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A real-life comparison of pulmonary and nasal outcomes in patients with severe asthma and nasal polyposis treated with T2-biologics

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ABSTRACT

Background: Severe asthma (SA) with comorbid chronic rhinosinusitis with nasal polyps (CRSwNP) is frequently associated with type 2 (T2) inflammatory endotype. Consequently, therapeutic targets are T2 biologics. The present retrospective study aimed to analyze and compare the clinical efficacy of mepolizumab, benralizumab, omalizumab, and dupilumab in patients with SA and comorbid CRSwNP.

Methods: 115 adult patients with SA and CRSwNP receiving 1 of the 4 biologics (mepolizumab n = 31; benralizumab n = 27; dupilumab n = 27; omalizumab n = 30) were included in the retrospective open monocentric study. Pulmonary and rhinological parameters were evaluated by Asthma Control Test (ACT), FEV1%, GINA-severity grade, rhinological questionnaires (CRS VAS-scores and sinonasal QoL RSOM-31) before and after 4–6 months of therapy.

Results: After 4–6 months of therapy, the Asthma Control Test and FEV1% significantly improved in all biologics groups ($p < 0.01$). GINA-score significantly improved in the omalizumab group only ($p < 0.01$). Overall, most nasal scores measured by VAS, total and nasal RSOM-31 subscores improved in all treatment groups ($p < 0.05$). Interestingly, the most significant differences in pre/post scores were observed in the patients receiving dupilumab, with the most notable improvement for all nasal symptoms, RSOM-31 total score, and RSOM-31 nasal subscore. There were no significant changes in the VAS scores loss of smell in the benralizumab group and postnasal drip in the mepolizumab group.

Conclusion: T2-targeting biologics effectively treat asthma in patients with severe asthma and comorbid CRSwNP. However, the efficacy of T2 biologics differs regarding the outcome in CRSwNP.

Keywords: Biologics, Severe asthma, Nasal polyps, T2 inflammation

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INTRODUCTION

Asthma is a heterogeneous chronic inflammatory disease affecting the lower airways. An estimated 400 million people worldwide have asthma,[1-3] leading to disability, impaired quality of life, and depleting health resources.[4] About 3–10% of asthma patients have severe asthma (SA),[5] defined as insufficient control of asthma under therapy with high-dose inhaled corticosteroids (ICS), long-acting beta2-agonist (LABA), long-acting muscarin-antagonist (LAMA), and additional medication (including oral corticosteroid; OCS) for at least 6 months per year, or by insufficient asthma control when high-intensity treatment is reduced.[5-9] Approximately 50–70% of the patients have type 2 asthma,[6,10,11] including eosinophilic and allergic asthma phenotypes.[10] Type 2 inflammation is defined by elevated fractional exhaled nitric oxide (FeNO) equal to or over 20 ppb; and/or blood eosinophils $\geq$150/µl; and/or elevated total IgE; and/or asthma that is clinically allergen-driven; and/or that requires OCS.[2] Clinical effects of therapies with type 2-targeting biologics mepolizumab or reslizumab (anti-IL-5 antibodies), benralizumab (anti-IL-5 Rα antibody), dupilumab (anti-IL-4Rα antibody inhibiting signaling of IL-4 and IL-13), and omalizumab (anti-IgE antibody) have shown efficacy in several placebo-controlled studies in asthma patients.[12-20] Response to biological treatments is evaluated after 4–6 months, and if treatment is considered adequate, it should be continued and re-evaluated every 4–6 months.[5,6,8]

Many patients with chronic rhinosinusitis with nasal polyps (CRSwNP) have a T2-driven endotype.[21-24] In 70% of these cases, the CRSwNP phenotype is associated with asthma.[25,26] Furthermore, up to 40% of patients with severe late-onset asthma have nasal polyps.[23,27-31]

There is a lack of head-to-head trials that include severe asthma patients with comorbid CRSwNP and comparing treatment outcomes with mepolizumab, benralizumab, dupilumab, and omalizumab with a detailed examination of nasal symptoms. A non-controlled, real-life, retrospective monocentric study was performed to evaluate pulmonary and nasal effects during treatment with T2-targeting biologics in 115 patients with severe asthma and comorbid nasal polyposis.

MATERIALS AND METHODS

Patients

Included patients were aged 18 years or older with severe asthma in use of biologic therapy according to pulmonologist-based standard recommendation. Patients were in use of T2-biologics as follows: mepolizumab n = 31; omalizumab n = 30; benralizumab n = 27; dupilumab n = 27. At the time of initiation of biologics, the patients received a high dose of ICS, LABA, and LAMA. Some of them also received OCS (see Fig. 2).

Patients with comorbid chronic rhinosinusitis with nasal polyps (CRSwNP) according to EPOS (European Position Paper on Rhinosinusitis and Nasal Polyps) criteria[21] were enrolled. All patients had a positive history of nasal sinus surgery due to nasal polyps.

Inclusion criteria for T2-biologics

Severe uncontrolled asthma according to Global Initiative for Asthma (GINA) step 5 following national and international asthma guidelines:[2,5,8]

For mepolizumab and benralizumab treatment.

- Severe eosinophilic asthma with two measurements of elevated eosinophils in peripheral blood (>300 eosinophils/µl) measured within the last two years, excluding blood counts during disease exacerbation;

For dupilumab treatment.

- Severe eosinophilic asthma with two measurements of elevated eosinophils in peripheral blood (>300 eosinophils/µl) measured within the last two years, excluding blood counts during exacerbations or two measurements of elevated FeNO concentrations (>20 ppb);

For omalizumab treatment.

- Severe IgE-mediated allergic asthma with sensitization to perennial aeroallergen;
- Dosage selection: total IgE values and weight according to the protocol of the manufacturer's instructions;

Exclusion criteria

Age less than 18 years.

Inability to complete questionnaires, immunodeficiency, pregnant or lactating female patients.

METHODS

Design of the study

This monocentric study recruited patients from 2012 to 2021. The local ethics committee approved the retrospective monocentric study (permit number EA 1/098/18). Standardized pulmonary examinations and therapies were performed in the local Comprehensive Allergy Center. Oto-rhino-laryngology (ORL) specialists of the Comprehensive Allergy Center confirmed the diagnosis of CRSwNP in all cases. Only patients who completed at least 4–6 months of therapy with 1 of the 4 target drugs were included.

Medical history

Age, gender, CRSwNP, and the number of nasal sinus surgeries for nasal polyps were evaluated. Further characterization of the phenotype data about frequencies of other comorbidities like nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD), eosinophilic granulomatosis with polyangiitis, or urticaria are summarized for the 115 included patients in Table 1.

Pulmonary parameters

Administration of asthma medication was recorded according to Global Initiative for Asthma (GINA).[5] The asthma control test (ACT)[32] and spirometric measurements (forced expiratory volume in 1 s, FEV1%) were assessed.

Rhinological parameters

The visual analogue scales (VAS) for chronic rhinosinusitis symptoms as blocked nose, runny nose, postnasal drip, and loss of smell with a maximum score of 100 were performed.[21] The sinonasal QoL was measured with the Rhinosinusitis Outcome

	Mepolizumab	Benralizumab	Dupilumab	Omalizumab
Sociographic parameters				
Number of patients	31	27	27	30
Age (*Y*), median	61	61	60	58
Sex: female, *n* (%)	18 (58)	9 (33)	17 (63)	17 (57)
Clinical parameters of phenotype				
Asthma, *n* (%)	31 (100)	27 (100)	27 (100)	30 (100)
CRSwNP, *n* (%)	31 (100)	27 (100)	27 (100)	30 (100)
Number of Nasal sinus surgeries, median (minimum/maximum)	2.4 (Min 1; Max 10)	2.4 (Min 1; Max 7)	2.8 (Min 1; Max 9)	2.7 (Min 1; Max 9)
N-ERD, *n* (%)	16 (52)	12 (44)	17 (61)	16 (52)
Eosinophilic granulomatosis with polyangiitis, *n* (%)	3 (10)	4 (15)	1 (4)	13 (43)
Urticaria, *n* (%)	4 (13)	5 (17)	3 (11)	5 (16)
Laboratory parameters of endotype				
Eosinophils (cells/μL), median (SD)	448 (298)	800 (327)	585 (278)	270 (486)
Total IgE (kU/l), median (SD)	342 (76.37)	147 (3206.86)	367 (297.84)	472 (125.69)
Positive specific IgE to aeroallergens, *n* (%)	10 (32)	13 (48)	14 (52)	30 (100)

Table 1. Clinical characteristics of patients at study baseline *CRSwNP: Chronic Rhinosinusitis with Nasal Polyps; N-ERD: Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)-Exacerbated Respiratory Disease; Min: Minimum; Max: Maximum; n: Number; SD: Standard Deviation.*

Measure-31 (RSOM-31) questionnaire[33] consisting of seven domains (nose, eye, sleep, ear, general symptoms, practical problems, and emotional consequences). The product of the magnitude scale (score ranging from 0 to 5, with 0 indicating "no complaints" and 5 "the worst imaginable complaints") and importance scale (score ranging from 1 to 4, with 1 indicating "not important" and 4 indicating "very important") creates the symptom-impact score of each item with mean symptom impact sub-scale scores and mean total scores.[33,34]

LABORATORY PARAMETERS

Total and specific IgE levels to seasonal/perennial aeroallergens according to the Global Asthma

	Mepolizumab			Benralizumab			Dupilumab			Omalizumab		
	Pre	Post	P	Pre	Post	P	Pre	Post	P	Pre	Post	P
ACT Median (SD)	15 (5.0)	20 (4.8)	***	14 (5.6)	20 (4.05)	***	15 (5.4)	23 (4.1)	**	12 (5.2)	19 (5.3)	***
FEV1 (%) Median (SD)	61 (17.8)	73 (22.3)	**	55 (14.9)	71 (19.1)	***	60 (19.3)	79 (14.0)	***	60 (15.4)	66 (16.2)	**
GINA-Steps Median (SD)	5 (0.5)	5 (1.0)	n.s.	5 (0.7)	4 (1.0)	n.s.	4 (0.8)	4 (1.1)	n.s.	5 (0.4)	5 (1.0)	**
VAS-Blocked nose Median (SD)	60.0 (31.1)	20.0 (21.8)	***	50.0 (22.8)	30.0 (25.0)	**	60.0 (23.0)	10.0 (11.0)	***	80.0 (26.9)	43.5 (33.2)	***
VAS-Loss of smell Median (SD)	90.0 (37.7)	40.0 (42.0)	**	80.0 (36.4)	80.0 (37.8)	n.s.	70.0 (39.4)	5.0 (29.9)	***	90.0 (39.3)	65.0 (39.8)	***
VAS-Runny nose Median (SD)	40.0 (25.0)	20.0 (20.7)	***	20.0 (33.8)	10.0 (29.0)	*	50.0 (27.8)	5.0 (14.6)	***	50.0 (29.8)	30.0 (27.4)	**
VAS-Postnasal drip Median (SD)	30.0 (25.1)	20.0 (25.0)	n.s.	20.0 (31.1)	2.0 (24.8)	*	50.0 (25.4)	5.0 (12.1)	***	60.0 (31.0)	35.0 (27.0)	**
RSOM-31 Nose Median (SD)	5.4 (3.8)	1.9 (2.2)	***	4.4 (3.8)	2.5 (2.6)	***	8.9 (3.9)	0.8 (0.8)	***	9.3 (4.8)	6.2 (4.4)	***
RSOM-31 Eye Median (SD)	0.5 (1.3)	0.0 (2.2)	n.s.	0.0 (2.4)	0.0 (1.2)	*	1.0 (1.4)	0.0 (0.4)	***	1.5 (5.3)	1.0 (2.9)	n.s.
RSOM-31 Sleep Median (SD)	9.0 (7.0)	2.0 (4.3)	***	13.8 (6.5)	1.0 (3.3)	***	9.0 (4.5)	1.0 (2.4)	***	9.0 (6.3)	4.0 (6.9)	**
RSOM-31 Ear Median (SD)	0.0 (3.6)	0.0 (2.3)	n.s.	0.0 (2.5)	0.0 (2.3)	n.s.	0.6 (4.1)	0.0 (1.1)	**	1.0 (3.6)	0.0 (3.2.)	n.s.
RSOM-31 General Median (SD)	9.0 (4.7)	1.1 (2.8)	***	8.1 (3.8)	1.1 (2.6)	***	8.9 (4.3)	0.9 (0.4)	***	10.3 (4.1)	4.0 (4.5)	***
RSOM-31 Practical problems Median (SD)	2.0 (2.9)	1.0 (2.2)	***	3.2 (1.1)	3.2 (1.9)	***	5.2 (2.2)	0.5 (0.4)	***	5.3 (6.1)	4.0 (5.3)	**
RSOM-31 Emotions Median (SD)	4.0 (3.8)	1.0 (2.2)	***	0.7 (0.3)	1.0 (0.7)	*	1.0 (1.9)	0.0 (0.5)	n.s.	8.0 (5.7)	3.0 (7.0)	n.s.
RSOM-31 Total Score Median (SD)	5.5 (2.7)	1.6 (1.6)	***	5.0 (2.0)	1.4 (1.9)	***	5.9 (2.3)	0.8 (0.4)	***	8.0 (3.4)	4.4 (3.7)	***

Table 2. Pulmonary and rhinological parameters before and after 4–6 months of treatment with T2 biologics mepolizumab, benralizumab, dupilumab, or omalizumab. Pneumological and rhinological parameters significantly improve in SA patients with CRSwNP *SA: Severe Asthma, CRSwNP: Chronic Rhinosinusitis with Nasal Polyps; ACT Asthma Control-Test; FEV1 Forced Expiratory Volume in 1 Second; GINA: Global Initiative for Asthma; VAS: Visual Analogue Scale; RSOM: Rhinosinusitis Outcome Measurement; SD Standard Deviation; P: P-value; *<0.05; **<0.01; ***<0.001.*

and Allergy European Network (GA2LEN) allergy diagnostic panel[35] and eosinophils were examined in peripheral blood.

Therapy with biologics

The standard pulmonary therapy with mepolizumab, benralizumab, dupilumab, and omalizumab was administered according to the drug approval standard protocols.

Time of examinations

According to national and international asthma guidelines,[5,8] we evaluated patients before and after 4–6 months of biologic therapy.

Evaluation of oral corticosteroids (OCS) under T2 biologics

The number of patients receiving OCS and the daily OCS dosage before and 4–6 months of biologic therapy were evaluated.

STATISTICS

Nonparametric tests (Friedman for more than 2 groups, Wilcoxon for pairwise comparison) were used for the comparison of the values of ACT-, FEV1-, GINA-, VAS-, and RSOM-31- scores ($p < 0.05$). Baseline values were compared with those after 4–6 months of treatment. The nonparametric Kruskal-Wallis test was used to test the effects of the different medications. Pairwise comparisons of therapy groups were performed if a significance level ($p < 0.05$) was reached. An alpha adjustment, according to Bonferroni, was applied (Bonferroni correction).

RESULTS

Spirometric measurements

FEV1% improved significantly in all biologic groups; mepolizumab $p = 0.004$ (pre median (Med) 61%/post Med 73%), benralizumab $p = 0.000$ (pre Med 55%/post 71%); dupilumab $p = 0.000$ (pre Med 60%/post 79%), and the omalizumab group $p = 0.002$ (pre Med 60%/post 66%) (see Table 2).

Asthma control test (ACT)-score

The ACT-score improved significantly in the mepolizumab (pre Med 15/post Med 20; $p = 0.000$), benralizumab (pre Med 14/post Med 20; $p = 0.000$) and omalizumab groups (pre Med 12/post Med 19; $p = 0.000$) and in the dupilumab group (pre Med 15/post Med 23; $p = 0.002$) (see Table 2).

GINA-severity

GINA-score improved significantly in the omalizumab group (pre 4.7/post MV 4.3; $p = 0.004$) and differed not significantly in the other groups (mepolizumab $p = 0.086$ pre Med 5/post Med 5; benralizumab $p = 0.125$ pre Med 5/post Med 4; dupilumab $p = 0.063$; pre Med 4/post 4, see Table 2).

Rhinological VAS-scores and RSOM-31

Rhinological VAS-scores

All examined sinonasal VAS-values for the parameters blocked nose, loss of smell, runny nose, and postnasal drip were significantly improved in the dupilumab and omalizumab groups. All values comparing data before and after treatment were reduced significantly in the dupilumab group ($p = 0.000$). Within the omalizumab group, all compared values were significantly lower after treatment, $p = 0.000$, and $p = 0.014$ for postnasal drip. In the mepolizumab group, the scores for blocked nose, loss of smell, and runny nose improved significantly ($p = 0.000$); postnasal drip differed not significantly. In the benralizumab group, the parameters blocked nose ($p = 0.003$), runny nose ($p = 0.018$), and postnasal drip ($p = 0.026$) improved significantly. In contrast, loss of smell ($p = 0.092$) did not differ significantly after 4–6 months of therapy (Table 2).

Rhinological QoL Rhinosinusitis Outcome Measure (RSOM)-31

The sinonasal QoL RSOM-31 total score improved significantly in all treatment groups after 4–6 months of biologics treatment ($p = 0.000$). The nasal symptom impact sub-scale score improved significantly in all treatment groups ($p = 0.000$), and the sleep symptom impact sub-scale score improved significantly in the mepolizumab, benralizumab, dupilumab (all three: $p = 0.000$), and omalizumab group ($p = 0.001$). Scores for eye symptoms improved significantly in the benralizumab and dupilumab group ($p = 0.021$; $p = 0.000$) and ear symptoms in the dupilumab group only ($p = 0.003$). All therapy groups significantly improved

in the scores for practical problems ($p = 0.000$). General problems also significantly improved (mepolizumab, benralizumab, dupilumab - all $p = 0.000$ and omalizumab $p = 0.005$). Scores reflecting emotional consequences were significantly reduced in the mepolizumab ($p = 0.000$) and benralizumab groups ($p = 0.012$), while in dupilumab and omalizumab groups, no significant differences were detectable ($p = 0.129$ and $p = 0.055$, respectively) (Table 2).

Pairwise comparison of pre/post differences of pulmonary and rhinological parameters

Pre/post differences in pulmonary and rhinological parameters are presented in Fig. 1. Pairwise comparison of pulmonary and nasal effects of the different T2 biologics revealed no significant differences in the pulmonary parameters (Table 3). The nasal parameters differed significantly between dupilumab and the other T2 biologics (Table 3). "Nasal obstruction" scored significantly better in the mepolizumab than in the benralizumab group. "Emotions" were rated significantly worse in the dupilumab than in the mepolizumab group; "Emotions" were rated significantly better in the mepolizumab and the omalizumab groups than in the benralizumab and group (Table 3).

Oral corticosteroids under T2 biologics

In the mepolizumab group, the number of patients (%) receiving OCS decreased from baseline 18/31 (58%) to 15/31 (48%) following 4–6 months. In the benralizumab group, the number of patients decreased from baseline 13/27 (48%) to 10/27 (37%). In the dupilumab group, the number of patients decreased from 10/27 (37%) to 5/27 (19%), and in the omalizumab group, from 12/30 (40%) to 7/30 (23%). In all therapy groups, the median daily dosage of OCS decreased under therapy without reaching a significance level (Fig. 2). It is of notice that benralizumab showed a statistical trend $p = 0.054$.

Safety aspects

Patients tolerated the therapies with mepolizumab, benralizumab, dupilumab, or omalizumab well. There was no need for nasal sinus surgery during the treatment period.

DISCUSSION

The present study is, to our knowledge, the first real-life monocentric open retrospective indirect comparison of T2-targeting biologic therapies with mepolizumab, benralizumab, dupilumab, or

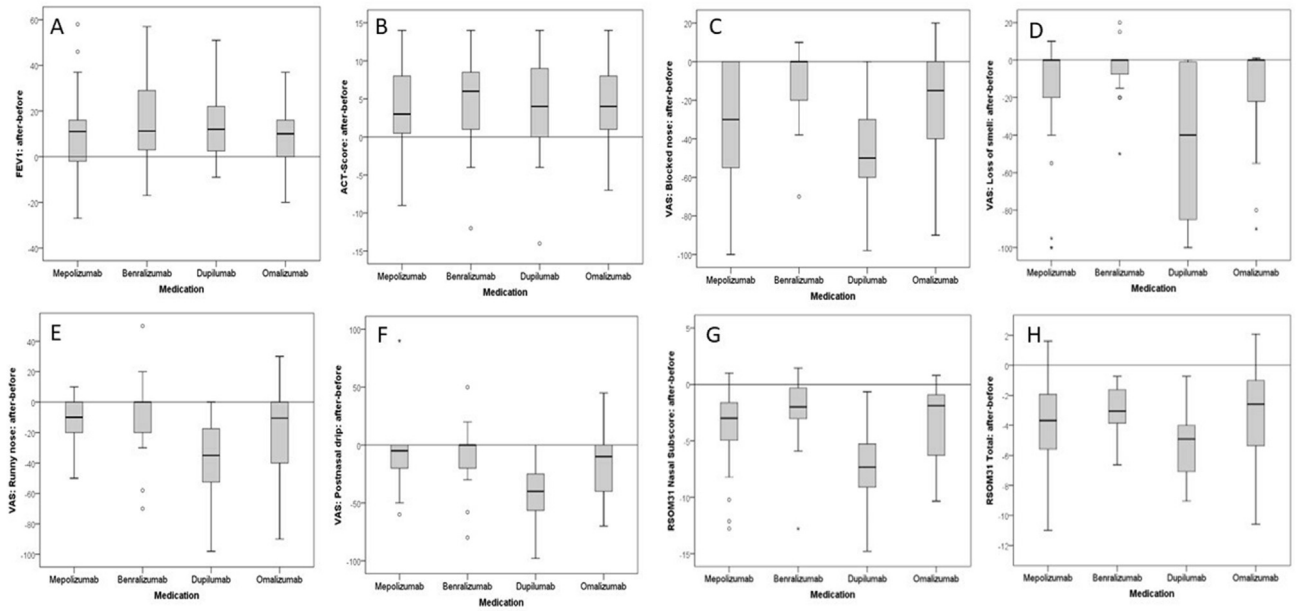

Fig. 1 Differences (in %) in pulmonary (A FEV1; B ACT-Score) and rhinological parameters (C VAS-Score Blocked nose; D VAS-Score Loss of smell; E VAS-Score Runny nose; F VAS-Score Postnasal drip; G RSOM-31 Nasal subscore; H RSOM-31 Total score) after 4–6 months of T2 biologics reveal the greatest changes in nasal parameters in the dupilumab group compared to baseline. FEV1: Forced Expiratory Volume in 1 Second; ACT: Asthma Control-Test; VAS: Visual Analogue Scale; RSOM: Rhinosinusitis Outcome Measurement.

Parameters	Sig-Total	D vs M	D vs O	D vs B	M vs O	M vs B	O vs B
ACT-Score: after-before	0.984	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
FEV1: after-before	0.658	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
GINA-Score: after-before	0.614	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
VAS: Blocked nose: after-before	0.000	**n.s.**	*	***	**n.s.**	*	**n.s.**
VAS: Loss of smell: after-before	0.000	*	*	***	**n.s.**	**n.s.**	**n.s.**
VAS: Runny nose: after-before	0.000	**	*	***	**n.s.**	**n.s.**	**n.s.**
VAS: Postnasal drip: after-before	0.000	***	**	***	**n.s.**	**n.s.**	**n.s.**
RSOM-31 Nasal Subscore: after-before	0.000	**	***	***	**n.s.**	**n.s.**	**n.s.**
RSOM-31 Eyes Subscore: after-before	0.038	**n.s.**	*	**n.s.**	**n.s.**	**n.s.**	**n.s.**
RSOM-31 Sleep Subscore: after-before	0.142	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
RSOM-31 Ears Subscore: after-before	0.207	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
RSOM-31 General: after-before	0.115	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
RSOM-31 Practical Problems: after-before	0.001	***	**	*	**n.s.**	**n.s.**	**n.s.**
RSOM-31 Emotions: after-before	0.000	**	**n.s.**	**n.s.**	**n.s.**	***	***
RSOM-31 Total: after-before	0.003	**n.s.**	**	**	**n.s.**	**n.s.**	**n.s.**

Table 3. Differential effects of the T2 biologics mepolizumab, benralizumab, dupilumab, and omalizumab in SA patients with CRSwNP. For the pulmonary parameters, no significant results were detectable. The nasal parameters in the dupilumab group were scored significantly better than the other T2 biologics. Statistics: Pairwise comparisons were performed if the Kruskal-Wallis test was significant ($p < 0.05$). A Bonferroni correction was applied *FEV1: Forced Expiratory Volume in 1 Second; ACT: Asthma Control Test; VAS: Visual Analogue Scale; RSOM: Rhinosinusitis Outcome Measurement; SA: Severe Asthma, CRSwNP: Chronic Rhinosinusitis with Nasal Polyps; M = mepolizumab; B = benralizumab; D = dupilumab; O = omalizumab; sig = significance; green: better effect for first drug vs second drug; orange: worse effect for first drug vs second drug; n.t. = not tested; n.s. = not significant; vs = versus; * = p < 0.05; ** = p < 0.01; *** = p < 0.001.*

omalizumab in patients with SA and CRSwNP analyzing detailed nasal symptoms.

After 4–6 months of biologic therapy, all therapy groups had significantly improved pulmonary parameters ACT and FEV1%. Both parameters are critical for asthma patients because they mirror the improvement in asthma control and a significant reduction in bronchial obstruction. The improvement of FEV1 as a result of the biologics reached the minimal clinically relevant difference of 10.4%;[36] reflecting an increase in patients' daily quality of life. Interestingly, we have not identified other publications dealing with

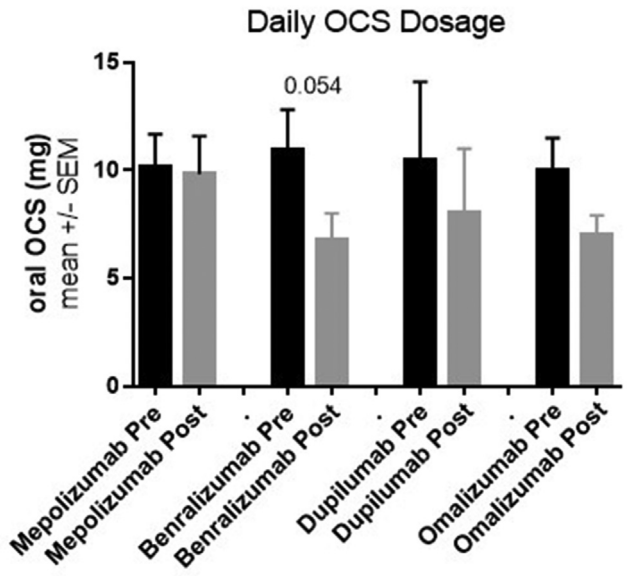

Fig. 2 The daily dosis (in mg) of oral corticosteroid (OCS) therapy of patients decreases in the treatment groups after 4–6 months without reaching significance level. It is of notice that benralizumab showed a statistical trend $p = 0.054$.

biologics' efficacy in SA that documented this parameter. GINA-score significantly improved in the omalizumab group. The daily OCS dosage was reduced in all treatment groups (see Fig. 2). Different nasal scores measured by VAS improved in most of the treatment groups. Additionally, all therapy groups significantly improved the total score and nasal subscore of Rhinonasal QoL (RSOM-31). Interestingly, the highest differences in pre/post scores for nasal parameters were seen in the dupilumab group (Fig. 1; Table 3).

Several biologics have been approved for T2-driven SA targeting the overlapping allergic and eosinophilic phenotypes. All of the biologics interfere with the adaptive T2 immune response: the IL-5 pathway (mepolizumab, benralizumab), the IL-4/IL-13 pathway (dupilumab), and the IgE pathway (omalizumab).[3]

Previous studies of mepolizumab, benralizumab, dupilumab and omalizumab in SA reported fewer exacerbations, improved health-related QoL scores, asthma control, and FEV1.[6] The present study showed a significant improvement after 4–6 months of biologics therapy. The response of T2-targeting biologics to bronchial parameters was comparable in all groups without significant differences in the pairwise comparison (Fig. 1, Table 3), which is also confirmed by meta-analyses comparing the therapeutic effects of various biologics in SA.[37,38] Our study focused on an asthma phenotype with comorbid nasal polyps associated with a T2 inflammatory endotype.[25,26]

Significant improvements in the VAS scores reflecting nasal symptoms such as olfactory disorders, blocked nose, and runny nose were seen after treatment with any of the four T2-targeting biologics. However, there were no significant changes in subjective olfactory abilities in the benralizumab group and no significant changes in postnasal drip after treatment with mepolizumab.

The total score and the nasal subscore of the rhinonasal QoL questionnaire RSOM-31 indicated significant improvements after treatment with all 4 biologics. Similarly, RSOM-31 subscores of the subdomains sleep, general and practical problems significantly improved in all therapy groups, similar to improved health-related QoL in patients with SA and self-reported nasal polyps reported by studies with dupilumab or benralizumab.[39,40]

The most striking improvements in nasal complaints of pre-/post comparisons and pairwise differences were found after treatment with dupilumab (see Fig. 1 and Table 3). Only the emotional subscore was significantly worse in the dupilumab group than in the mepolizumab group. Our results must be evaluated cautiously since the nasal polyp-score was not performed during treatment. However, we included in the study only patients diagnosed with nasal polyps by board-certified ORL specialists, and all of the patients had undergone sinus surgery due to nasal polyps prior to the start of biologic treatment.

Placebo-controlled phase-3 studies of mepolizumab, benralizumab, dupilumab, and omalizumab were performed for patients with CRSwNP.[41–44] Only patients with severe uncontrolled CRSwNP were included in these studies. In the published studies, asthma was an optional inclusion criterion, and patients with a SA were not included. These phase-3 studies showed significant improvements in nasal parameters, including nasal polyp-scores.

In recent meta-analyses, therapeutic effects of mepolizumab, dupilumab, benralizumab, and omalizumab in CRSwNP were compared.[45–47] The

most significant results for nasal parameters, including the nasal polyp-scores, were found for treatment with dupilumab, as confirmed by our study using real-life data. Our observations were similar to a small multicentric retrospective head-to-head study of SA patients with comorbid asthma (combined group of mepolizumab/benralizumab n = 26; dupilumab n = 15 and omalizumab n = 9), where also nasal symptoms improved mainly in the dupilumab group. However, as in our study, the authors used a general VAS score (VAS nasal symptoms) without further nasal differentiation. The rhinonasal QoL questionnaire Sino-Nasal Outcome-Test (SNOT)-20 improved significantly, similar to the RSOM-31 used in our study.[48]

In the present study, no side effects were found for the biologicals used during the 4–6 months of treatment. Due to the retrospective character of the study and the inclusion criteria of a treatment period of 4–6 months, disruption of the treatment due to side effects is not recorded in this study.

CONCLUSIONS

All tested T2-targeting biologics showed a similar response regarding pulmonary parameters. However, there was a significantly better response to dupilumab in rhinological parameters in the CRSwNP phenotype. This observation should be further investigated in randomized, double-blind follow-up studies with the inclusion of nasal polyp scores since indirect comparisons of therapies can be biased. T2-targeting biologics represent efficient therapies regarding pulmonary and rhinological parameters in the SA phenotype with comorbid CRSwNP. Our results imply that the efficacy of biologics differs regarding nasal parameters, but further studies are needed. Currently, an individualized patient-centered approach can be recommended.

Abbreviations

ACT, Asthma Control-Test; B, Benralizumab; CRS, Chronic rhinosinusitis; CRSwNP, Chronic Rhinosinusitis with Nasal Polyps; D, Dupilumab; EPOS, European Position Paper on Rhinosinusitis and Nasal Polyps; FENO, Fractional exhaled nitric oxide; FEV1, Forced Expiratory Volume in 1 Second; GINA, Global Initiative for Asthma; ICS, Inhaled corticosteroids; IL, Interleukin; LABA, Long-acting beta2-agonist; LAMA, Long-acting muscarin-antagonist; M, Mepolizumab; Max, Maximum; Med, Median; Min, Minimum; N-ERD, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)-Exacerbated Respiratory Disease; n, Number; n.t, Not tested; n.s., Not significant; O, Omalizumab; OCS, Oral corticosteroid; P, P-value; RSOM, Rhinosinusitis Outcome Measurement; QoL, Quality of life; SA, Severe Asthma; SD, Standard Deviation; Sig, Significance; T2, Type 2 inflammation; VAS, Visual Analogue Scale; Vs, Versus

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Availability of data and materials

Data and materials are available.

Credit author statement

Ulrike Förster-Ruhrmann (MD): 1. The conception and design of the study, data acquisition and analysis and interpretation of data, 2. Drafting the article and revising it critically for important intellectual content, 3. Final approval of the version to be submitted.
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Ethics statement

This study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The local ethics committee approved the retrospective monocentric study (permit number EA 1/098/18).

Conflict of interest

Fees from AstraZeneca, GSK, Novartis and Sanofi for adboards, meetings and lectures; Intakt-BMBF Grant, outside of this work. European Commission Action HORIZON 2020, TIN-ACT (Research School for TINnitus Assessment, Causes and Treatments) grant number 764604/ESR11, outside of this submitted work. No financial support for this project. Member of the Allergy Board of the German ENT-Society. No financial support for this submitted project.
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Submission declaration

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