Multi-centric real-world effectiveness of mepolizumab in severe chronic rhinosinusitis with nasal polyps in Germany

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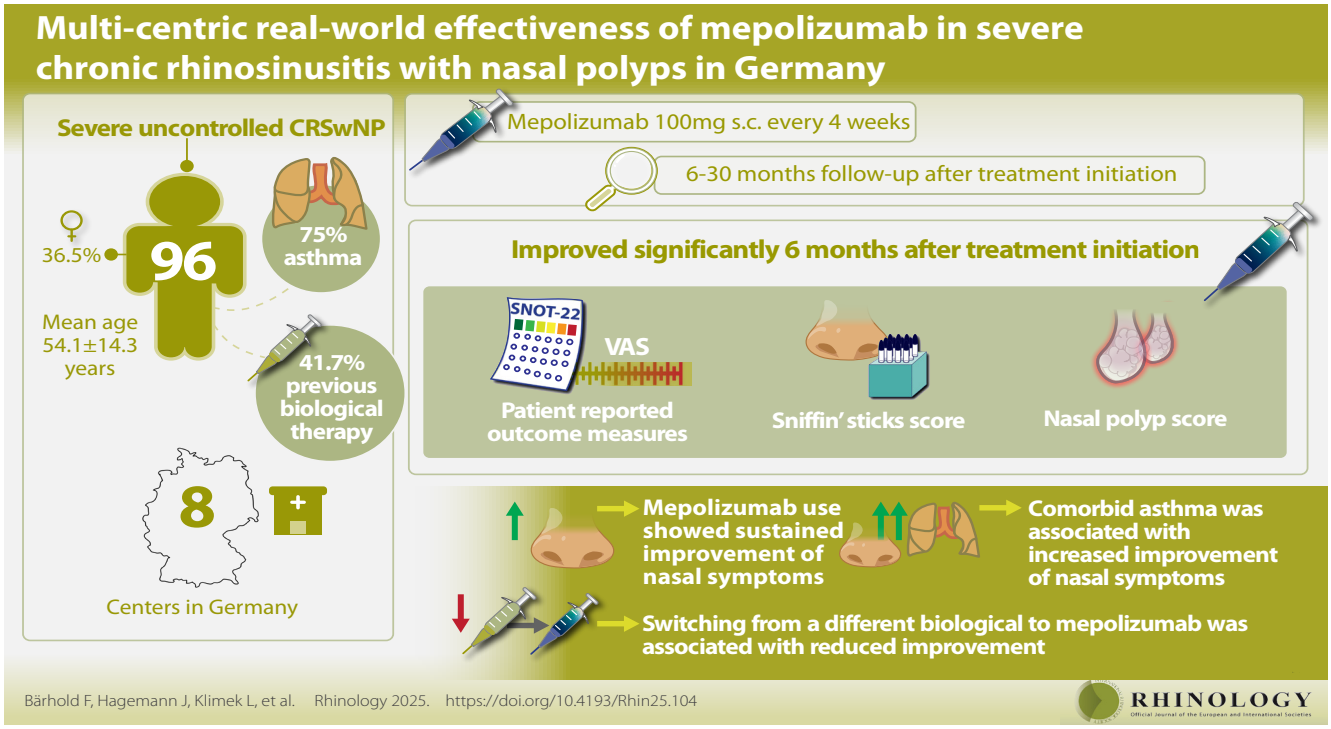
Rhinology 63: 5, 0 - 0, 2025

https://doi.org/10.4193/Rhin25.104



Abstract

Background: Within the last years, monoclonal antibodies (biologicals) have revolutionized the treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) and significantly improved symptom control in otherwise refractory cases. The effectiveness of the biological mepolizumab, an IL-5 receptor antibody, has not yet been investigated extensively. This multi-centric study assesses its impact on a large German patient cohort including biological naïve and switched patients. **Methodology**: In this retrospective multi-centric study, patients with the diagnosis of severe CRSwNP treated with mepolizumab by German tertiary referral centers were included. Data were collected retrospectively from patient records. The change from baseline regarding patient reported symptom control, serum biomarkers, nasal polyp score (NPS), and sense of smell were analysed over a course of up to 30 months. **Results**: 96 patients from 8 tertiary treatment centers were included, 36.5% female, with a mean age of 54.1±14.3 years. Patient reported outcome measures, smell, and NPS improved significantly within 6 months after treatment initiation or switch from a different biological to mepolizumab. Change from baseline in outcome parameters was smaller in the switch-group, whereas comorbid asthma indicated greater treatment success. **Conclusions**: Our real-world data show a sustained therapeutic effect of mepolizumab in CRSwNP, including a large proportion of patients who were previously treated with a different biological. This study is the largest real-world cohort to date depicting realistic treatment and disease situations, confirming a broad range of indication for mepolizumab in severe CRSwNP.

Key words: nasal polyps, biological therapy, biological switch, type 2 inflammation, quality of life

Introduction

Chronic Rhinosinusitis (CRS) is a common inflammatory disease affecting approximately 3-11% of the population in Europe [1, 2]. It is characterized by the persistence of at least two of the following symptoms for 12 weeks or more: nasal congestion, impaired sense of smell or anosmia, rhinorrhea, facial pressure or pain. Most patients suffer from the above-mentioned impairments for many years without satisfactory symptom control which leads to a high socio-economic burden for health care systems [3-5].

CRS is divided into the two phenotypes CRS without nasal polyps (CRSsNP) and with nasal polyps (CRSwNP) [6]. In contrast to CRSsNP, the inflammation in CRSwNP is driven by a type 2 response in the majority of patients, with Th2, ILC2 and Tc2 cells, IgE, eosinophils and mast cells (MCs) with interleukin (IL)-4 and IL-5, and IL-13 as the main effector cytokines [7]. In clinical routine, elevated levels of eosinophils and IgE in the blood as well as a predominantly eosinophilic infiltration in polyp tissue are used for diagnosis of this endotype [8, 9]. These patients have a higher probability of developing concomitant type 2 diseases, most commonly asthma [10]. Due to the underlying systemic mechanisms, patients with CRSwNP are also at a higher risk of experiencing disease exacerbation, leading to a higher frequency of rescue treatments, including corticosteroids (OCS) and endoscopic sinus surgery (ESS) [11, 12].

Biologicals are a new treatment option available for recurrent or refractory cases of severe CRSwNP, who are insufficiently controlled under continuous treatment with intranasal glucocorticosteroids (INCS). These monoclonal antibodies specifically block relevant type-2 inflammatory pathways. The antibodies dupilumab (anti-IL-4Rα antibody inhibiting signaling of IL-4 and IL-13), omalizumab (anti-IgE), and mepolizumab (anti-IL-5) are approved in the German market for add-on use with INCS [13-15]. Eligibility criteria for biological therapy were established by EPOS/EUFOREA in 2020 and updated in 2023 [16, 17]. Due to the high cost, biologic drugs are restricted to patients with severe CRSwNP with impaired quality of life, type 2 comorbidities, anosmia, and a history of sinus surgery or OCS treatment [17]. Until today, no reliable biomarkers exist for prediction of therapy response or for guidance with regards to which biological agent to choose. Therefore, all available biological drugs in the indication for severe CRSwNP are eligible in absence of contraindications.

mepolizumab is a humanized monoclonal antibody that specifically targets IL-5, a key cytokine involved in the differentiation, maturation, activation, and survival of eosinophils, which are implicated in the pathophysiology of CRSwNP [18, 19]. By binding to IL-5, mepolizumab inhibits its interaction with the IL-5 receptor on eosinophils, reducing their recruitment and survival, which can be measured by a decrease in blood eosinophilic count [14, 20]. The use of mepolizumab in CRSwNP was shown to reduce nasal polyp size, symptom burden, to improve sense of smell and reduced need for rescue treatments such as systemic corticosteroids or surgery in randomised controlled trials (RCT) [20-23] and real-world evidence (RWE) studies [24-26]. However, RWE on its effectiveness and safety remains limited, particularly in multicentric approaches.

RWE complements RCTs by capturing patient heterogeneity, treatment settings, and adherence in real-world practice. This study aims to provide insight into the real-world applicability, long term effectiveness and safety of the recently approved biological mepolizumab in CRSwNP.

Materials and methods

This multicentric, retrospective study collected data on the treatment effectiveness and safety of mepolizumab. Eight tertiary referral centers in Germany contributed to the study.

Primary objective and endpoints

The primary objective was to assess the treatment effectiveness and safety of mepolizumab for the treatment of CRSwNP. The primary endpoints were change from baseline in nasal polyp score (NPS), patient reported outcome measures (PROMs) (Sinonasal Outcome Test 22, SNOT22; visual analogue scale, VAS), and smell function. Secondary endpoints were overall treatment response according to the EPOS/EUFOREA update on indication and evaluation of Biologics in CRSwNP [17], and rescue treatment (OCS, ESS).

Patient population

Patients aged 18 and above with the diagnosis of severe CRSwNP and an indication for biological treatment with mepolizumab according to the German guideline were included in the study [27]. All patients received treatment with mepolizumab 100 mg subcutaneously (s.c). every 4 weeks between 2021 and 2024 with continued application of INCS.

The study conformed to the 1976 Declaration of Helsinki and was approved by the local ethics committee under the project number 873/2018BO2. All patients gave formal consent for data collection.

Data collection and outcome measures

The following data was retrospectively collected from patient files: Demographic information, type 2 comorbidities, NPS (scoring between 0 and 8, as previously established [20]), serum IgE (kU/l) and blood eosinophil count (BEC) (cells per µl), and psychophysical olfactory testing using the Sniffin' Sticks 12-Item Identification Test (SSIT12) or 16-Item Identification Test (SSIT16). For improved comparability, scores from the SSIT16 were converted based on equipercentiles to a scale of 0-12 as described by Lawton et al. [28]. Patient reported outcome measures assessed were the SNOT22 with a minimum of 0 and a maximum of 110

Table 1. Demographic data.

age [years] ± SD (n)	54.1±14.3
-female	51.2±12.2 (35)
-male	55.8±15.1 (61)
gender [%] (n)	
-female	36.5 (35)
-male	63.5 (61)
Type 2 comorbidities [%] (n)	
-Asthma	75.0 (72)
-Allergic Rhinitis	36.5 (35)
-Atopic Dermatitis	3.1 (3)
-Urticaria	1.0 (1)
-HES	1.0 (1)
Prior ESS [%] (n)	95.8 (92)
Presence of eosinophilia in histopathological examination [%]	84.4 (38)
EPOS2023 criteria met [%] (n)	
-Evidence of type 2 inflammation	88.5 (85)
-need for OCS or contraindication	87.5 (84)
-significantly impaired quality of life	94.8 (91)
-significant impairment of smell	49 (47)
-diagnosis of comorbid asthma	75 (72)
Number of EPOS2023 criteria met [%] (n)	
-1	1 (1)
-2	11.5 (11)
-3	31.3 (30)
-4	38.5 (37)
-5	17.7 (17)
-≥3	87.5 (84)

Overview of demographic data and patient history. Distribution of gender, age, and type two comorbidities within the study population. History of endoscopic sinus surgery (ESS), presence of eosinophilia in histopathological examination, and necessity of at least one course of oral corticosteroids (OCS) within the last 6 months prior to biologic treatment are shown. The percentages provided were computed based on the proportion of patients with available data. Abbreviations: HES: hypereosinophilic syndrome, ESS: endoscopic sinus surgery, OCS: oral corticosteroids.

(the higher the score, the more severe the impact on quality of life), and mean score on a visual analog scale (VAS) with scores 0-10 (10 describing maximum impact of symptoms and 0 no impact at all) rating the severity of nasal congestion, facial pain/pressure, fatigue, and rhinorrhea. For each symptom, a VAS was obtained and the overall mean used for further statistical evaluation. The outcome measures were assessed at baseline and in 6-month intervals allowing ±3 months deviation. Treatment response was assessed according to the EPOS/EUFOREA 2023 update on biologics in CRSwNP [17]. It was defined by the number of improved criteria out of the following five: reduced NPS, reduced need for OCS, improved quality of life, improved sense of smell, and reduced impact of comorbidities (0 criteria fulfilled: non-responder, 1-3 criteria: poor-moderate responder, 4-5 criteria: good-excellent responder)[17]. A relevant improvement in the respective criteria was defined as a reduction of NPS by 1, reduction of the SNOT22 score by 8.9 [29], increased SSIT12 or equally converted smell test by 2 points [30], and reduced need for OCS.

Statistical analysis

All patient data were analysed after anonymisation. Demographic data and patient history were analysed using descriptive statistics. Results are given as the mean ± standard deviation (SD) with percentages of available data points. The change from baseline was assessed using a mixed model due to missing values. Tukey correction for multiple testing was conducted. Group comparisons over time were performed using repeated measures ANOVA with gender, asthma as comorbidity, age, switch of biological, and OCS intake prior to treatment with mepolizumab as intersubject variables. Pearson's chi-squared test was calculated for dichotomous nominal data. Outliers were not excluded. Statistical significance was set at $p < 0.05$.
All statistical analyses were performed using IBM SPSS Statistics Version 28.0.0.0 (190), Armonk, NY, USA, and GraphPad Prism Version 10.4.0, Boston, MA, USA.

Results

Data from 96 patients from eight tertiary referral centers were included, 36.5% female, with a mean age of 54.1±14.3 years (males: 55.8±15.1 years; females: 51.2±12.2 years). 8 patients did not finish the 6-month interval and were therefore excluded from longitudinal analysis. All patients were diagnosed with severe CRSwNP and received mepolizumab with a mean treatment duration of 10.4±7.0 months (min: 6, max: 30).
Before administration of a biological drug, 87.5% (n=84) of patients had received at least one trial of oral corticosteroids, and 95.8% (n=92) of patients had undergone one or more sinus surgeries. 32.6% (n=30) had one surgery, 31.5% (n=29) two surgeries, and 33.7% (n=31) three or more surgeries (min. 0, max. 15, mean: 2.6±2.5), with two patients without the number of previous surgeries available. The mean time between the last surgery and treatment with mepolizumab was 6.4±5.4 years (min. 0 years, max. 23 years). Elevated eosinophil counts in histopathological examinations were observed in 38 out of 45 (84.4%) patients with prior ESS and available reports. Further demographic data and comorbidities are presented in Table 1. 41.7% (n=40) of patients had received a different biological drug prior to treatment with mepolizumab. 75.0% (n=30) had previously received dupilumab, 5.0% (n=2) omalizumab, and 17.5% (n=7) both biologicals, for one switched patient this data was not available. Although these patients had previously received a different biological, symptoms and clinical appearance of 80.0% (n=32) of patients were severe enough to formally fulfill EPOS/EUFOREA indication criteria [17] versus 91.5% in the non-switch group (n=43; only patients with data available included, data of nine patients incomplete). Five out of the eight patients in the

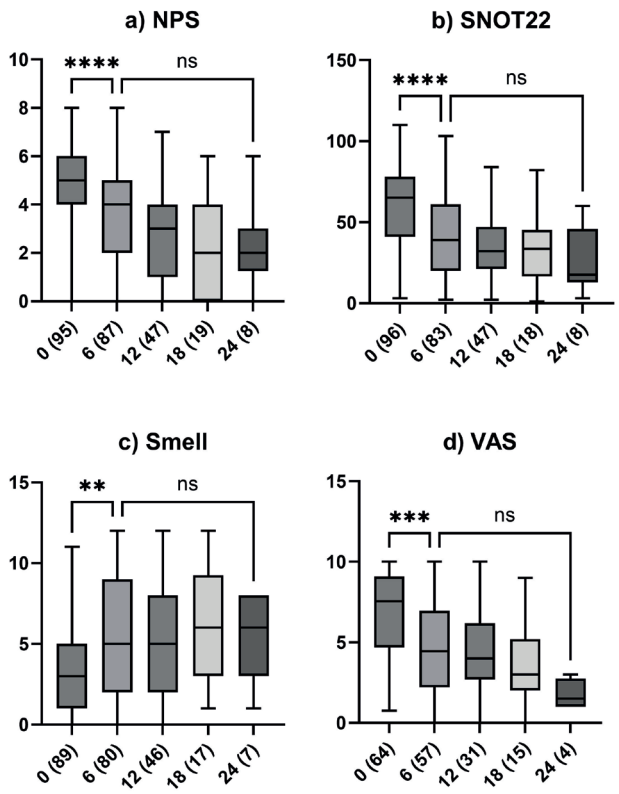


Figure 1. Change from baseline in outcome criteria. This figure contains boxplots illustrating the change over time in the following clinical outcome parameters: a) NPS, b) smell function, c) SNOT22, and d) VAS, with months from treatment initiation with mepolizumab and number of patients (n) included in the statistical analysis at the respective points of time on the x-axis. Asterisks indicate statistical significance (****: $p < 0.0001$; ***: $0.0001 < p < 0.0005$; **: $0.0005 < p < 0.005$). NPS=nasal polyp score, SNOT22=sinonasal outcome test with 22-items, VAS=visual analog scale.

switch-group who did not fulfill ≥3 criteria switched due to side effects under dupilumab, which justified the change of treatment despite previous clinical response.

Patient reported outcomes and clinical appearance

Prior to treatment with mepolizumab, the mean SNOT22 score was 59.1±23.7 (n=96), the mean VAS score was 6.9±2.6 (n=64), the mean NPS 4.7±1.8 (n=95), and the average smell score was 3.5±2.8 (n=89), with 72.0% (n=64) classifying as anosmic. Two patients had a NPS of 0 at treatment initiation with mepolizumab, but had previously received dupilumab, all other patients had endoscopically visible nasal polyps. Overall, 87.5% (n=84) of patients fulfilled at least three out of five indication criteria according to EPOS/EUFOREA [17] (Table 1), 96.9% fulfilled the indication criteria according to the German guideline [27].

After 6 months of treatment, the mean SNOT22 decreased by 16.8±23.1 points (p <0.001), VAS decreased by 2.2±3.3 points (p <0.001), the mean NPS by 1.3±2.0 points (p <0.001), and smell function increased by 2.1±4.7 points (p <0.001), with only 36.4% (n=37) still anosmic. When comparing the 6-month follow-up visit with 12, 18, and 24 months after treatment initiation, improvement can again be found for all above-mentioned items, except for the smell function. However, these effects did not reach statistical significance. The 30-month follow-up was excluded from statistical analysis due to the small sample size. For more details on longitudinal data see Figure 1.

The average improvement in outcome measures was higher in the non-switch group compared to the switch group. Still, change from baseline was significant in both groups for all evaluated criteria, except for the SNOT22 in the switch group. However, the difference between the two groups in change from baseline after 6 months was statistically significant for smell (p=0.006), OCS under biological therapy (n=15, p <0.001; exclusively patients in the switch-group received OCS during treatment with mepolizumab), SNOT22 (p=0.007), and mean VAS (p=0.016). The results are presented in Table 2.

The impact of comorbid asthma on symptom improvement was also evaluated. The change from baseline in smell function (p=0.015), SNOT22 (p=0.025), and VAS (p=0.016) was significantly higher in the asthma group compared to patients without asthma after 6 months of treatment. Further details are given in Table 3. The largest gender specific difference was the significantly greater improvement in the SNOT22 score (mean reduction: females: 24.5 points; males: 12.7 points, p=0.025).

Treatment response

Treatment response was analysed for patients with data on all 5 criteria available (n=28). 10.7% (n=3) of patients were good - excellent responders, 85.7% (n=24) poor - moderate responders, and 3.6% (n=1) non-responders after 6 months. High levels of eosinophils before treatment with mepolizumab were found to be a significantly influencing factor on treatment response (p=0.034), no effect was found for gender, switch from a different biological, and diagnosis of comorbid asthma.

Laboratory results

BEC significantly decreased compared to baseline at all follow-up examinations (-504.2±455.0/µ, p<0.001 after 6 months), which is the targeted effect of mepolizumab [14]. No significant change over time was found for IgE serum levels.

Adverse events and rescue treatment

Adverse events occurred in 13.5% (n=13) of patients. The most frequent adverse events were joint or back pain (n=3), followed by conjunctivitis (n=2). All other adverse events were reported by one patient each (allergic reaction to plasters, headache, aggravation of urticaria, itching, tendovaginitis, diarrhea, chest pressure, muscle ache, impaired vision). The adverse events led

Table 2. Group comparison switch vs. no switch.

	no switch		switch	
	Baseline (n=47)	6-month interval (n=42)	Baseline (n=40)	6-month interval (n=37)
SNOT22	63.1±22.5	40.1±24.1 (-23.0)**	52.6±24.4	46±24.8 (-6.6)*
smell score	3.3±2.6	5.9±5.2 (+2.6)*	2.9±2.3	4.2±3.7 (+1.3)*
Polyp Score	5.3±1.7	3.8±2.2 (-1.5)**	4.3±1.9	3.2±2 (-1.1)*
VAS	7.3±2.4	5.1±2.4 (-2.2)*	6.5±2.7	5.1±2.8 (-1.4)*

This table shows the outcome criteria given as means with SD comparing pre-treatment to 6 months after treatment initiation with mepolizumab divided by patients who were switched from a different biological and patients who received mepolizumab as their first biological. Data on previous biologic treatment was available from 87 out of 96 patients included in the study. The mean difference from baseline is given in brackets, statistical significance is indicated with an asterisk (*p<0.05, **p<0.001). Biological switch significantly impaired improvement in smell (p=0.008), NPS (p=0.035), VAS (p=0.016), and SNOT22 (p=0.007). Abbreviations: SNOT22: sinonasal outcome test 22, VAS: visual analogue scale, NPS: nasal polyp score 1 according to EPOS/EUFOREA guidelines [17].

Table 3. Group comparison asthma vs. no asthma.

	comorbid asthma		no asthma	
	Baseline (n=72)	6-month interval (n=64)	Baseline (n=24)	6-month interval (n=23)
SNOT22	63.6±22.6	43.4±25.6 (-20.2)**	47.1±23.8	39.7±21.5 (-7.4)*
smell score	3.6±2.6	5.9±3.9 (+2.3)**	3.0±2.5	3.1±2.8 (+0.1)
NPS	4.8±1.8	3.3±2.0 (-1.2)**	4.7±1.8	3.9±2.2 (-0.8)*
VAS	7.4±2.4	5.6±2.7 (-2.8)**	5.7±2.7	5.2±2.5 (-0.5)
Eosinophils 1/µl	637±452	108±126 (-529)**	519±494	62.5±44.8 (-457)**
Eosinophils >300/µl at baseline	62.5% (n=45)		66.6% (n=16)	
switch	42.9% (n=27)		54.2% (n=13)	

This table shows the outcome criteria given as means with SD comparing pre-treatment to 6 months after treatment initiation with mepolizumab divided by patients diagnosed with comorbid asthma versus no asthma. The mean difference from baseline is given in brackets, statistically significant results are indicated with an asterisk (*p<0.05, **p<0.001). Asthma as an intersubject variable significantly influenced improvement in smell (p=0.015), SNOT22 (p=0.025), and overall VAS (p=0.016). Abbreviations: SNOT22: sinonasal outcome test 22, VAS: visual analogue scale, NPS: nasal polyp score.

to discontinuation of treatment in 5.2% of patients (n=5). Rescue treatment was necessary for a group of 17 patients (21.3%, data available from n=80 patients), including 5 patients that underwent sinus surgery and 15 patients receiving between one and four courses of oral corticosteroids during treatment with mepolizumab. One patient had surgery because of a symptomatic mucocele, another because of suspected inverted papilloma due to single sided polyp persistence. One patient received both ESS and OCS treatment due to worsening symptoms and two patients had surgery for other reasons despite adequate treatment-response.

27 patients discontinued treatment with mepolizumab, 20 patients due to insufficient symptom control (n=10 in the switch-group and n=10 in the non-switch group), 5 patients due to adverse events, one because of both. One patient wished to switch to dupilumab, but switched back to mepolizumab after 6 months because of a significant eosinophilic leukocyte increase of >1200 cells per microliter. 21 patients switched to a different biologic drug, whereas 5 patients discontinued biologic treatment.

Discussion

This retrospective multi-centric study, which includes the largest number of patients in a RWE-study focusing on this chronic disease so far, found a sustained and significant therapeutic effect in patients with severe CRSwNP treated with mepolizumab. All investigated outcome parameters improved significantly after 6 months of treatment with further improvement of SNOT22, NPS, and mean VAS after 12, 18, and 24 months of treatment, without reaching statistical significance. Furthermore, this study presents important experiences in patients with prior type-2 biological treatment and switch of agent due to side effects or

insufficient treatment response, which to our knowledge has not been published so far.

Previous RCTs showed treatment effects similar to those observed in our study (reduction in SNOT22 by 16-23 points; present study: 16.8, reduction of symptoms on a VAS by 1.8-2; present study: 2.2, reduced NPS by 0.7-1.5; present study: 1.3) [20, 23]. The improvement of symptom scores in other RWE studies was overall greater compared to RCTs and our results (reduction in SNOT22 by 21.6-63 points, reduction of symptoms on a VAS by 3.8-4, reduced NPS by 0.9-4)[24, 31, 32].

Asthma as a relevant comorbidity may explain the greater subjective benefit in RWE studies compared to RCT, which typically include a higher percentage of patients without comorbidities. The significantly improved outcome in patients diagnosed with comorbid asthma compared to patients without asthma in the present study supports this assumption. Elevated serum eosinophils and comorbid asthma in CRSwNP patients are both currently part of the indication criteria for treatment with a biological [17], which frequently occur in combination. In the present study, pre-treatment elevated eosinophil counts were predictive of a better treatment response. However, the diagnosis of (eosinophilic) asthma might be of greater relevance than the mere elevation or consecutive reduction of eosinophils. In 2023, the indication criteria cut-off value for biologicals in CRSwNP was even reduced from 250 to 150 eosinophils/µl [17], which is in the normal range of the average laboratory reference value. Concerning the predictive value of eosinophils, the currently available literature is inconclusive. It is well established that high serum eosinophil counts are predictive of a greater treatment response with fewer exacerbations in asthmatic patients treated with mepolizumab [33, 34]. However, post hoc analysis of the SYNAPSE study demonstrated equal treatment responses in patients independent of eosinophil levels in CRSwNP (35).

The incidence of adverse events during treatment with mepolizumab was low, affecting 13.5% of patients in our cohort. No severe side effects occurred. The safety of mepolizumab is well-established and has been shown for other indications with comparable results [20, 36-38]. The known side effect of dupilumab to increase blood eosinophil counts does not occur in mepolizumab, leading to the recommendation by some authors to prefer mepolizumab over dupilumab in patients with elevated baseline BEC [39].

The indication criteria according to the German guideline differs slightly from the internationally recommended criteria by EPOS/EUFOREA, as they do not include a specific NPS or impact of type 2 comorbidities [40]. Therefore, some of the patients treated in-label in Germany might not conform to the international recommendations. For better comparability, the indication and evaluation criteria by EPOS/EUFOREA were used to further analyse the patient data.

In contrast to previous studies, our analysis included many patients (41.7%) who had switched to mepolizumab after receiving a different biological, enabling a more realistic insight into the real-world management of CRSwNP. Reasons for switching were non-response and side effects (mainly under dupilumab). The change from baseline in the switch-group did not reach the MCID for SNOT22, smell, and VAS (-6.6, 1.3, -1.4, respectively), whereas the improvement of symptoms in the biological naïve group was comparable to other RWE studies (-23.0, 2.6, -2.2, respectively; NPS reduction of 1.5). Other authors reported an overall switching rate of between 4.4% and 16.0% in a retrospective cohort, mostly from mepolizumab to dupilumab. The most frequent reason for switching off mepolizumab in those studies was poor response, whereas most patients switched off dupilumab due to side effects [41, 42]. Our cohort also contained patients that switched to mepolizumab despite sufficient treatment response with dupilumab due to side effects, explaining the smaller change from baseline in all outcome criteria for this group.

In our cohort, of the 40 patients switched to mepolizumab, 76.9% had received dupilumab, 5.1% Omalizumab, and 17.9% both biologicals. All these biologicals interfere with mediators of type 2 inflammation [7, 43] and a significant improvement for CRSwNP has been shown in several clinical trials and RWE for all of these agents.. Nonetheless, 27 patients (28.1%) terminated the treatment with mepolizumab in the present study, in most cases (78.0%, n=21) due to insufficient treatment response, which is a relatively large number. 88.5% of patients presented with a type 2 profile, all other patients with a non-type 2 or mixed endotype, making the prediction of therapy response and choice of biological a challenge. The pathophysiologic mechanisms of type 2 inflammation and the detailed molecular effect of biologic therapy are still not fully understood and require further experimental research.

When comparing the effectiveness of mepolizumab with other biologicals, the highest response rate was seen for dupilumab in RWE-studies [44]. Meta-analyses and indirect treatment comparisons concluded that all biologicals currently approved for CRSwNP account for a significant clinical benefit. The authors also reported a large variety in treatment outcomes with a slightly better response under treatment with dupilumab [45, 46]. The response rate in the present study was also lower than previously reported for dupilumab. However, subgroup analyses are necessary to provide a targeted and personalised treatment approach and thereby reduce the number of non-responders and side effects.

For a systematic comparison of treatment efficacy, it is a prerequisite to provide clear definitions of the necessary evaluation criteria with the corresponding cut-off values. However, definition of the minimal clinically important difference (MCID) on a VAS scale has only recently been defined for CRS symptoms [47], which makes the SNOT22 the more established and preferred

measure. Furthermore, PROMs, such as SNOT22 and smell scores depend on a variety of influencing factors, e.g. comorbidities and socio-economic status [48]. This leads to an increased heterogeneity of results, makes individual scores less comparable and less reliable. To better differentiate between controlled and uncontrolled CRS, Fokkens et al. (2024) proposed a binary question, which might be more practical and equally precise as VAS or SNOT22, so long as no exact cut-off points can be advised [49]. Furthermore, the MCID in NPS was suggested to be 1, but has not been validated according to gold standard [50]. Subjective measures correlate rather poorly with polyp size, but nasal polyps should still be included as relevant outcome measures as a parameter of mucosal disease. These restrictions in clear definitions and and clinical significance of parameters are also limiting the significance of the present study.

The primary limitation of this study is its retrospective design. The immunologic mechanisms influenced by biologic treatment are still not fully understood, prospective randomised and experimental trials are needed to fill in our knowledge gaps. The role of eosinophils in tissue and blood, predictive parameters of treatment response and causes of poor treatment response in eligible patients are only few of the unanswered questions. The study cohort contains many treatment discontinuations (overall 28.1% of patients), which might influence the results due to a survivorship bias.

Although this study includes a large patient cohort, it is not entirely representative of the treatment reality in Germany. The number of patients treated with a biological by a local otorhinolaryngologist has increased after the initial refusal due to concerns about recourse claims. Unfortunately, participation of private practices in clinical trials is scarce and was also not included in this study. A further limiting factor regarding data evaluation were missing values due to incomplete data sets in the primary source material.

Conclusion

This study demonstrated a significant and sustained therapeutic effect for mepolizumab in severe CRSwNP over the course of up to 30 months. All currently suggested outcome parameters improved after 6 months of treatment while at the same time presenting a good safety profile. The effectiveness was influenced by prior treatment with different type-2 biologicals and presence of comorbid asthma, nonetheless confirming a broad range of indication for mepolizumab.

Acknowledgements

None.

Authorship contribution

SB and FB conceived of the presented idea and designed the study. Data was collected and structured by all authors. Statistical analysis was performed by FB. FB drafted the first version of the manuscript, JH, LK, PH, MG, AGL, BPE, CB, TD, UF, HO, MC, NG, JM, ML, TA, CM and SB substantially contributed to the writing and correcting of the manuscript.

Conflict of interest

FB, LK, PH, TD, NG, JM, CM and ML stated no conflicts of interest. AGL received lecture fees, research fees and fees for consulting functions in advisory boards from GlaxoSmithKline GmbH & Co. KG, Sanofi Aventis Deutschland GmbH, and CSL Vivorpharm. BPE got fees for presentations, advisory boards and research from GlaxoSmithKline (GSK). CB has been a speaker/advisor for ALK-Abelló, GlaxoSmithKline (GSK), Novartis, Sanofi-Genzyme, and AstraZeneca since 2020. HO received lecture fees and fees for consulting functions in advisory boards; AstraZeneca CmbH, GlaxoSmithKline GmbH & Co. KG, Novartis Pharma GmbH, Sanofi-Aventis Deutschland GmbH. JH received speaker honoraria and fees for advisory boards from HAL Allergy, Synofi Genzyme D GmbH, GlaxoSmithKline (GSK) D GmbH, GSK Global, Novartis Pharma D GmbH, LETI Pharma, and Stallergenes outside the here-submitted work. MC received personal fees for lectures from ALK-Abelló, Allergopharma, AstraZeneca, Bencard Allergy Therapeutics, Celltrion, GlaxoSmithKline (GSK), HAL Allergy, LETI Pharma, Novartis, Roxall, Sanofi-Aventis, and Stallergenes outside the here submitted work. Other non-financial interests: German Society of Allergology (AeDA), German Society of Otorhinolaryngology, Head and Neck Surgery. MG declares consulting fees from Sanofi, GlaxoSmithKline (GSK), AstraZeneca, and Novartis. SB got fees for presentations, advisory boards and research from ALK-Abelló, Allergopharma, Allergy Therapeutics, Ambu, AstraZeneca, Altamira AG, Auris medical, Bencard Allergie, GSK, HAL Allergie, MSD, Mylan, Novartis, Sanofi-Genzyme, Stryker und Viatris. SB is Vice President of the German Society of Allergology (AeDA), Chair of the working group for clinical immunology, allergology and environmental medicine of the German Society of Otorhinolaryngology, Head and Neck Surgery and Vice-Chair of the German CRS-Registry. TA received speaker honoraria and fees for advisory boards from HAL Allergy, Sanofi Genzyme D GmbH, GlaxoSmithKline (GSK) D GmbH, Novartis Pharma D GmbH outside the here submitted work. UF received honoraria for adboards and lectures from AstraZeneca, GlaxoSmithKline (GSK), Sanofi and Novartis Pharma.

Funding

This work received no funding.

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Rhinology 63: 5, 0 - 0, 2025
https://doi.org/10.4193/Rhin24.227

Received for publication:
May 26, 2024
Accepted: April 28, 2025

Associate Editor:
Basile Landis

This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

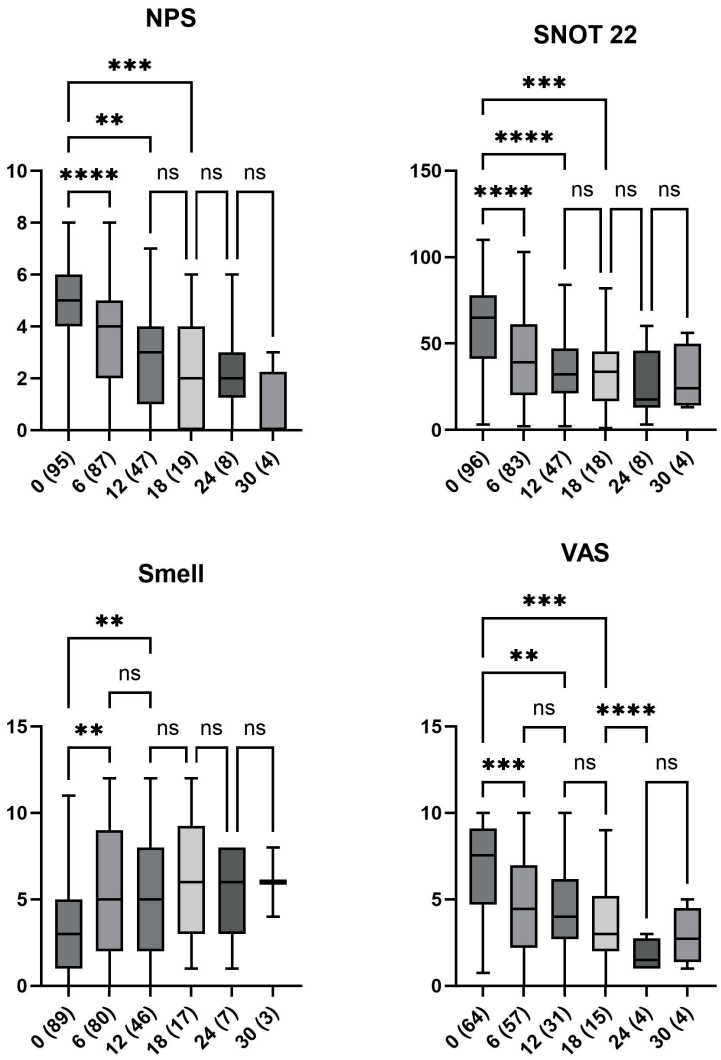

Figure S1.

PROVIDE LEGEND