Biologics as well as inhaled anti-asthmatic therapy achieve clinical remission: Evidence from the Severe Asthma Network in Italy (SANI)

Giorgio Walter Canonica, MD[a,b]*, Francesco Blasi, PhD[c,d], Pierluigi Paggiaro, MD[e], Enrico Heffler, PhD[a,b], Fulvio Braido, MD[f,g], Luisa Brussino, PhD[h], Giulia Scioscia, PhD[i], Cristina Cardini, MsC[j], Chiara Oriecuia, MsC[k,l], Isabella Sala, MsC[m,n] and Vincenzo Bagnardi, PhD[m], on behalf of the SANI (Severe Asthma Network in Italy) study group

ABSTRACT

Background: This study aimed to evaluate the impact of severe asthma (SA) treatments after 12 months in achieving clinical remission (CR) within the context of the Severe Asthma Network in Italy (SANI) using the recent SANI definition of CR on treatment.

Methods: CR has been defined by SANI as complete, partial, and no CR. Complete CR is defined by the absence of oral corticosteroids (OCS), no symptoms, no exacerbations, and stable lung function, and partial CR requires the absence of OCS and the fulfillment of 2 out of the other 3 criteria. Patients who do not meet the previous criteria do not reach CR.

Results: After 12 months of treatment, 283 patients were selected to evaluate the effectiveness of biologics (225 patients) and inhaled therapy (58 patients) in achieving CR. Among patients treated with biologic agents, 45.8% reached complete CR, 23.1% partial CR, and 31.1% no CR. Differences in CR achievement according to type of biologic agent administered were observed. Interesting results were found when assessing the inhaled therapy (ICS/LABA/LAMA and no biologics) effectiveness: 34.5% patients reached complete CR, 34.5% partial CR, and 31.0% did not reach CR. This finding is noteworthy since it further supports the efficacy of inhaled treatment in certain SA patients and highlights the relevance of using CR as a modern outcome of SA treatments. Chronic rhinosinusitis with nasal polyps (CRSwNP) comorbidity was associated, though not significantly, with CR achievement in patients treated with biologics. Asthma Control Test (ACT) and Asthma Control Questionnaire (ACQ) scores significantly impacted CR (p = 0.003 and p = 0.027, respectively), while biomarkers, namely IgE, blood eosinophils, or fractional exhaled nitric oxide (FeNO), were not associated with CR achievement.

Conclusions: This study confirmed the effectiveness of biologics in reaching CR and demonstrated also inhaled therapies able to achieve CR. These innovative findings should encourage post hoc analysis of randomized clinical trials or even retrospective analysis of SA patient cohorts to

[a]Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, 20090 Pieve Emanuele, Milan, Italy
*Corresponding author. Department of Translational Biomedicine and Neuroscience"DiBraiN", University of Bari Aldo Moro, Bari, Italy. E-mails: canonica.gw@gmail.com; giorgio_walter.canonica@hunimed.eu
Full list of author information is available at the end of the article
http://doi.org/10.1016/j.waojou.2024.101016

INTRODUCTION

Asthma is a prevalent chronic respiratory condition affecting millions globally, with symptoms including wheezing, shortness of breath, chest tightness, and coughing.[1] The disease's impact is widespread, with an estimated 262 million individuals affected in 2019, especially children, leading to high mortality rates and economic costs.[2] The current estimate of asthma patients is close to 300 million, according to the Global Initiative For Asthma (GINA) 2024 Report.[3]

Outcomes of asthma treatments have been recently revised since the beginning and are now focusing on a multicriteria tool named Clinical Remission (CR).[4] Several definitions of remission have been proposed [5-7] and used in evaluating different cohorts of severe asthma patients treated with biologics.[8,9] Also, National registries [10] have been a source of analysis of CR evaluation in patients treated with biologics. Using a Delphi procedure, the Severe Asthma Network in Italy (SANI) defined a simple tool to evaluate *Complete* or *Partial* CR treatment.

In Complete CR, the patient no longer requires oral corticosteroids (OCS) and must meet 3 additional criteria: absence of symptoms, no exacerbations or attacks, and stable lung function over a minimum of 12 months. Patients reaching Partial CR should not need OCS and meet 2 of the previously listed criteria. The scores for the Asthma Control Test (ACT) and the Asthma Control Questionnaire (ACQ) in *Complete* CR are identical to those required for *Partial* CR, reinforcing the high level of asthma control needed to achieve this status.[4]

Studies have shown varying effectiveness of biologics for asthma in real-world settings, especially among patients with diverse comorbidities, indicating a need for more comprehensive research to understand their performance across different patient profiles. While biologics like mepolizumab and benralizumab have improved asthma control, real-world data suggests significant variability in patient responses, emphasizing the importance of ongoing research to tailor these therapies based on individual patient needs and phenotypes.[11,12]

Comorbidities such as obesity, cardiovascular diseases, and GastroEsophageal Reflux Disease (GERD) are common among asthma patients, complicating management and impacting health outcomes significantly.[13-17]

AIM OF THE STUDY

This study aimed to investigate the likelihood by which SA treatments can achieve CR among patients within the SANI cohort, adopting the recent proposal of CR on treatment by SANI.[4] Specifically, we focused on individuals who initiated treatment with biologic drugs or inhaled therapies and were followed for 1 year. Subsequently, we assessed the occurrence of *Partial or Complete* clinical remission, or lack thereof, and compared their baseline characteristics. Finally, we explored the remission outcomes of this cohort in comparison to patients treated exclusively with inhalation therapy for 1 year.

MATERIALS AND METHODS

The SANI registry was set up in 2017 [18] and published the first data in 2019,[19] showing, for instance, the high percentage of SA patients on OCS (>64%) and impacting comorbidities such as CRSwNP (>42%). In the present study, from an initial cohort of 2500 patients, we identified those who initiated treatment with biologic agents (omalizumab, mepolizumab, benralizumab,

dupilumab, or tezepelumab) and subsequently underwent a one-year follow-up visit. Exclusion criteria were applied to ensure the availability of complete data necessary for evaluating CR status by the SANI definition [4] previously described. Variables assessed included pulmonary function, asthma control metrics, exacerbation rates, and corticosteroid utilization. Classification of remission status into complete, partial, or absent categories was performed using criteria defined by the SANI definition tool.

i. No need for any OCS therapy during the 12-month follow-up;

ii. Absence of asthma symptoms, defined as a value of ACT≥20 or ACQ<1.5 at the follow-up visit;

iii. No asthma exacerbations during the 12-month follow-up;

iv. Stable lung function, defined as a decrease in FEV1 value of no more than 100 mL during the 12-month follow-up.

Additionally, we extracted a cohort of SA patients with a one-year interval between visits who were treated exclusively with inhalation therapy, accordingly to GINA 2024 [3] (*high dose inhaled corticosteroids [ICS] plus add on long-acting β2-agonist [LABA]/long-acting muscarinic-antagonist [LAMA]*), and also had complete data for the variables required to evaluate clinical remission. Remission status for this cohort was similarly classified into the 3 categories.

STATISTICAL ANALYSIS

The data were presented stratified by the occurrence of remission (*Complete*, *Partial*, and *No Remission*). Continuous variables were expressed as means and standard deviations (SD) or medians and interquartile ranges (IQR), as appropriate, while dichotomous variables were represented as counts and percentages.

Pairwise comparisons between subgroups were made using t-tests for means, Wilcoxon tests for medians, and Chi-squared (χ2) tests (or Fisher's exact tests when appropriate) for proportions.

A two-tailed p-value <0.05 was considered statistically significant. Statistical analyses were performed using SAS statistical software version 9.4.

RESULTS

Patients selection

Fig. 1 reports the selection of SANI patients responding to the analysis criteria: 12 months of treatment with biologics (225 patients) or inhaled treatments without biologics (58 patients). Table 1 shows the baseline characteristics of the SA patients treated with biologics or inhaled therapies. The analysis of demographic characteristics of the 2 groups highlights few statistical differences: the Body Surface Area (BSA) significantly differs (p = 0.015), and the Body Mass Index (BMI) is close to significance (p = 0.057) as the absolute eosinophil count (p = 0.050). A clearcut significant difference is provided by the average ACQ score (p = 0.008), indicating a worse Quality of Life (QoL) in patients who underwent treatment with biologics.

At one-year follow-up, patients treated with monoclonal antibodies exhibited varying degrees of remission: 45.8% achieved *Complete* CR, 23.1% had *Partial* CR, and 31.1% did not achieve remission. In contrast, among those treated solely with _inhaled therapy,_ outcomes were more evenly distributed, with 34.5% achieving *Complete* CR, 34.5% achieving *Partial* CR, and 31.0% having no CR (Table 2 and Fig. 2). Although the percentages suggested a higher rate of complete CR among patients treated with biologics, the difference was not statistically significant.

Demographic characteristics

The analysis of _demographic characteristics_ at the initiation of biologic therapy across different remission outcomes showed no significant differences for age (p = 0.179) or gender distribution (p = 0.959, Table 3). While Body Mass Index (BMI) varied slightly, the differences were not statistically significant: 82.2% of patients in the complete remission group had a BMI under 30, compared to 69.2% in the partial remission group and 82.6% in the no remission group. Similarly, no significant differences were observed for body surface area (BSA) or smoking status.

Comorbidities

Rhinitis and _nasal polyps_ were highly prevalent across all groups of patients treated with
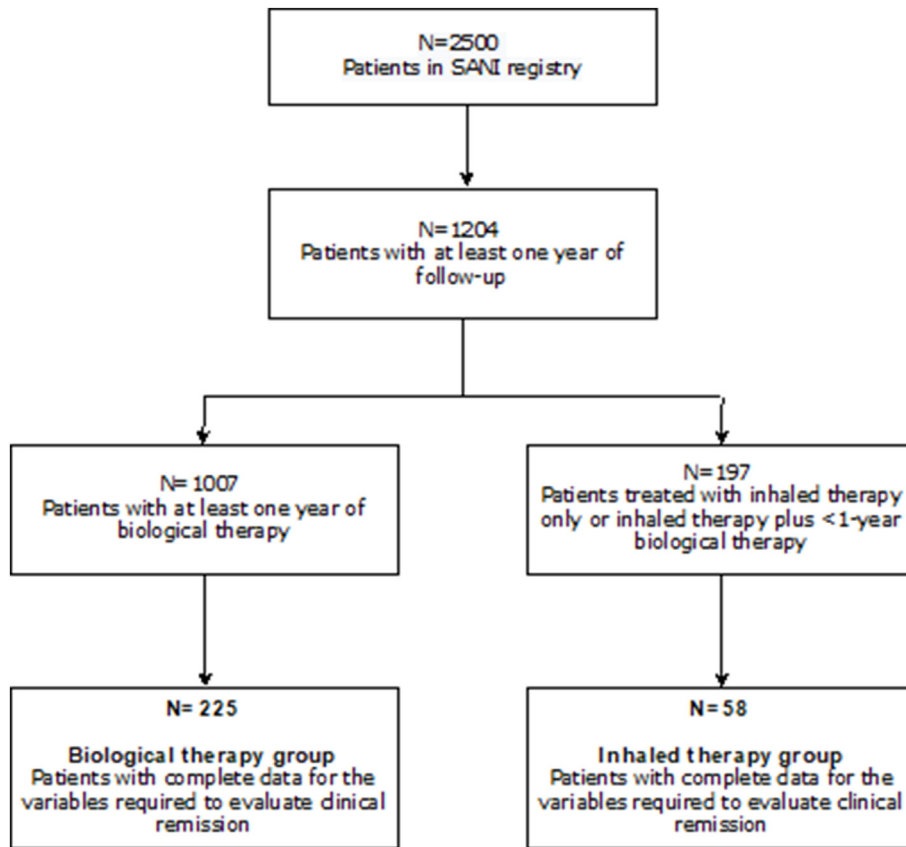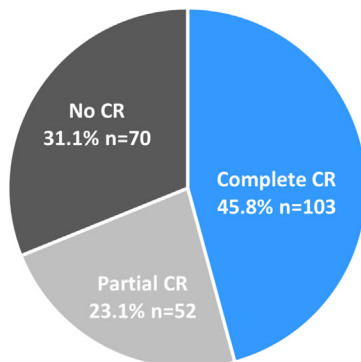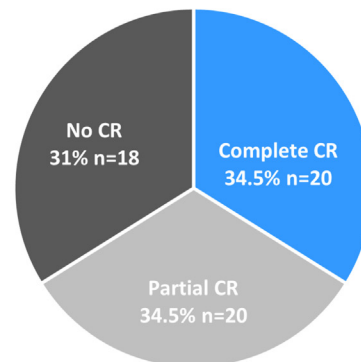
Fig. 1 Flowchart of patients' selection

Fig. 2 Percentage of clinical remission (*Complete-Partial-No Remission*) reached by treating patients with biologics or just inhaled therapy

monoclonal antibodies; subsequently, chronic rhinosinusitis without nasal polyps was reported in a less percentage of patients. Similarly, *bronchiectasis* was diagnosed consistently across groups. Furthermore, the prevalence of *cardiovascular disease* increased with worsening asthma control: 24.5% in *Complete* CR, 30.4% in *Partial* CR, and peaking at 38.3% in *No Remission*. Interestingly, *renal insufficiency* appeared in only 2.0% of the partial remission group. Moreover, mental health conditions such as *anxiety* and *depression* were more prevalent in the partial remission group, affecting 12.5% and 10.2% of patients, respectively. Finally, *diabetes* was reported consistently across groups.

None of these baseline comorbidities showed statistically significant differences between the CR

groups, except for chronic rhinosinusitis with nasal polyps (CRSwNP), consistent with a recent report by Scelo et al. JACIP 2024.[20]

No statistically significant differences were found between complete or partial CR and no CR in patients treated with inhaled therapies as well.

Regarding rhinitis, ongoing cases were prevalent across all groups, with 60% of patients in the complete CR clinical remission group, 65% in the partial CR group, and 44.4% in the no CR group.

Chronic rhinosinusitis without polyposis was more common in the no CR group (44.4%) compared to the partial CR (30%) and complete CR (10%) groups. Former cases were also more frequent in the partial CR group (20%) than in the other groups.

Nasal polyps were reported in 30% of the complete CR group, 25% of the partial CR group, and 16.7% of the no CR group, with different polyposis grading.

Bronchiectasis was most frequent in the partial CR group (30.8%), followed by the complete CR group (23.1%), and least frequent in the no CR group (13.3%). Cardiovascular diseases were more prevalent in the partial CR group (44.4%), followed by the no CR group (38.9%) and the complete CR group (22.2%), but these differences were not statistically significant.

Kidney failure was rare, with only 1 case reported in the no CR group. Anxiety was slightly more common in the no remission group (18.7%) compared to the complete CR group (11.1%), with no cases reported in the partial CR group. However, this variation was not statistically significant (p = 0.163). Depression and diabetes were also rare across all subgroups.

All the comorbities data are reported in Table 3.

Biomarkers, pulmonary function, quality of life

At the initiation of biologic therapy for asthma, clinical data was collected to evaluate various health metrics across 3 distinct patient groups: *Complete, Partial* CR, and *No Remission*. The data included assessments of peripheral blood eosinophil counts, serum IgE levels, lung function parameters, and QoL evaluations. Data from patients treated with **monoclonal antibodies** are reported below.

The eosinophil count for patients in *Complete* CR was 0.5 (IQR: 0.3–0.8), while those in *Partial* CR reported slightly lower counts at 0.4 (IQR: 0.2–0.6). Those with *No Remission* had counts similar to those in the complete remission group, at 0.5 (IQR: 0.2–0.8).

Regarding the percentage of eosinophils, patients in *Complete* CR had a median of 6.5% (IQR: 3.3–10.9), which was higher compared to 5.3% (IQR: 2.5–7.2) in *Partial* CR and 5.8% (IQR: 2.1–9.6) in *No Remission*. Median *total IgE* levels varied across the groups, with *Complete* CR patients having 177.5 kU/L (IQR: 67.3–441.2), those in *Partial* CR at 135.0 kU/L (IQR: 59.8–251.0), and those in *No Remission* showing the highest levels at 201.0 kU/L (IQR: 53.3–626.0).

No significant differences in FeNO were detected across the groups with means of 55.6 ppb (SD = 53.6), 45.5 (SD = 49.0), and 51.4 (SD = 42.0) in patients in *Complete*, *Partial* CR, and *No Remission*, respectively.

Pulmonary function was assessed using several metrics: the Forced Vital Capacity (FVC) and Forced Expiratory Volume in 1 s (FEV1), both pre- and post-bronchodilator (BD) administration. FVC pre-BD revealed that patients generally maintained similar lung volumes with means around 3.3 L, except in the no remission group, where it slightly decreased to 3.1 L. Post-bronchodilator administration, the mean FVC remained consistent across all groups at 3.3 L. The FEV1 pre-bronchodilator results showed a decline from *Complete* CR at 2.2 L to *Partial* CR at 2.1 L and to *No Remission* at 2.0 L. Post-bronchodilator FEV1 measurements were consistent across the groups at a mean of 2.2 L. The Tiffeneau Index, indicating the ratio of FEV1 to FVC pre- and post-BD, showed no significant changes, suggesting stable airway obstruction status across the groups.

The absence of asthma symptoms was established using validated instruments: the Asthma Control Test (ACT) and the Asthma Control Questionnaire (ACQ). Baseline ACT scores were significantly higher (p = 0.003) in the *Complete* and *Partial* CR groups (mean 17.0, SD = 5.5 and 15.9, SD = 5.3 respectively) compared to the no

	Treatment group		p-value
	Biological therapy **N = 225**	**Inhaled therapy** **N = 58**	
Age, median (IQR)	55 (48–64)	60 (50–68)	*0.083*
Sex, n (%)			*0.095*
Female	128 (56.9)	40 (69.0)	
Male	97 (43.1)	18 (31.0)	
Ethnicity, n (%)			*0.235*
Caucasian	214 (95.1)	57 (100)	
African	5 (2.2)	0	
Other	6 (2.7)	0	
Not reported	0	1	
BMI, n (%)			*0.555*
<30	176 (78.2)	48 (82.8)	
≥30	46 (20.4)	10 (17.2)	
Not reported	3 (1.3)	0	
BMI (kg/m^2), median (IQR)	26.0 (22.8–29.3)	24.1 (22.4–28.8)	*0.057*
BSA (m^2), median (IQR)	1.8 (1.7–1.9)	1.7 (1.6–1.9)	*0.015*
Smoking stratus, n (%)			*0.152*
Never	149 (67.1)	34 (59.6)	
Current smoker	7 (3.2)	5 (8.8)	
Ex smoker	66 (29.7)	18 (31.6)	
Not reported	3	1	
Pack years[a], median (IQR)	10.0 (5.2–23.8)	7.5 (1.5–12.0)	*0.083*
Absolute eosinophil count, median (IQR)	0.5 (0.2–0.8)	0.3 (0.1–0.5)	*0.050*
N missing	32	12	
Total IgE level (kU/L), median (IQR)	177.5 (62.5–484.8)	138.0 (53.0–420.0)	*0.648*
N missing	87	24	
FeNO (ppb)[b], mean (SD)	51.7 (48.9)	40.8 (36.1)	*0.243*
FVC pre-BD (L), mean (SD)	3.2 (1.0)	3.0 (2.3–0.8)	*0.144*
N missing	6	2	
FVC post-BD (L), mean (SD)	3.3 (1.0)	3.0 (0.9)	*0.127*
N missing	153	34	
FEV1 pre-BD (L), mean (SD)	2.1 (0.8)	2.0 (0.6)	*0.293*
FEV1 post-BD (L), mean (SD)	2.2 (0.8)	2.1 (0.7)	*0.721*
N missing	138	27	
ACT, mean (SD)	15.9 (5.5)	17.4 (5.2)	*0.071*
ACQ, mean (SD)	2.6 (1.5)	1.9 (1.1)	*0.008*

	Treatment group		p-value
	Biological therapy N = 225	Inhaled therapy N = 58	
ICU admissions[c], n (%)			*0.427*
0	192 (98.0)	48 (98.0)	
1	1 (0.5)	1 (2.0)	
≥2	3 (1.5)	0	
Not reported	29	9	
Emergency room admissions[c], n (%)			*0.762*
0	185 (83.7)	51 (87.9)	
1	20 (9.0)	5 (8.6)	
2	12 (5.4)	1 (1.7)	
≥3	4 (1.8)	1 (1.7)	
Not reported	4	0	
Hospitalizations for asthma[c], n (%)			*0.810*
0	196 (88.7)	52 (89.7)	
1	17 (7.7)	5 (8.6)	
≥2	8 (3.6)	1 (1.7)	
Not reported	4	0	
Number of exacerbations with steroid use, median (IQR)	2 (0–3)	1 (0–3)	*0.435*
Patients with at least 1 exacerbation with steroid use, n (%)	147 (65.3)	38 (65.5)	*0.794*

Table 1. (Continued) Baseline demographic and clinical characteristics of biological and inhaled therapy groups. *Abbreviations: ACT, asthma control test; ACQ: asthma control questionnaire; BD: bronchodilator; BMI, body mass index; BSA, body surface area; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation. [a]Pack years was calculated among current and ex smokers. [b]FeNO result was calculated among patients for which it was applicable (biological therapy group: n = 147, inhaled therapy group: n = 34). [c]The variable was evaluated in the last 12 months*

CR group (mean 14.2, SD = 5.4). A statistically significant difference was also revealed between the average ACQ score of 2.1 (SD = 1.6) for patients in *Complete* CR and the progressively higher values in the partial and no remission groups, 2.9 (SD = 1.4) and 3.0 (SD = 1.3), respectively. Quality of life was assessed by the Asthma Quality of Life Questionnaire (AQLQ). The AQLQ scores illustrated a decrease correlating with remission status, with the highest average score in the complete remission group at 4.6 (SD = 1.4), decreasing to 4.0 (SD = 1.3) in *Partial* CR and further to 3.7 (SD = 1.2) in *No Remission*.

In patients treated **with inhaled therapy**, the absolute eosinophil count was slightly higher in the no remission group, with a median of 0.5 (IQR: 0.3–0.6), compared to 0.3 (IQR: 0.1–0.6) of those in *Complete* CR and 0.2 (IQR: 0.1–0.4) in *Partial* CR. Although this suggests a trend of higher eosinophil counts in patients who did not achieve remission, the difference approached but did not reach statistical significance (p = 0.063). Similarly, the percentage of eosinophils was higher in the no remission group (median 5.3%, IQR: 2.2-10.2) compared to the complete and partial CR groups. Total IgE levels were notably higher in the partial

	Complete CR	Partial CR	No CR	p-value[a]
Treatment group				*0.991*
Biological therapy, n = 225	103 (45.8)	52 (23.1)	70 (31.1)	
Inhaled therapy, n = 58	20 (34.5)	20 (34.5)	18 (31.0)	

Table 2. Comparison between patients treated with biological or inhaled therapy according to clinical remission status at one-year follow-up visit. *Abbreviation: CR, clinical remission. [a]p-value for* complete or partial CR *vs* no CR

(median 211.5 kU/L, IQR: 92.0–452.0) and no remission groups (median 238.0 kU/L, IQR: 38.0–1211.0) compared to the complete CR group (median 83.9 kU/L, IQR: 46.1–184.0). FeNO levels were also elevated in the no remission group (mean 55.5 ppb, SD = 49.2) compared to both the complete and partial CR groups (31.5 ppb). However, these differences in biomarkers were not statistically significant.

FVC and FEV1, both pre- and post-BD administration, showed no significant differences among the groups, indicating that lung function, as measured by these parameters, did not vary substantially with remission status. For instance, FEV1 post-BD was similar across all groups (*Complete* CR: 2.2 L, *Partial* CR: 2.0 L, *No Remission*: 2.1 L). The Tiffeneau index pre- and post-BD also showed no significant differences. However, the no remission group had a slightly higher post-BD percentage (mean 92.9%, SD = 15.3) than the other groups (p = 0.097).

Asthma control, as measured by the ACT and ACQ, showed a trend where the no CR group had lower ACT scores (mean 15.9, SD = 4.1) and higher ACQ scores (mean 2.2, SD = 1.2), indicating poorer asthma control compared to the other groups, though these differences were not statistically significant (ACT: p = 0.069; ACQ: p = 0.245). The AQLQ scores were significantly lower for patients in *No Remission* (mean 4.2, SD = 1.1) compared to those in *Complete* (mean 5.1, SD = 1.3) and *Partial* CR (mean 5.0, SD = 1.5), with a p-value of 0.030, indicating a significant association between remission status and quality of life.

The number of workdays lost and the rate of hospitalizations for asthma were higher in the no CR group, though these differences were not statistically significant (workdays lost: p = 0.093; hospitalizations: p = 0.068). However, the number of exacerbations requiring steroid use was significantly higher for patients in *No Remission* (median 2, IQR: 2–5) compared to those in *Complete* (median 1, IQR: 0–2) and *Partial* CR (median 1, IQR: 0–1), with a p-value of 0.001. Additionally, the proportion of patients experiencing at least 1 exacerbation with steroid use was significantly higher in the no CR group (88.9%) compared to the complete CR (65.0%) and partial CR (45.0%) groups (p = 0.031).

Biological therapy CR effectiveness

Table 3 reports clinical data of patients at the initiation of biologic therapy (Visit 1) according to the type of remission.

The distribution of remission statuses among asthma patients varied with different monoclonal antibody treatments Table 4. Among patients treated with omalizumab, 37.5% achieved *Complete* or *Partial* CR, and 25.0% had *No Remission*. For those treated with mepolizumab, 38.3% reached *Complete* CR, 24.3% *Partial* CR, and 37.4% *No Remission*. Benralizumab showed a notable variation in outcomes, with 60.0% of patients achieving *Complete* CR, 14.5% *Partial* CR, and 25.5% *No Remission*. Interestingly, although dupilumab was the least used treatment, it yielded promising results, with 73.3% of patients achieving *Complete* CR, 6.7% *Partial* CR, and 20.0% *No Remission*.

However, even though some monoclonal antibody treatments appear more effective in achieving remission (either complete or partial), the differences were not statistically significant (p = 0.240).

Inhaled therapy CR effectiveness

Table 5 reports the types of inhaled therapy administered to the 58 patients not receiving

DEMOGRAPHIC CHARACTERISTICS

	Biological therapy group				Inhaled therapy group			
	Complete CR N = 103	Partial CR N = 52	No CR N = 70	p-value[a]	Complete CR N = 20	Partial CR N = 20	No CR N = 18	p-value[a]
Age, median (IQR)	54 (46–62)	57 (52–67)	56 (49–67)	0.179	58 (50–67)	60 (50–67)	63 (50–68)	0.820
Sex, n (%)				0.959				0.770
Female	57 (55.3)	31 (59.6)	40 (57.1)		14 (70.0)	13 (65.0)	13 (72.2)	
Male	46 (44.7)	21 (40.4)	30 (42.9)		6 (30.0)	7 (35.0)	5 (27.8)	
Ethnicity, n (%)				0.902				1
Caucasian	98 (95.1)	50 (96.2)	66 (94.3)		20 (100)	19 (100)	18 (100)	
Other	4 (3.9)	0	2 (2.9)		0	0	0	
Not reported					0	1	0	
BMI, n (%)				0.411				0.708
<30	83 (82.2)	36 (69.2)	57 (82.6)		15 (75.0)	17 (85.0)	16 (88.9)	
≥30	18 (17.8)	16 (30.8)	12 (17.4)		5 (25.0)	3 (15.0)	2 (11.1)	
Not reported	2	0	1		0	0	0	
BMI (kg/m²), median (IQR)	24.5 (22.5–28.4)	26.4 (23.4–32.1)	26.8 (23.3–28.7)	0.514	24.2 (22.2–29.7)	24.2 (22.4–28.9)	23.7 (22.6–27.0)	0.769
BSA (m²), median (IQR)	1.8 (1.7–1.9)	1.8 (1.7–2.0)	1.8 (1.7–1.9)	0.280	1.8 (1.6–1.9)	1.7 (1.6–1.8)	1.7 (1.6–1.9)	1
Smoking stratus, n (%)				0.699				0.560
Never	69 (67.6)	33 (64.7)	47 (68.1)		13 (65.0)	12 (63.2)	9 (50.0)	
Current smoker	2 (2.0)	2 (3.9)	3 (4.3)		1 (5.0)	2 (10.5)	2 (11.1)	
Ex smoker	31 (30.4)	16 (31.4)	19 (27.5)		6 (30.0)	5 (26.3)	7 (38.9)	
Not reported	1	1	1		0	1	0	
Pack years[b], median (IQR)	9 (5–18)	9 (4–26)	13 (6–30)	0.365	8 (1–35)	8 (2–12)	6 (3–10)	0.801

CLINICAL CHARACTERISTICS

	Biological therapy group				Inhaled therapy group			
	Complete CR N = 103	Partial CR N = 52	No CR N = 70	p-value[a]	Complete CR N = 20	Partial CR N = 20	No CR N = 18	p-value[a]
Biomarkers								
Absolute eosinophil count, median (IQR)	0.5 (0.3–0.8)	0.4 (0.2–0.6)	0.5 (0.2–0.8)	0.484	0.3 (0.1–0.6)	0.2 (0.1–0.4)	0.5 (0.3–0.6)	0.063
N missing	18	4	10		6	4	2	
Percentage of eosinophils, median (IQR)	6.5 (3.3–10.9)	5.3 (2.5–7.2)	5.8 (2.1–9.6)	0.919	2.9 (2.4–9.7)	3.0 (2.1–5.4)	5.3 (2.2–10.2)	0.351
N missing	26	7	11		6	5	4	

CLINICAL CHARACTERISTICS

	Biological therapy group				Inhaled therapy group			
	Complete CR N = 103	Partial CR N = 52	No CR N = 70	p-value[a]	Complete CR N = 20	Partial CR N = 20	No CR N = 18	p-value[a]
Total IgE level (kU/L), median (IQR)	177.5 (67.3–441.2)	135.0 (59.8–251.0)	201.0 (53.3–626.0)	0.550	83.9 (46.1–184.0)	211.5 (92.0–452.0)	238.0 (38.0–1211.0)	0.777
N missing	41	19	27		10	6	8	
FeNO (ppb)[c], mean (SD)	55.6 (53.6)	45.5 (49.0)	51.4 (42.0)	0.963	31.5 (18.1)	31.5 (25.8)	55.5 (49.2)	0.123
Pulmonary function								
FVC pre-BD (L), mean (SD)	3.3 (1.0)	3.2 (1.2)	3.1 (0.9)	0.282	2.9 (0.8)	3.0 (0.9)	3.0 (0.9)	0.817
FVC pre-BD (%), mean (SD)	92.1 (18.7)	94.9 (21.9)	92.1 (20.3)	0.746	91.9 (16.9)	94.1 (16.7)	95.1 (21.1)	0.610
FVC post-BD (L), mean (SD)	3.3 (1.0)	3.3 (1.2)	3.3 (0.9)	0.996	3.3 (0.9)	2.8 (0.9)	2.3 (0.6)	0.088
N missing	7	32	51		10	11	13	
FVC post-BD (%), mean (SD)	92.9 (18.3)	98.6 (21.4)	98.6 (10.6)	0.489	89.1 (15.5)	92.3 (9.7)	82.7 (18.0)	0.320
N missing	70	32	52		10	11	13	
FEV1 pre-BD (L), mean (SD)	2.2 (0.8)	2.1 (0.9)	2.0 (0.7)	0.166	2.0 (0.6)	2.0 (0.7)	2.0 (0.7)	0.987
FEV1 pre-BD (%), mean (SD)	74.7 (21.4)	77.5 (23.4)	73.1 (19.8)	0.414	76.7 (18.1)	75.1 (18.6)	78.5 (21.9)	0.429
FEV1 post-BD (L), mean (SD)	2.2 (0.8)	2.1 (0.9)	2.2 (0.8)	0.757	2.2 (0.6)	2.0 (0.6)	2.1 (0.9)	0.429
N missing	65	30	43		7	10	10	
FEV1 post-BD (%), mean (SD)	83.7 (23.1)	76.5 (24.9)	82.0 (19.1)	0.858	82.3 (16.0)	80.6 (11.9)	78.2 (23.9)	0.573
N missing	67	30	44		7	10	11	
Tiffeneau index pre-BD, mean (SD)	66.0 (12.6)	66.1 (13.3)	64.6 (11.7)	0.435	69.0 (7.7)	64.4 (7.4)	67.8 (10.0)	0.443
Tiffeneau index post-BD (%), mean (SD)	69.7 (30.1)	60.9 (25.9)	62.2 (33.0)	0.643	73.3 (8.2)	79.8 (6.9)	92.9 (15.3)	0.097
N missing	83	43	58		13	15	15	

Tiffeneau index post-BD, mean (SD)	65.9 (12.7)	61.6 (14.7)	66.1 (10.8)	0.604	72.1 (6.4)	69.6 (6.9)	69.1 (12.1)	0.887
N missing	70	32	51		10	11	13	
ACT, mean (SD)	17.0 (5.5)	15.9 (5.3)	14.2 (5.4)	0.003	18.0 (6.3)	18.2 (5.0)	15.9 (4.1)	0.069
N missing	6	3	3		4	1	1	
ACQ, mean (SD)	2.1 (1.6)	2.9 (1.4)	3.0 (1.3)	0.027	2.0 (1.1)	1.7 (1.1)	2.2 (1.2)	0.245
N missing	43	20	13		9	3	4	
Asthma and quality of life								
Age at asthma onset, median (IQR)	35 (25-46)	33 (15-49)	32 (19-49)	0.938	41 (27-50)	32 (10-53)	31 (20-50)	0.948
Age at asthma diagnosis, median (IQR)	35 (26-47)	40 (19-50)	38 (23-50)	0.580	47 (27-50)	50 (23-61)	42 (23-59)	0.964
AQLQ score, mean (SD)	4.6 (1.4)	4.0 (1.3)	3.7 (1.2)	0.001	5.1 (1.3)	5.0 (1.5)	4.2 (1.1)	0.030
Number of workdays lost[c], median (IQR)	0 (0-10)	0 (0-6)	0 (0-10)	0.568	0 (0-5)	0 (0-0)	2 (0-10)	0.093
Low adherence test, n (%)				0.365				0.066
None	90 (94.7)	39 (88.6)	52 (92.9)		18 (100)	13 (92.9)	10 (76.9)	
Yes, clinical evaluation	2 (2.1)	0	3 (5.4)		0	1 (7.1)	1 (7.7)	
Yes, objective clinical examination	0	2 (4.5)	0		0	0	0	
Yes, both	3 (3.2)	3 (6.8)	1 (1.8)		0	0	2 (15.4)	
Not reported	8	8	14		2	6	5	
ICU admissions[d], n (%)				0.694				0.306
0	91 (100.0)	39 (90.7)	62 (100.0)		19 (100)	15 (100)	14 (93.3)	
1	0	1 (2.3)	0		0	0	1 (6.7)	
≥2	0	3 (7.0)	0		0	0	0	
Not reported	12	9	8		1	5	3	
Emergency room admissions[d], n (%)				0.016				0.517
0	92 (92.0)	42 (82.4)	51 (72.9)		18 (90.0)	18 (90.0)	15 (83.3)	
1	6 (6.0)	4 (7.8)	10 (14.3)		2 (10.0)	1 (5.0)	2 (11.1)	
2	2 (2.0)	4 (7.8)	6 (8.6)		0	1 (5.0)	0	

CLINICAL CHARACTERISTICS

	Biological therapy group				Inhaled therapy group			
	Complete CR N = 103	Partial CR N = 52	No CR N = 70	p-value[a]	Complete CR N = 20	Partial CR N = 20	No CR N = 18	p-value[a]
≥3	0	1 (2.0)	3 (4.3)		0	0	1 (5.6)	
Not reported	3	1	0		0	0	0	
Hospitalizations for asthma[d], n (%)				0.302				0.068
0	93 (93.0)	44 (86.3)	59 (84.3)		19 (95.0)	19 (95.0)	14 (77.8)	
1	5 (5.0)	5 (9.8)	7 (10.0)		1 (5.0)	1 (5.0)	3 (16.7)	
≥2	2 (2.0)	2 (3.9)	4 (5.7)		0	0	1 (5.6)	
Not reported	3	1	0		0	0	0	
Number of unscheduled visits[d], median (IQR)	0 (0–2)	0 (0–1)	0 (0–2)	0.763	0 (0–0)	0 (0–0)	0 (0–2)	0.144
Patients with at least 1 unscheduled visit, n (%)	30 (33.7)	11 (26.2)	18 (33.3)	0.787	4 (20.0)	3 (15.0)	5 (27.8)	0.295
Number of exacerbations with steroid use[c], median (IQR)	2 (0–3)	2 (0–3)	2[1-3]	0.323	1 (0–2)	1 (0–1)	2[2-5]	0.001
Patients with at least 1 exacerbation with steroid use, n (%)	63 (63.6)	35 (72.9)	49 (76.6)	0.151	13 (65.0)	9 (45.0)	16 (88.9)	0.031

COMORBIDITIES

	Biological therapy group				Inhaled therapy group			
	Complete CR N = 103	Partial CR N = 52	No CR N = 70	p-value[a]	Complete CR N = 20	Partial CR N = 20	No CR N = 18	p-value[a]
Rhinitis, n (%)				0.133				0.319
Never	21 (20.4)	19 (36.5)	21 (30.4)		7 (35.30)	7 (35.0)	9 (50.0)	
Yes, former	7 (6.8)	1 (1.9)	8 (11.6)		1 (5.0)	0	1 (5.6)	
Yes, ongoing	75 (72.8)	32 (61.5)	40 (58.0)		12 (60.0)	13 (65.0)	8 (44.4)	
Not reported	0	0	1		0	0	0	
Chronic rhinosinusitis without polyposis, n (%)				0.392				0.170
Never	63 (61.8)	34 (65.4)	49 (72.1)		15 (75.0)	10 (50.0)	9 (50.0)	
Yes, former	15 (14.7)	6 (11.5)	8 (11.8)		3 (15.0)	4 (20.0)	1 (5.6)	

				p-value				p-value
Yes, ongoing	24 (23.5)	12 (23.1)	11 (16.2)		2 (10.0)	6 (30.0)	8 (44.4)	
Not reported	1	0	2		0	0	0	
Nasal polyps, n (%)				0.536				0.663
No	32 (31.1)	30 (57.7)	32 (46.4)		14 (70.0)	14 (70.0)	15 (83.3)	
Yes, TC or endoscopic confirmation	65 (63.1)	21 (40.4)	33 (47.8)		6 (30.0)	5 (25.0)	3 (16.7)	
Yes, suspected	6 (5.8)	1 (1.9)	4 (5.8)		0	1 (5.0)	0	
Not reported	0	0	1		0	0	0	
Polyposis grading[e], n (%)				0.631				0.063
No polyps	2 (3.7)	0	0		0	0	0	
Small polyps in the middle meatus not reaching below the inferior border of the middle turbinate	23 (42.6)	8 (50.0)	9 (31.0)		0	4 (66.7)	0	
Polyps reaching below the lower border of the middle turbinate	10 (18.5)	3 (18.8)	8 (27.6)		1 (25.0)	1 (16.7)	2 (100)	
Large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate	15 (27.8)	2 (12.5)	9 (31.0)		3 (75.0)	1 (16.7)	0	
Large polyps causing complete obstruction of the inferior nasal cavity	4 (7.4)	3 (18.8)	3 (10.3)		0	0	0	
Not reported	17	6	8		2	0	1	
Number of polypectomies[e], n (%)				0.194				0.275
0	9 (16.4)	7 (36.8)	4 (11.8)		2 (40.0)	1 (25.0)	0	
1	18 (32.7)	2 (10.5)	14 (41.2)		0	3 (75.0)	1 (33.3)	
2	16 (29.1)	6 (31.6)	11 (32.4)		2 (40.0)	0	1 (33.3)	
$\geq$3	12 (21.8)	4 (21.1)	5 (14.7)		1 (20.0)	0	1 (33.3)	
Not reported	16	3	3		1	2	0	
Bronchiectasies, n (%)				0.844				0.445
No	54 (65.9)	27 (69.2)	39 (68.4)		10 (76.9)	9 (69.2)	13 (86.7)	
Yes	28 (34.1)	12 (30.8)	18 (31.6)		3 (23.1)	4 (30.8)	2 (13.3)	
Not reported	21	13	13		7	7	3	
Cardiovascular diseases, n (%)				0.090				0.687
No	74 (75.5)	32 (69.6)	37 (61.7)		14 (77.7)	10 (55.6)	11 (61.1)	
Yes	24 (24.5)	14 (30.4)	23 (38.3)		4 (22.2)	8 (44.4)	7 (38.9)	
Not reported	5	6	10		2	2	0	
Kidney failure, n (%)				1				0.321
No	96 (100.0)	48 (98.0)	61 (100.0)		19 (100)	19 (100)	17 (94.4)	
Yes	0	1 (2.0)	0		0	0	1 (5.6)	
Not reported	7	3	9		1	1	0	
Anxiety, n (%)				0.251				0.163
No	92 (95.8)	42 (87.5)	52 (88.1)		16 (88.9)	18 (100)	13 (81.3)	
Yes	4 (4.2)	6 (12.5)	7 (11.9)		2 (11.1)	0	3 (18.7)	
Not reported	7	4	11		2	2	2	

(continued)

COMORBIDITIES

	Biological therapy group				Inhaled therapy group			
	Complete CR N = 103	Partial CR N = 52	No CR N = 70	p-value[a]	Complete CR N = 20	Partial CR N = 20	No CR N = 18	p-value[a]
Depression, n (%)				1				0.543
No	94 (95.9)	44 (89.8)	57 (95.0)		16 (94.1)	19 (100)	16 (94.1)	
Yes	4 (4.1)	5 (10.2)	3 (5.0)		1 (5.9)	0	1 (5.9)	
Not reported	5	3	10		3	1	1	
Diabetes, n (%)				1				1
No	90 (91.8)	45 (91.8)	56 (93.3)		18 (94.7)	18 (94.7)	17 (100)	
Yes	8 (8.2)	4 (8.2)	4 (6.7)		1 (5.3)	1 (5.3)	0	
Not reported	5	3	10		1	1	1	

Table 3. (Continued) Baseline patients' demographic, clinical characteristics and comorbidities according to clinical remission status at one-year follow-up visit in biological and inhaled therapy groups. Abbreviations: ACT, asthma control test; ACQ: asthma control questionnaire; AQLQ, asthma quality of life questionnaire; BMI, body mass index; BD: bronchodilator; BSA, body surface area; CR, clinical remission; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; ICU, intensive care unit; IQR, interquantile range; SD, standard deviation. [a]p-value for Complete or Partial CR vs no CR. [b]Pack years was calculated among current and ex smokers. [c]FeNO result was calculated among patients for which it was applicable: Biological therapy group: n = 62 patients in complete CR, n = 38 in partial CR, and n = 47 in no CR.- Inhaled therapy group: n = 10 patients in complete CR, n = 10 in partial CR, and n = 14 in no CR. [d]The variable was evaluated in the last 12 months. [e]Polyposis grading and number of polypectomies were reported among patients with nasal polyps (confirmed or suspected)

biologic treatment, categorized by their clinical remission status. Among those treated with ICS/LABA, 34.6% achieved *Complete* CR, 26.9% *Partial* CR, and 38.5% had *No Remission*. In contrast, patients on ICS/LABA/LAMA showed 32.3% *Complete* CR, 41.9% *Partial* CR, and 25.8% no CR. Despite these variations, the comparison of remission outcomes (complete or partial) versus *No Remission* did not reach statistical significance (p = 0.582).

DISCUSSION

The study aimed to compare remission outcomes after one year of observation between patients treated with monoclonal antibodies and those on inhaled therapy alone to obtain insightful data on the efficacy of these treatment modalities in managing asthma. Among those receiving monoclonal antibodies, the remission rates were distributed as follows: 45.8% achieved *Complete* CR, 23.1% reached *Partial* CR, and 31.1% experienced *No Remission*. This contrasts with the outcomes observed in patients using only inhaled therapy, where the remission was more uniformly distributed across the categories: 34.5% achieved *Complete* CR, 34.5% *Partial* CR, and 31.0% *No Remission*. Nonetheless, this is an innovative observation since, to our knowledge, no report about inhaled severe asthma therapy and clinical remission has been published yet. Statistical analysis revealed no significant differences in remission rates between the 2 treatment groups, suggesting that while monoclonal antibodies are often considered more targeted and potentially more effective for specific patient subgroups, inhaled therapies continue to hold substantial therapeutic value and effectiveness. The results emphasize the need for further studies to explore the factors influencing the efficacy of these treatments to guide asthma management strategies better. Patients treated with biologics or just inhaled treatment are different in severity and/or eligibility for further add-on treatment. However, all of them are initially on high-dose ICS, according to GINA 2024.

This is not the first study reporting the effect of treatments other than biologics on clinical remission in severe asthma; in fact, less specific interventions such as azithromycin have been recently described to induce clinical remission in adults with

	Complete CR (1)	Partial CR (2)	No CR (3)	p-value[a]
Type of biologic therapy, n (% row)				**0.240**
Omalizumab n = 40	15 (37.5)	15 (37.5)	10 (25.0)	
Mepolizumab, n = 115	44 (38.3)	28 (24.3)	43 (37.4)	
Benralizumab, n = 55	33 (60.0)	8 (14.5)	14 (25.5)	
Dupilumab, n = 15	11 (73.3)	1 (6.7)	3 (20.0)	

Table 4. Type of biologic therapy administered according to clinical remission group. *Abbreviation: CR, clinical remission.* [a]*p-value for* complete *or* partial *CR vs no CR*

	Complete CR N = 20	Partial CR N = 20	No CR N = 18	p-value[a]
Type of inhaled therapy				*0.582*
Single therapy (ICS), n = 1	1 (100)	0	0	
Dual therapy (ICS + LABA or LAMA[b]), n = 26	9 (34.6)	7 (26.9)	10 (38.5)	
Triple therapy (ICS + LABA + LAMA), n = 31	10 (32.3)	13 (41.9)	8 (25.8)	

Table 5. Type of inhaled therapy administered according to clinical remission group. *Abbreviation: CR, clinical remission; ICS, inhaled corticosteroids; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist.* [a]*p-value for* complete *or* partial *CR vs no CR.* [b]*All patients received ICS + LABA treatment, with the exception of 1 patient in complete CR who was treated with ICS + LAMA*

persistent uncontrolled asthma.[21] This was a secondary analysis of a randomized, double-blind, placebo-controlled AMAZES trial.[22] A significantly higher proportion in the azithromycin arm achieved clinical remission (50.6% vs 38.9%; p = 0.032) and clinical remission plus lung function criteria (50.8% vs 37.1%; p = 0.029) compared with placebo. As underlined, a high rate of patients reaching remission was compared to reported data for biologics, and they suggested the possible explanation was due to a lower baseline disease severity, known to be associated with a greater likelihood of achieving remission. The current observation about the effectiveness of inhaled therapy in SA patients in achieving *Complete* or *Partial* CR in a percentage of patients similar to the biologics is possibly related to a lower baseline disease severity (ACQ scores are significantly different). This observation of the possibility of achieving remission using ICS/LABA or ICS/LABA/LAMA will prompt the evaluation of this effect in different prospective cohorts or also retrospectively in post hoc analysis of previous trials to better define the populations able to reach clinical remission with inhaled treatments.

Clinical data of patients at the initiation of biologic therapy (Visit 1) according to the type of remission revealed distinct differences in eosinophil counts, IgE levels, lung function, and quality of life across 3 patient groups: those in *Complete* CR, *Partial* CR, and *No Remission*. Eosinophil profiles varied slightly between groups, with median counts being similar in incomplete and no remission groups and slightly lower in the partial remission group. Median IgE levels were highest in the no remission group, indicating potentially higher allergic activity or a different inflammatory profile. Also, FeNO dosage did not differentiate between *Complete*, *Partial* CR, and *No Remission*.

Lung function, assessed through pre- and post-bronchodilator FVC and FEV1, showed that while baseline lung volumes were slightly reduced in the no remission group, post-BD measurements were consistent across all groups. This suggests that biologic therapy helps to maintain lung function despite varying levels of disease control. The Tiffeneau Index, which assesses airway obstruction, indicated stable airway obstruction statuses across all groups, supporting the effectiveness of the biologics in managing airway dynamics.

There was a significant difference in asthma control between patients with *Complete* CR and *No Remission*, as confirmed by a higher ACT score and the minimum ACQ values.

Furthermore, as measured by the AQLQ, quality of life demonstrated a clear correlation with remission status, with the highest scores observed in the complete remission group and progressively lower scores in the partial and no remission groups. This suggests that patients with better baseline quality of life, as indicated by higher AQLQ scores, may have a greater likelihood of achieving remission, underscoring the potential impact of initial disease control on long-term outcomes. These findings emphasize the critical role of targeted biological therapies in managing severe asthma, controlling the disease, and enhancing patients' overall health outcomes. Such data is essential for guiding treatment strategies and optimizing therapy to ensure the best possible outcomes for asthma patients.

The analysis of comorbidities in asthma patients initiating biologic therapy highlights the significant prevalence of various health conditions accompanying different remission outcomes, suggesting complex interrelations impacting management and therapy efficacy. Rhinitis was notably prevalent across all groups, as most patients also reported chronic rhinosinusitis without nasal polyps. Additionally, CRSwNP was confirmed in a significant portion of the cohort, with 63.1% of patients in *Complete* CR having this condition, compared to 40.4% in *Partial* CR and 47.8% in *No Remission*. Bronchiectasis was diagnosed in 34.1% of patients in *Complete* CR, slightly lower at 30.8% in *Partial* CR, and 31.6% in *No Remission*. Patients with cardiovascular disease at baseline were more likely to have poorer asthma control, with the prevalence of cardiovascular disease peaking at 38.3% in those who did not achieve remission. Mental health conditions such as anxiety and depression were more prevalent in the partial remission group; diabetes was consistently reported across CR groups.

These findings underscore the complexity of treating severe asthma, mainly when significant comorbidities exist. Conditions such as chronic rhinosinusitis and nasal polyposis are prevalent, particularly among those with *Partial* CR or *No Remission*, aligning with previous studies indicating that severe asthma is often associated with higher comorbidity burdens. This discussion highlights the importance of considering comorbid conditions in therapeutic decision-making to optimize patient outcomes. It emphasizes the necessity for integrated care approaches that address asthma and its comorbid conditions. Effective management strategies often involve targeted biological therapies, which have been shown to improve outcomes in patients with specific inflammatory profiles characteristic of severe asthma.

The monoclonal antibody therapy usage analysis across different asthma remission statuses demonstrates significant variations in treatment preferences and efficacy. Among therapies examined, the present study confirmed the efficacy of biologics in achieving clinical remission as in similar studies. Differences in the impact of different monoclonal antibodies have been detected, confirming previous data.[23] Depending on the biologic, the *Complete* CR ranges from 37.5% to 73.3%. We wish to underline that these data cannot be considered final data but just confirmation of previous data with additional information, such as the evaluation of *Partial* CR (ranging from 37.5% to 6.7%). Our data suggest implementing the monitoring of the clinical response measured as CR, possibly at different intervals, to detect the onset of such an effect and possibly evaluate differences between different biologics. The statistical analysis indicated a significant difference in the choice of monoclonal therapy between complete and partial remission groups (p = 0.027), suggesting tailored treatment approaches based on remission status. However, the lack of significant differences in therapy choice between *Complete* CR and *No Remission* (p = 0.195) and between *Partial* CR and *No Remission* (p = 0.721) indicates a more uniform treatment selection in these categories. This data underscores the complexity of asthma management and the importance of personalized therapy strategies to optimize treatment outcomes based on individual patient responses and CR status. Different data about biologics to reach different CR degrees prompt additional studies to further define patient eligibility for different biologics.

This work presents some limitations. The number of patients in remission with inhaled treatment in the current SANI cohort is small, and we cannot separate different inhaled treatments and their effectiveness on clinical remission. Also, a potential

criticism is the possible different phenotyping of patients treated with biologics or just inhaled therapy. Although it is conceivable that patients treated just with inhaled treatment were not eligible for biologic treatments, this would define a different population.

The different impacts of each biologic on clinical remission should be carefully considered since the number of patients involved in some cases is narrow. Nonetheless, a recent study by Hansen et al[23] achieved similar results, using the Menzies-Gow & coll definition of Clinical Remission in SA.[5]

A possible further limitation is the evaluation of clinical remission after 12 months (as stated in the SANI definition.[4] Thomas's study on azithromycin-induced remission [21] was also detected after 6 months. This should also be evaluated as the effect of biologics, more often evaluating long-term effects (3 years) as in the SANI reports.[24,25] Such an evaluation should also be performed on SA patients treated with different inhaled therapies.

CONCLUSIONS

The key messages from the current analysis of the SANI data demonstrated the confirmation of the effectiveness of biological treatments in reaching CR and the innovative observation of the effectiveness of inhaled therapy (Dual or Triple) in reaching CR.

This last observation should prompt the analysis of RCT studies databases (post hoc analysis) or even retrospective SA patient cohorts to evaluate CR with different inhaled treatments to further define the populations eligible for each treatment.

Abbreviations
ACT: Asthma Control Test; ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; BD: BronchoDilator; BMI: Body Mass Index; BSA: Body Surface Area; CR: Clinical Remission; CRSwNP: Chronic Rhinosinusitis with Nasal Polyps; FeNO: Fractional Exhaled Nitric Oxide; FEV1: Forced Expiratory Volume in the first second; FVC: Forced Vital Capacity; GERD: GastroEsophageal Reflux Disease; GINA: Global Initiative for Asthma; ICS: Inhaled Corticosteroids; IQR: InterQuartile Range; IgE: ImmunoglobulinE; LABA: Long-Acting β2-Agonist; LAMA: Long-Acting Muscarinic-Antagonist; OCS: Oral Corticosteroids; QoL: Quality of Life; SA: Severe Asthma; SANI: Severe Asthma Network Italy; SD: Standard Deviation.

Author details
[a]Dept of Biomedical Sciences, Humanitas University, via Rita Levi Montalcini 4, 20090 Pieve Emanuele, Milan, Italy. [b]Asthma & Allergy Unit-IRCCS Humanitas Research Hospital, via Manzoni 56, 20089 Rozzano, Milan, Italy. [c]Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy. [d]Internal Medicine Department, Respiratory Unit and Cystic Fibrosis Center, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy. [e]Department of Surgery, Medicine, Molecular Biology and Critical Care, University of Pisa, Pisa, Italy. [f]Respiratory Diseases and Allergy Department, IRCCS Polyclinic Hospital San Martino, Genoa, Italy. [g]Department of Internal Medicine (DIMI), University of Genoa, Genoa, Italy. [h]S.C.D.U. Immunologia e Allergologia, A.O. Ordine Mauriziano Torino, Italy. [i]Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy. [j]Fondazione per la Salute Respiratoria della Società Italiana di Pneumologia SIP-IRS, Milan, Italy. [k]Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy. [l]Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy. [m]Department of Statistics and

Quantitative Methods, University of Milano-Bicocca, Milan, Italy. [n]Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy.

REFERENCES

1. Hashmi MF, Cataletto ME. *Asthma.* https://www.ncbi.nlm.nih.gov/books/NBK430901/.

2. https://www.who.int/news-room/fact-sheets/detail/asthma.

3. GINA-2024-Strategy-Report-24_05_22_WMS.

4. Canonica GW, Blasi F, Carpagnano GE, et al. Severe asthma Network Italy definition of clinical remission in severe asthma: a Delphi consensus. *J Allergy Clin Immunol Pract.* 2023;11(12):3629–3637. https://doi.org/10.1016/j.jaip.2023.07.041.

5. Menzies-Gow A, Bafadhel M, Busse WW, et al. An expert consensus framework for asthma remission as a treatment goal. *J Allergy Clin Immunol.* 2020;145(3):757–765. https://doi.org/10.1016/j.jaci.2019.12.006.

6. Thomas D, McDonald VM, Pavord ID, Gibson PG. Asthma remission- what is it and how can it be achieved? *Eur Respir J.* 2022;60(5). https://doi.org/10.1183/13993003.02583-2021.

7. Lommatzsch M, Brusselle GG, Canonica GW, et al. Disease-modifying anti-asthmatic drugs. *Lancet.* 2022;399(10335):1664–1668. https://doi.org/10.1016/S0140-6736(22)00331-2.

8. Pavord ID, Hanania NA, Corren J. Controversies in allergy: choosing a biologic for patients with severe asthma. *J Allergy Clin Immunol Pract.* 2022;10(2):410–419. https://doi.org/10.1016/j.jaip.2021.12.014.

9. Lugogo NL, Heffler E, Plaza V, et al. Baseline systemic oral corticosteroid use in patients with asthma initiating Dupilumab treatment in the real world: from the RAPID global registry. *J Asthma Allergy.* 2024;17:551–556. https://doi.org/10.2147/JAA.S451689.

10. McDowell PJ, McDowell R, Busby J, et al. Clinical remission in severe asthma with biologic therapy: an analysis from the UK Severe Asthma Registry. *Eur Respir J.* 2023;62(6). https://doi.org/10.1183/13993003.00819-2023.

11. Gibson PG, Prazma CM, Chupp GL, et al. Mepolizumab improves clinical outcomes in patients with severe asthma and comorbid conditions. *Respir Res.* 2021;22(1). https://doi.org/10.1186/s12931-021-01746-4.

12. Paoletti G, Pepys J, Casini M, et al. Biologics in severe asthma: the role of real-world evidence from registries. *Eur Respir Rev.* 2022;31(164). https://doi.org/10.1183/16000617.0278-2021.

13. Wang Z, Li Y, Gao Y, et al. Global, regional, and national burden of asthma and its attributable risk factors from 1990 to 2019: a systematic analysis for the Global Burden of Disease Study 2019. *Respir Res.* 2023;24(1). https://doi.org/10.1186/s12931-023-02475-6.

14. Yang X, Liu X, Jalaludin J, Hu S. *Global Trends in the Incidence and Mortality of Asthma from 1990 to 2019: An Age-Period-Cohort Analysis Using the Global Burden of Disease Study.* 2019.

15. McLoughlin RF, McDonald VM. The management of extrapulmonary comorbidities and treatable traits; obesity, physical inactivity, anxiety, and depression, in adults with asthma. *Frontiers in Allergy.* 2021;2. https://doi.org/10.3389/falgy.2021.735030.

16. Tomisa G, Horváth A, Sánta B, Keglevich A, Tamási L. Epidemiology of comorbidities and their association with asthma control. *Allergy Asthma Clin Immunol.* 2021;17(1). https://doi.org/10.1186/s13223-021-00598-3.

17. Getty images/pollyana ventura credits. https://www.who.int/news-room/fact-sheets/detail/asthma.

18. Senna G, Guerriero M, Paggiaro PL, et al. SANI-Severe Asthma Network in Italy: a way forward to monitor severe asthma. *Clin Mol Allergy.* 2017;15(1). https://doi.org/10.1186/s12948-017-0065-4.

19. Heffler E, Blasi F, Latorre M, et al. The severe asthma Network in Italy: findings and perspectives. *J Allergy Clin Immunol Pract.* 2019;7(5):1462–1468. https://doi.org/10.1016/j.jaip.2018.10.016.

20. Scelo G, Torres-Duque CA, Maspero J, et al. Analysis of comorbidities and multimorbidity in adult patients in the international severe asthma registry. *Ann Allergy Asthma Immunol.* 2024;132(1):42–53. https://doi.org/10.1016/j.anai.2023.08.021.

21. Thomas D, McDonald VM, Stevens S, et al. Effect of azithromycin on asthma remission in adults with persistent uncontrolled asthma: a secondary analysis of a randomized, double-anonymized, placebo-controlled trial. *Chest.* 2024;166(2):262–270. https://doi.org/10.1016/j.chest.2024.02.048.

22. Gibson PG, Yang IA, Upham JW, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2017;390(10095):659–668. https://doi.org/10.1016/S0140-6736(17)31281-3.

23. Hansen S, Baastrup Søndergaard M, von Bülow A, et al. Clinical response and remission in patients with severe asthma treated with biologic therapies. *Chest.* 2024;165(2):253–266. https://doi.org/10.1016/j.chest.2023.10.046.

24. Quarato CMI, Tondo P, Lacedonia D, et al. Clinical remission in patients affected by severe eosinophilic asthma on Dupilumab therapy: a long-term real-life study. *J Clin Med.* 2024;13(1). https://doi.org/10.3390/jcm13010291.

25. Bagnasco D, Bondi B, Caminati M, et al. Evaluation of clinical remission in best-performing severe asthmatic patients treated for three years with Mepolizumab. *Biomedicines.* 2024;12(5). https://doi.org/10.3390/biomedicines12050960.