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RESEARCH ARTICLE

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Improvement in health-related quality of life questionnaires with biologic treatment in severe asthma and comorbid chronic rhinosinusitis with or without nasal polyposis: a real-life experience

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ABSTRACT

Background: Patients with severe asthma frequently have comorbid chronic rhinosinusitis (CRS) with or without nasal polyps, that can increase the symptom burden and complicate treatment. Real-life clinical data on the impact of biologic treatments on CRS-specific quality-of-life questionnaires are still lacking.

Materials and methods: In this retrospective real-life study, we collected data from patients with severe asthma with comorbid CRS with/without nasal polyposis at baseline, and after 3, 6 and 12 months of treatment with omalizumab, mepolizumab, benralizumab or dupilumab. In particular, we evaluated improvements in HRQoL as measured by SinoNasal Outcome Test-22 (SNOT-22, 0 – 110), Visual Analog Scale symptom scores (VAS, 0–10), and Asthma Control Test (ACT, 5–25) and the proportion of patients meeting the minimal clinically important difference (MCID).

Results: Disease-specific HRQoL, as measured by SNOT 22 and VAS score improved in all patients at 3, 6, and 12 months of treatment compared with baseline (SNOT-22: 14, IQR: 0–52 vs 10, IQR:0–30 vs 0, IQR:0–15 vs 0, IQR:0–12, $p < 0.001$, VAS score: 1, IQR: 0–5 vs 0, IQR:0–3 vs 0, IQR:0-2 vs 0, IQR 0–1, $p < 0.001$). After 3 months of treatment >80% of patients reached the MCID for ACT, while only patients on dupilumab showed to reach a MCID in 100% of cases. The effect size depended upon the symptom burden at baseline.

Conclusions: The study confirms the efficacy of omalizumab, mepolizumab, benralizumab, and dupilumab in a real-life setting, with a rapid improvement in CRS-specific HRQoL and general health status. These data highlight the importance of targeting type 2 inflammation in asthmatic patients with co-existing upper and lower airways disease.

The Authors disclose that preliminary data and analysis of the present study have been presented in abstract form during the "X International Workshop on Lung Health – Respiratory Disease and Immune Response", held in Nice on 19–21 January 2023.

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Introduction

Severe asthma is a complex and heterogeneous disease of the airways that affects approximately 5–10% of patients with asthma [1]. Severe asthma is defined as asthma that remains uncontrolled despite optimized treatment with high-dose ICS-LABA, or that requires high-dose ICS-LABA to prevent it from becoming uncontrolled [1]. Severe asthma is associated with an ongoing and burdensome symptom profile, frequent asthma attacks and multiple comorbidities. Patients with asthma frequently have comorbid chronic rhinosinusitis (CRS) with or without nasal polyps, which worsens the disease burden and often hinders the treatment response. In these conditions chronic inflammation has a crucial role, and targeting the underlying immunological mechanisms that sustain the inflammatory response has been

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Table 1. Current indications for different biologic treatments for severe asthma. CRSwNP: chronic rhinosinusitis with nasal polyposis; EGPA: eosinophilic granulomatosis with polyangiitis; IV: intravenous; SC: subcutaneous.

Class	Agent name	Age	Asthma indication	Other indications
Anti-IgE	Omalizumab (SC)	≥6 years	Severe allergic asthma	Nasal polyposis, chronic spontaneous urticaria
Anti-IL5	Mepolizumab (SC)	≥6 years	Severe eosinophilic/ Type 2 asthma	Mepolizumab: EGPA, CRSwNP, hypereosinophilic syndrome
Anti-IL5R	Reslizumab (IV)	≥18 years		
	Benralizumab (SC)	≥12 years		
Anti-IL4R	Dupilumab (SC)	≥6 years	Severe eosinophilic/ Type 2 asthma, or maintenance OCS	Moderate-severe atopic dermatitis, CRSwNP
Anti-TSLP	Tezepelumab (SC)	≥12 years	Severe asthma	

shown to improve the management of patients with severe asthma [2]; in fact, about 70–80% of patients with severe asthma have a type 2 inflammation signature, defined as increased blood and airway eosinophils, elevated fraction of exhaled nitric oxide (FeNO) levels, and elevated levels of serum immunoglobulin E (IgE) [3]. In this scenario, biological therapies such as omalizumab (anti-immunoglobulin E), mepolizumab (anti-interleukin-5), benralizumab (anti-interleukin-5R), intravenous reslizumab (anti-interleukin-5R), dupilumab (anti-interleukin-4Rα) and tezepelumab (anti-thymic stromal lymphopoietin) (Table 1) have demonstrated a significant clinical efficacy both on lung function and disease control, with a good safety profile [4]. Due to the shared T2 inflammatory footprint, most of the available biologics share their beneficial asthma effects also on chronic rhinosinusitis and nasal polyposis [4].

Health-related quality of life (HRQoL) in patients with severe asthma is greatly affected by the disease and by the presence of comorbidities. Indeed, some treatments may not improve symptoms, but could greatly improve quality of life, and vice versa. HRQoL is defined as a multidimensional concept that includes domains related to physical, mental, emotional, and social functioning [5], and specific questionnaires can be used to assess the impact of symptoms and the effectiveness of treatment on a patients daily life. To date, if biologics for severe asthma might positively effect HRQoL in patients with concomitant CRS with or without nasal polyposis in a real-life scenario is still unknown.

Aim of the present study was to describe the long-term effects of different biologic therapies on HRQoL in patients with severe asthma and CRS with/without nasal polyposis.

Material & methods

This was a retrospective real-life study in which patients with a confirmed diagnosis of severe asthma and comorbid chronic rhinosinusitis with or without nasal polyposis referring to the severe asthma outpatient clinic of the Pulmonary Unit of L. Sacco University Hospital (Milan, Italy) were consecutively enrolled. Patients were included if had started a biologic treatment for asthma between January 2018 and December 2021 and were followed up for at least 12 months. Inclusion criteria were: a) ≥18 years old; b) an indication for biological treatment based on current international guidelines [1]. Patients were excluded if: a) had a concomitant clinically significant chronic respiratory disease; b) were shifted to another biological treatment before completing 12 months of follow-up; c) had a severe exacerbation or a hospitalization that caused the suspension or the interruption of the biologic treatment; d) underwent nasal or sinus surgery during follow up; e) had poor adherence to biologic treatment; e) had treatment-related adverse effects that precluded the continuation of the biologic treatment. Patients that were shifted to another biological treatment after at least 12 months of observation were included in the study and data concerning the first 12 months of therapy were used for the analysis. The presence of nasal polyposis was confirmed by means of nasal endoscopy.

As for internal standard operating procedures and as suggested by international recommendations, before initiating a biologic treatment and at each control visit, patients were asked to complete the following questionnaires: SinoNasal Outcome Test-22 (SNOT-22, score from 0 to 110, with higher scores indicating higher symptoms), Visual Analog Scale nasal symptoms score (VAS; score from 0 to 10, with higher score indicating a higher symptom burden), and the Asthma Control Test (ACT; score from 5 to 25, with higher scores indicating a better asthma control).

Electronic charts were reviewed for anthropometrical, clinical and functional characteristics at baseline. Questionnaires' scores before and after 3, 6, and 12 months from biologic initiation were extracted, anonymized and stored in a database. The minimal clinically important difference (MCID) was calculated for each patient according to established thresholds for ACT (MCID = +3) [6], SNOT-22 (MCID = −12) [7] and VAS rhinitis score (−0.5) [8].

Study objectives

The primary objective was to assess the effect of 12 months of treatment with biologic therapies on

HRQoL questionnaires in patients with severe asthma and CRS with/without nasal polyposis.

Secondary objectives were to investigate any possible difference in the effect of biologics in improving disease control and HRQoL and to assess the proportion of patients meeting the MCID for ACT, SNOT-22 and VAS rhinitis based on different biologic treatments.

Statistics

Due to the lack of previous literature on the topic, the real-life observational approach, and the pivotal nature of the study, the sample size calculation was not possible. Qualitative variables were presented as absolute and relative (percentage) frequencies. The Shapiro Wilk test was used to assess the normality of data distribution. Parametric and non-parametric quantitative variables were described with means (standard deviation, SD) and medians (inter-quartile ranges, IQRs), respectively, as necessary. Friedman's test was used to compare the variations over time for ACT, VAS, and SNOT-22 scores. Independent-samples Kruskal Wallis test was used to compare baseline between-groups differences in the case of non-parametric variables, while analysis of variance was used to compare normally distributed data. To compare the proportion of patients meeting a MCID during follow-up, a χ^2 test was adopted.

A two-tail p-value < 0.05 was considered statistically significant. All statistical computations were performed with 'IBM SPSS Statistics for Windows', Version 23 (IBM Corp, Armonk, NY, USA).

Results

Patients' characteristics

A total of 39 patients (49% males, mean age 58 years old) satisfied the inclusion criteria and were enrolled (Table 2): 8 patients on omalizumab, 8 on mepolizumab, 15 on benralizumab, and 8 on dupilumab. Of these, 30 patients presented CRS with nasal polyposis and 12 (31%) had GERD. The median (IQR) annual exacerbation rate before starting the biologic treatment was 3.8 (2.5), 25.6% had experienced at least a severe exacerbation in the previous year, while 20.5% of patients were on oral corticosteroids (Table 2). At baseline, the distribution of comorbidities, clinical characteristics and biomarkers did not differ between groups except for inhaled corticosteroids daily/dose and exacerbations in the year before starting biologic therapy, which were the highest in patients treated with omalizumab ($p=0.006$ and $p=0.017$, respectively, for between group comparison).

QoL questionnaires at baseline

Patients treated with mepolizumab and benralizumab tended to have higher ACT baseline scores compared with groups treated with omalizumab and dupilumab (Figure 1 and Supplementary Table 1; $p=0.013$ for between-group comparison). Baseline SNOT-22 scores differed between groups, being significantly higher in patients treated with dupilumab [median (IQR) 64 (52–70)] compared with patients treated with omalizumab, mepolizumab and benralizumab (Figure 1 and Supplementary Table 1; $p<0.001$ for between group comparison). The

Table 2. Anthropometric and clinical characteristics of the whole study population and divided by biologic treatment. Data are presented as mean (standard deviation) or median (inter quartile range) if not stated otherwise. Abbreviations: GERD : gastro-esophageal reflux disease; CRS: chronic rhinosinusitis.

Characteristic	All patients ($N=39$)	Mepolizumab ($N=8$)	Omalizumab ($N=8$)	Benralizumab ($N=15$)	Dupilumab ($N=8$)	p-value*
Male, *N* (%)	19 (48.7)	6 (75)	3 (37.5)	6 (40)	4 (50)	0.380
Age, years	58 (12)	60 (52–76)	63 (56–71)	56 (48–70)	49.5 (43–60)	0.082
Previous/current smoker, *N* (%)	12 (30.8)	3 (37.5)	5 (62.5)	2 (13.3)	2 (25)	0.320
Exacerbations/year	3.8 (2.5)	5 (5–6)	3 (2.7–4.7)	2 (2–5)	2 (2–3)	0.017
Severe exacerbations/year	0 (0–1)	1 (0-2.5)	0 (0–1.2)	0 (0–0.2)	0 (0–0)	0.109
Comorbidities						
CRS with nasal polyposis, N (%)	30 (76.9)	4 (50)	7 (87.5)	11 (73.3)	8 (100)	0.099
Perennial allergen sensitization, N (%)	10 (25.6)	4 (50)	2 (25)	3 (20)	1 (12.5)	0.624
Emphysema, N (%)	2 (5.1)	0 (0)	0 (0)	2 (13.3)	0 (0)	0.357
GERD, N (%)	12 (30.8)	2 (25)	3 (37.5)	7 (46.7)	1 (12.5)	0.726
Arterial hypertension, N (%)	7 (17.9)	2 (25)	2 (25)	2 (13.3)	1 (12.5)	0.879
Autoimmune allergic diseases, N (%)	22 (56.4)	5 (62.5)	5 (62.5)	9 (60)	3 (37.5)	0.069
Atopic dermatitis, N (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	–
Pharmacological treatments						
Budesonide equivalent daily dose, mcg	800 (640–880)	960 (400–1000)	640 (238–640)	400 (184–640)	320 (300–640)	0.006
Oral corticosteroids, *n* (%)	8 (20.5)	2 (25)	3 (37.5)	2 (13.3)	1 (12.5)	0.303
Serum biomarkers						
Total IgE count, kU/L	286 (130–524)	414 (305–634)	503 (53–1431)	270 (64–318)	209 (111–374)	0.173
Eosinophils, %	11 (6.8)	14.9 (11–20.6)	19 (7.9–17.2)	6.8 (6.0–11.3)	7.3 (6.3–11.3)	0.077
Eosinophils, cells/μL	921 (628)	1400 (525–1665)	1260 (427–1245)	600 (410–930)	430 (392–510)	0.178

*Kruskal Wallis for independent samples for between biologic treatment comparison.

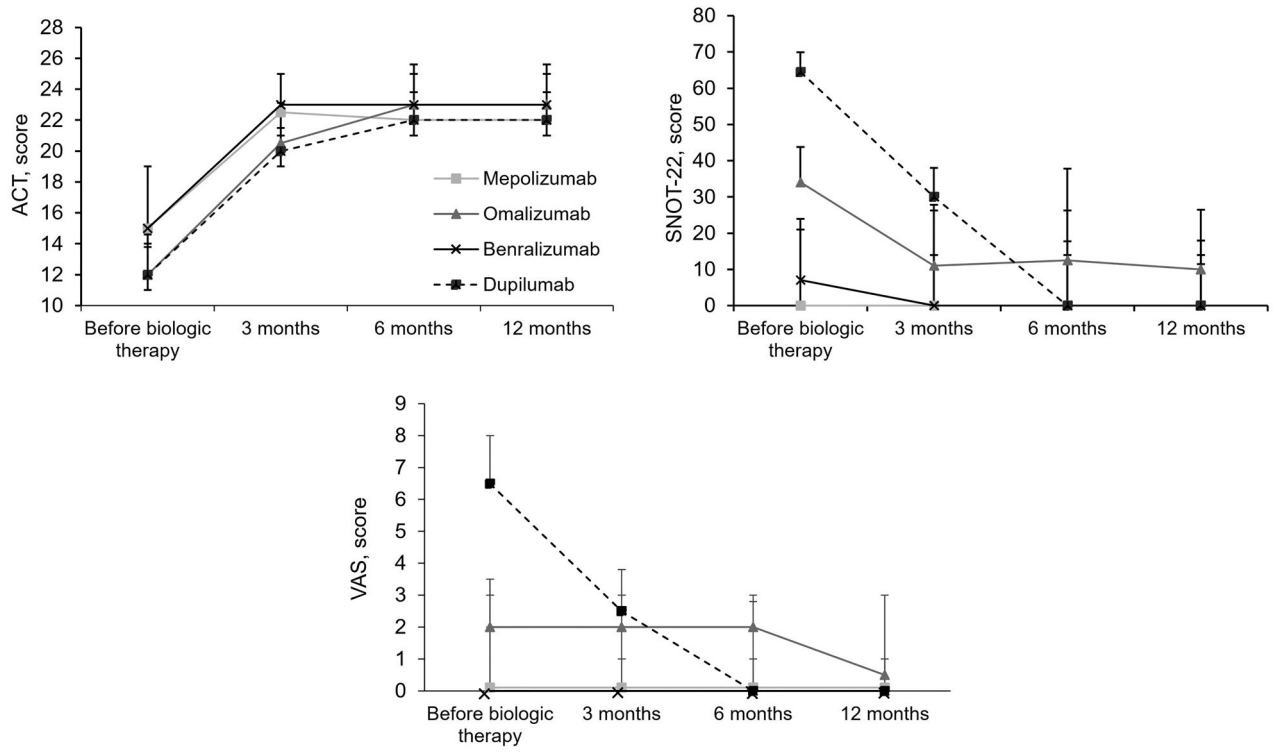

Figure 1. Changes over time in ACT (panel a), SNOT-22 and VAS scores in patients treated with mepolizumab (light grey squares), omalizumab (grey triangles), benralizumab (black crosses) and dupilumab (black squares and dotted line). Data are represented as median values. Vertical bars indicate the 75th percentile. ACT = Asthma Control Test; SNOT-22 = SinoNasal Outcome Test-22; VAS score = Visual Analog Scale symptom scores. Values at different time points were compared with Friedman test for continuous variables. ** $p < 0.001$ for all interventions except mepolizumab ($p = 0.026$); †† $p = 0.01$ for omalizumab and $p < 0.001$ for dupilumab; N.S. = not significant for mepolizumab ($p = 0.392$) and for benralizumab ($p = 0.290$); ‡ ‡ $p = 0.015$ for omalizumab and $p < 0.001$ for dupilumab; N.S. = not significant for mepolizumab ($p = 0.999$) and for benralizumab ($p = 0.465$).

baseline VAS rhinitis score was also differently distributed, being highest in patients initiated with dupilumab [6.5 (6–8)] and lowest in patients that started mepolizumab and benralizumab (Figure 1 and Supplementary Table 1; $p < 0.001$ for between-group comparison).

Effect of biologics treatment

We observed an overall significant improvement in disease-specific health-related quality of life, as measured by SNOT-22 and VAS scores at 3, 6, and 12 months of treatment compared with baseline (Figure 1 and Supplementary Table 1).

When each biologic therapy was considered separately, patients on omalizumab and dupilumab demonstrated a significant improvement in SNOT-22 and VAS scores that were present and maintained since the 3rd month of treatment (SNOT-22: $p = 0.010$ and $p < 0.001$; VAS rhinitis: $p = 0.015$ and $p < 0.001$ for omalizumab and dupilumab, respectively), while no difference were found across the 12 months of observation in patients on mepolizumab and benralizumab (SNOT-22 $p = 0.392$ and $p = 0.290$; VAS rhinitis: $p = 0.999$ and $p = 0.465$, for mepolizumab and benralizumab, respectively; Figure 1 and Supplementary Table 1).

Asthma control, as measured by the ACT, significantly improved in all patients compared with baseline ($p < 0.001$; Figure 1 and Supplementary Table 1). Subgroup analysis for each biologic therapy showed significant ACT score improvements in all treatment groups (Figure 1 and Supplementary Table 1).

No differences in terms of ACT, SNOT-22, and VAS score improvement was found between patients with and without nasal polyposis (data not shown).

Overall, by the end of follow-up, 92.3% of patients met the MCID improvement for ACT, while 35.9% and 41% reached the MCID for SNOT-22 and VAS rhinitis score, respectively (Figure 2). The large majority of patients in all treatment groups reached the MCID for ACT already after 3 months of biologic therapy (Figure 3). Patients treated with dupilumab had the highest proportion of patients meeting a MCID for SNOT-22, which reached the 100% of patients after 6 months of follow-up (Figure 3, panel D; $p < 0.001$ for all time lags, between-group comparison). The proportion of patients meeting an MCID for VAS score gradually increased in

the omalizumab and mepolizumab groups, while it reached 100% of patients beginning from 3 months of treatment in patients treated with dupilumab (Figure 3; $p < 0.001$ for all time lags, between-group comparison).

Discussion

Patients with severe asthma have lower QoL, experience poor life satisfaction and require a range of health services to manage their conditions. Biologic therapies, primarily monoclonal antibodies, have been developed to target specific pathways thought to be important in the pathogenesis of asthma. These agents have shown the ability to reduce asthma exacerbations providing a pharmacoeconomic justification for their use. Adherence to therapy is a determinant of improved asthma control and hence better QoL in severe asthma.

Our real-life study showed that patients with severe asthma and concurrent CRS, whether associated or not with nasal polyposis when exposed to biologic treatments, demonstrated an overall improvement both in disease control and HRQoL. These changes were also reflected by the large proportion of patients that met the MCID in ACT, SNOT-22 and VAS scores already after 3 months of biologic therapy.

When analyzing the effect of different biological treatments, although the size of each treatment group was limited, the aforementioned response in terms of CRS-specific QoL questionnaires depended upon the baseline nasal symptom burden. In fact, patients treated with omalizumab and dupilumab, which showed the largest effect on SNOT-22 and VAS rhinitis, had the highest baseline SNOT-22, with patients treated with dupilumab having also the highest overall VAS score. These observations were also reflected by the

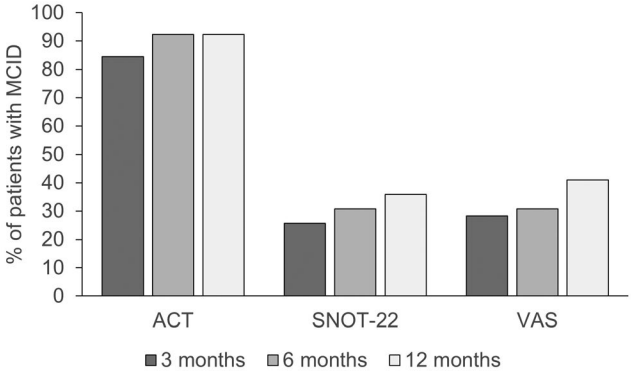

Figure 2. Proportion of patients among the whole population meeting an MCID at 3, 6 and 12 months of follow-up in ACT, SNOT-22 and VAS rhinitis scores. See text for MCID thresholds.

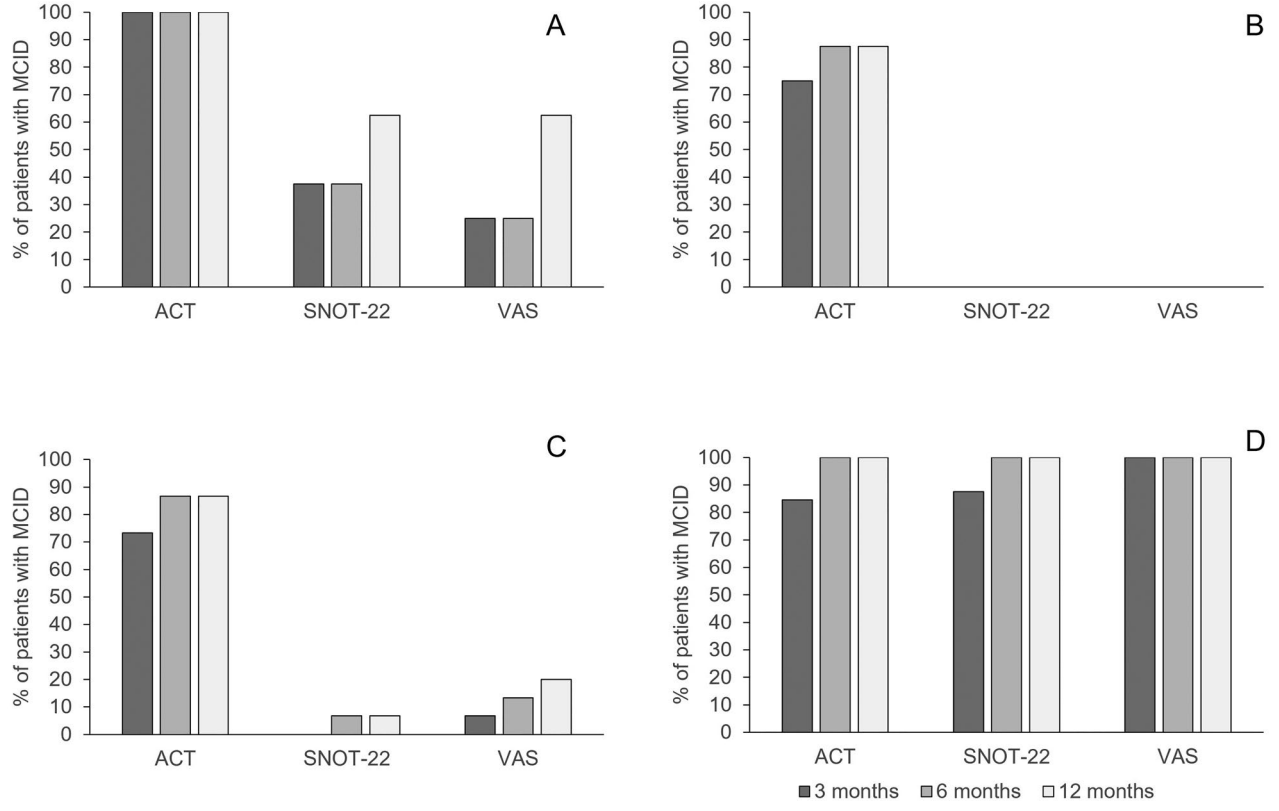

Figure 3. Proportion of patients meeting an MCID at 3, 6, and 12 months of follow-up in ACT, SNOT-22, and VAS rhinitis scores divided by biologic treatment: omalizumab (panel a), mepolizumab (panel B), benralizaumab (panel C) and dupilumab (panel D). See text for MCID thresholds. * $p < 0.001$ for all time lags between group comparisons.

marked proportion of patients meeting the MCID in all questionnaires in the dupilumab treatment group. Interestingly, when present, the biologic effect on nasal symptoms was already clinically evident beginning from the 3rd month of therapy and was sustained throughout the 12-month follow-up period, confirming the efficacy profile of biologic therapy in patients with severe asthma and concomitant CRS. The number of patients without nasal polyposis was small, with limited opportunity to investigate any possible difference between treatment groups. According to our observations, such difference should not be present, but should be confirmed in further larger observational studies.

In this real-life study, we focused on the multidimensional concept of health-related quality of life (HRQoL) related on the effectiveness of biologic treatment in severe asthma with comorbid chronic rhinosinusitis (CRS) with or without nasal polyps. In particular, we reported that many patients achieved an improvement in quality of life after being treated for 1 year with different biologics.

To date, studies have focused on the effectiveness of biological therapy separately in patients with asthma and CRS [9,10]. As an example, in adult patients with severe CRSwNP, dupilumab reduced polyp size, sinus opacification, and severity of symptoms [9]. Accordingly, omalizumab was shown to significantly improve endoscopic, clinical, and patient-reported outcomes in severe CRSwNP with inadequate response to intranasal corticosteroids [11]. Also, mepolizumab treatment improved nasal obstruction, reducing nasal polyps size, compared with placebo, in patients with recurrent, refractory severe chronic rhinosinusitis with nasal polyps [12]. Moreover, after receiving benralizumab for a year, significant improvements in the score of Sino-Nasal Outcome Test-22 (SNOT-22) were observed in patients with CRS[2]. Indeed, the use of biologics is also associated with a significant improvement in exacerbation rates and lung function, justifying a significant parallel improvement of the ACT score [10].

According to these studies and our results, biologic therapy not only improves overall control of asthma, but also ameliorates nasal symptom, and consequently quality of life.

The present study has several limitations. The sample size was limited, but the presence of statistically significant differences and the duration of the follow up should assist for statistical power calculation of future studies on the topic. Second, our observation was limited to the effect of biologics on specific HRQoL questionnaires and disease control, and the possible interference of exacerbations and lung function changes with our results could not be investigated. Finally, due to the real-life and retrospective design of the study, the baseline symptom burden among different treatment groups was not balanced and limited the generalizability of our observations when considering subgroup analysis.

Conclusions

In conclusion, this study confirms the efficacy of omalizumab, mepolizumab, benralizumab, and dupilumab in a real-life setting in providing a rapid improvement in health status and CRS-specific HRQoL scores in patients with severe asthma and concomitant CRS, independent of the presence of nasal polyps. These data highlight the importance of targeting type 2 inflammation in patients with coexisting upper and lower airway disease. Future larger real-life studies should address the potential differences in biologics' efficacy in patients stratified by symptom burden and clinically meaningful confounding factors.

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Ethical approval

The study was conducted according to the amended declaration of Helsinki (2013), was approved by the local Ethical Committee (Comitato Etico Milano Area 1- 28/02/2018) and all patients provided their written informed consent.

Authors' contributions

Conceptualization, P.S., M. S., D.R.; Data curation, P.S., M. S., D. R., A.C., R.L., L.M., F.D., P.B.; Formal analysis, P.S., M. S., D. R., A.C., L.M., F.D.; Methodology, P.S., D.R.; Supervision, P.S., D.R.; Writing-original draft P.S., D.R., M.S., A.C., L.M., F.D. Writing-review & editing, all Authors. All Authors have read and agreed to the final version of the manuscript.

Disclosure statement

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Data availability statement

The anonymized datasets used and analyzed during the current study are available from the corresponding Author on reasonable request.

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