab increased during the study time. Secondly, omalizumab was licensed for CRSwNP in Austria two years after approval of dupilumab. Thirdly, due to a special reimbursement situation by health insurances in Austria, prescription for dupilumab is easier and more likely to be approved by health insurances as compared to omalizumab for patients who had prior surgery. Furthermore, as this study was conducted in a tertiary center with different clinicians being present in the outpatient clinic, there may have been a non-avoidable interobserver bias as well as a bias towards more severely suffering patients. We contribute to the currently scarce patient data of antibody switching by being the first to show that switching from omalizumab to dupilumab is efficient and safe, regardless of whether switching is performed with a washout phase or directly.

Conclusion

Switching to dupilumab due to insufficient symptom control or treatment side-effects of omalizumab seems to be safe apart from known side-effects and effective in CRSwNP. Our preliminary results indicate that a switch without a washout appears

to be safe, which would be in accordance with recent data of antibody switching in asthma. Due to above-noted limitations of the study including the small sample size, our observations warrant further validation in larger-scale studies.

Authorship contribution

FFB, CB, and SS had the initial idea for the retrospective analysis and FFB, RK, TB, KG, and EV performed all data collection. FFB, DTL, and JED interpreted the data and designed the figures. FFB, JED, and SS wrote the initial version of the manuscript. All authors critically revised the manuscript. FFB and DTL advised on and performed key statistical analyses.

Conflict of interest

SS served as a speaker and/or consultant and/or advisory board member for Sanofi and Novartis. SS is an investigator for Novartis and AstraZeneca (grants paid to his institution). TB received personal fees from Sanofi and Novartis. CB has received personal fees from Mylan, LEO Pharma, Pfizer, Sanofi Genzyme, Eli Lilly, Novartis, and AbbVie. CB is an investigator for Novartis, Sanofi, Abbvie, Elli Lilly, LEO Pharma and Galderma (grants paid to her institution). JED served as a speaker and/or consultant and/or advisory board member for Sanofi, Allergopharma, AstraZeneca, GSK and Novartis. JED is an investigator for Novartis and AstraZeneca (grants paid to her institution). All other authors declare no conflict of interest.

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This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Detailed characteristics of individual patients transitioning between two biologics.

Number	Sex	Age	Ab1	Duration Ab1	Side Effects Ab1	Eos pre-Ab1	Eos post-Ab1	Washout	Ab2	Duration Ab2	Side Effects Ab2	Eos pre-Ab2	Eos post-Ab2
1	f	26.9	Omalizumab	15.4	0	0.4	0.2	1	Dupilumab	11.4	0	n.k.	0.8
2	f	47.0	Omalizumab	13.2	0	n.k.	0.1	0	Dupilumab	11.0	0	n.k.	n.k.
3	f	70.4	Omalizumab	10.6	0	0.1	0.2	1	Dupilumab	21.9	0	n.k.	0.1
4	f	48.7	Omalizumab	7.3	0	0.3	0.2	1	Dupilumab	11.7	0	n.k.	0.5
5	f	45.0	Omalizumab	3.3	0	n.k.	0.5	1	Dupilumab	5.6	0	n.k.	n.k.
6	f	48.3	Omalizumab	16.8	0	0.7	0.5	0	Dupilumab	13.8	0	n.k.	0.4
7	m	61.2	Omalizumab	27.0	0	n.k.	0.3	0	Dupilumab	12.2	0	n.k.	n.k.
8	m	72.5	Omalizumab	32.6	0	0.7	0.5	0	Dupilumab	16.1	0	n.k.	0.3
9	m	42.9	Omalizumab	8.9	0	n.k.	n.k.	0	Dupilumab	5.3	0	n.k.	n.k.
10	m	47.4	Omalizumab	47.4	0	n.k.	0.2	0	Dupilumab	13.4	0	0.2	0.2
11	f	26.5	Omalizumab	11.8	0	0.1	0.2	1	Dupilumab	6.1	0	n.k.	0.1
12	f	18.1	Omalizumab	2.1	0	n.k.	n.k.	1	Dupilumab	31.6	0	n.k.	n.k.
13	m	67.1	Omalizumab	8.1	0	0.2	0.3	0	Dupilumab	5.4	0	0.3	0.1
14	m	45.2	Omalizumab	11.4	0	n.k.	0.1	1	Dupilumab	18.2	0	0.9	0.7
15	f	52.7	Omalizumab	11.7	Joint pain	n.k.	0.1	1	Dupilumab	26.3	0	n.k.	n.k.
16	m	33.1	Omalizumab	19.8	0	0.3	0.2	0	Dupilumab	6.7	Keratoconjuctivitis sicca	0.2	0.2
17	f	64.9	Omalizumab	7.0	0	0.4	0.2	0	Dupilumab	6.0	0	0.2	0.3
18	f	48.0	Dupilumab	9.9	Psoriasis	0.7	n.k.	0	Omalizumab	12.8	0	n.k.	n.k.
19	m	49.6	Benralizumab	9.2	0	n.k.	n.k.	0	Dupilumab	13.6	0	n.k.	0.2
20	m	48.5	Benralizumab	6.9	0	n.k.	n.k.	0	Dupilumab	11.6	0	0.0	0.0
21	f	24.6	Mepolizumab	0.8	0	n.k.	n.k.	0	Dupilumab	15.2	0	n.k.	n.k.
22	m	62.4	Mepolizumab	29.5	0	n.k.	n.k.	0	Dupilumab	13.6	0	0.0	0.1
23	m	52.2	Mepolizumab	32.5	0	n.k.	n.k.	0	Dupilumab	6.1	0	n.k.	0.0

Ab1: first monoclonal antibody treatment, Ab2: second monoclonal antibody treatment; Eos: total eosinophil count in Giga/liter; f: female; m: male; 1: yes; 0: no; n.k: not known.

Supplementary Table 2. Response to omalizumab prior to switch to dupilumab according to EUFOREA criteria.

Patient	Reduced NPS	Improved QoL	Improved sense of smell	Reduced impact of comorbidites	Total number of fulfilled criteria
1	0	1	1	0	2
2	0	1	1	0	2
3	1	1	1	0	3
4	0	0	0	1	1
5	0	0	0	1	1
6	1	1	0	0	2
7	0	1	0	0	1
8	1	1	0	0	2
9	1	1	1	0	3
10	n.k.	1	1	0	n.k.
11	0	0	0	1	1
12	0	n.k.	n.k.	n.k.	n.k.
13	1	0	0	n.k.	n.k.
14	1	1	0	0	2
15	0	0	0	1	1
16	0	1	1	0	2
17	0	n.k.	n.k.	n.k.	n.k.

Reduced NPS: yes - if NPS reduction >1, no - if NPS reduction ≤1; improved QoL: yes - if SNOT-20 reduction ≥8.9 points, no - if SNOT-20 reduction <8.9 points; improved sense of smell: yes - if SNOT-20 item "Impaired smell" reduction >1 point, no - if SNOT-20 item "Impaired smell" reduction ≤ 1 point; reduced impact of comorbidities: yes - if ACT improved by >3 points, no - if ACT improved by ≤3 points; NPS: nasal polyp score; QoL: Quality of Life, SNOT-20: sino-nasal outcome test-20; ACT: asthma control test; 1: yes; 0: no; n.k.: not known.

Supplementary Table 3. Response to dupilumab after the switch from omalizumab according to EUFOREA criteria.

Patient	Reduced NPS	Improved QoL	Improved sense of smell	Reduced impact of comorbidites	Total number of fulfilled criteria
1	0	1	1	1	3
2	0	1	1	0	2
3	0	n.k.	1	0	n.k.
4	1	1	1	0	3
5	1	1	1	0	3
6	1	0	1	0	2
7	0	n.k.	n.k.	n.k.	n.k.
8	1	n.k.	1	0	n.k.
9	1	1	1	0	3
10	0	0	1	0	1
11	1	1	1	0	3
12	1	n.k.	n.k.	n.k.	n.k.
13	0	1	1	n.k.	n.k.
14	1	n.k.	0	0	1
15	n.k.	n.k.	n.k.	n.k.	n.k.
16	0	1	1	0	2
17	0	1	0	0	1

Reduced NPS: yes - if NPS reduction >1, no - if NPS reduction ≤1; improved QoL: yes - if SNOT-22 reduction ≥8.9 points, no - if SNOT-22 reduction <8.9 points; improved sense of smell: yes - if SNOT-22 item "Impaired smell" reduction >1 point, no - if SNOT-22 item "Impaired smell" reduction ≤ 1 point; reduced impact of comorbidities: yes - if ACT improved by >3 points, no - if ACT improved by ≤3 points; NPS: nasal polyp score; QoL: quality of life; SNOT-22: sino-nasal outcome test-22; ACT: asthma control test; 1: yes; 0: no; n.k.: not known.