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Severe asthma: follow-up after one year from the Italian Registry on Severe Asthma (IRSA)

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Key words

Severe asthma; biologics; asthma management; real-world; phenotyping; registry.

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Impact statement

This study provides real-world registry-based evidence of the improvement in severe asthma outcomes after one year of follow-up in the Italian Registry on Severe Asthma. For optimal and fine-tuned severe asthma management, treatments must be implemented as part of a planned follow-up strategy.

Summary

Background. *Asthma affects millions of people worldwide, with a subgroup suffering from severe asthma (SA). Biologics have revolutionized SA treatment, but challenges remain in managing different patient traits. This study analyzed data from the Italian Registry on Severe Asthma (IRSA) to investigate changes in SA characteristics and effectiveness of treatments after one year of follow-up, and to identify factors associated with response to treatments in a real-world setting.* ***Methods.*** *Data on SA patients with one year of follow-up were extracted from IRSA. Asthma control, exacerbations, lung function, and treatments, were assessed at follow-up and analyzed against baseline characteristics.* ***Results.*** *After one year of follow-up, notable improvements were observed in all the outcomes of SA of the included patients (n = 570). The effectiveness of biologic therapies was particularly evident, as they contributed significantly to these positive outcomes. Additionally, certain factors were found to be associated with improvement, namely T2 phenotype, baseline eosinophil count (BEC), and area of residence. On the other hand, comorbidities (obesity, gastro-esophageal reflux disease) and poor lung function were risk factors. Notably, poor-responders to biologics exhibited lower level of education, BEC, and exacerbations, and higher frequency of atopy and ACT score ≥ 20.* ***Conclusions.*** *The findings demonstrate the effectiveness of biologics in asthma management, when implemented as part of a planned follow-up strategy aimed at optimizing and fine-tuning the therapy. Moreover, the study highlights the importance of considering key traits such as the T2 phenotype, BEC, education, and comorbidities when tailoring SA treatment. Overall, this study contributes to enhancing our understanding of SA management and guiding the development of personalized treatment approaches for patients with SA.*

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Introduction

Asthma is the most common chronic inflammatory airway disease, affecting more than 300 million people worldwide (1). Most asthmatics have mild to moderate asthma, which is effectively treated by the combination of inhaled corticosteroids (ICS) and long-acting bronchodilators. Even though severe asthma (SA) affects up to 10% of asthmatic patients, it represents a major economic issue worldwide (2, 3), and is characterized by a high mortality (4). According to the Global Initiative for Asthma (GINA) recommendations (5), SA is defined if patients are on regular treatment with: 1) high doses of ICS and long-acting β2-agonists (LABAs); or 2) medium/high doses of ICS/LABA + leukotriene receptor antagonist (LTRA); or 3) medium/high doses of ICS/LABA + theophylline; or 4) oral corticosteroids (OCS) for at least 150 days/year + inhalation therapy. In the last 20 years, the availability of biologics, as add-on treatments for patients with SA, deeply changed not only the burden of the disease, in terms of reduction of asthma exacerbations, hospitalizations and OCS consumption, but also our understanding of disease through the application of precision medicine and the ability to identify the treatable trait "inflammation T2 high" (6). Despite these advances, real-world management of SA can be challenging not only for patients with a treatable trait "inflammation T2 low", due to the lack of a specific therapy, but also for patients with the treatable trait "inflammation T2 high", because head-to-head efficacy studies among biologics are lacking, or due to the poor accuracy of available biomarkers, which overlap for the same treatable trait (6, 7). Registries of SA appear to be a useful tool to evaluate the effectiveness of biologics and evaluate the presence and management of unmet needs of SA. Several European and International registries on SA have been designed with the purpose of achieving better understanding of its epidemiology, inflammatory profile, different phenotypes and treatment characteristics, and several data has been published so far (8-12). However, few longitudinal analyses were performed, focused only on specific aspects. The United Kingdom Severe Asthma Registry (UKSAR) (9) documented the changes in prescription of biologics, including switching (12.1%), which allowed to achieve a significant and stable improvement of the outcomes of therapy in 77.6% of patients. The follow-up of the Italian severe/uncontrolled asthma registry (RItA) (10) where the only biologic used was omalizumab showed that the implementation of a registry itself, in addition to the treatments, allow improvement in asthma control, after one year of follow-up. The third registry-based study evaluated the effectiveness of 36 months of treatment in 90 patients affected by severe eosinophilia asthma treated with biologics, confirming the high level (77.5%) of the effectiveness of biologic therapy, even though only 39 patients completed 3 years of follow-up (11). In 2017 the Italian Association of Hospital Allergists and Immunologists (AAIITO) and the Italian Thoracic Society (ITS – AIPO) set up the Italian Registry on Severe Asthma (IRSA), aimed to collect data in SA patients in a real life setting (13), whose methodology and baseline results have been previously published (13, 14).

The objective of this study is to extract longitudinal data from IRSA, investigating the changes from baseline after 1 year of follow-up in the characteristics of SA, as well as the effectiveness of therapy. Additionally, the study aims to identify factors associated with response.

Materials and methods

Data collection

Details on the set-up of the registry and methods of data collection have been previously reported (14). All the patients with a follow-up visit were included in the analysis. Only centers authorized to prescribe biologics were included in IRSA. For the definition of T2 status, two cut-off values for eosinophils have been used (15), reflecting the criteria for prescription of biologics in Italy:

- T2_300 phenotype ($T2_{high}$): total IgE > 150 and/or eosinophils > 300 and/or Fractional Exhaled Nitric Oxide (FeNO) > 25;
- T2_150 phenotype ($T2_{high}$ + $T2_{low}$): total IgE > 150 and/or eosinophils > 150 and/or FeNO > 25.

Patients not included in the two above-mentioned categories were considered as "non-T2 phenotype" (*i.e.*, total IgE ≤ 150 + eosinophils ≤ 150 + FeNO ≤ 25).

Statistical analysis

In the descriptive part of this "natural history" study, the difference from baseline (V0) to follow-up (V1) were calculated for the main outcomes of interest and reported as follow:

- Control of asthma, assessed as overall clinical judgement and with Asthma Control Test (ACT): average score, frequency of patients with ACT score ≥ 20, frequency of patients obtaining a 3 point of minimum clinically important difference (MCID) in ACT score.
- Exacerbations, assessed as incidence rate ratio (IRR: ratio of exacerbations/person × year) and frequency of patients with one, two, or > 2 exacerbations from V0.
- Lung function, measured with FEV_1, FEV_1/FVC: absolute and relative values, frequency of patients reaching relevant cut-off values: FEV_1+100 ml; lower limit of normal (LLN) FEV_1/FVC (16, 17).
- Treatments – Frequency and dose of treatments, response to biologic treatments assessed as ≥ 50% decrease of OCS maintenance dose and decrease in exacerbation rate in OCS-dependent patients or ≥ 50% decrease of exacerbation rate and improved asthma control in non-OCS-dependent patients, respectively (18).

In the analytical cohort prospective analysis of this study, the baseline characteristics of patients at V0 were investigated to identify factors associated with asthma improvement at V1, assessed with the abovementioned outcomes of interest. McNemar's chi-squared test (change from baseline of categorical variables), and paired t-test were performed to study change from baseline of categorical and normal continuous variables, respectively. Cohen's kappa test was used for agreement analyses between variables. A *post-hoc* power calculation was performed for each comparison. Logistic or linear regression models, as appropriate, were conducted and adjusted for the specific confounders of each outcome as assessed by directed acyclic graphs. Pearson's or Spearman's test for correlation were adopted, as appropriate. Receiver operating curves (ROC) were generated to investigate the diagnostic accuracy of the baseline characteristics in detecting the outcomes of interest at follow-up, reported as Area Under the Curve (AUC), sensitivity and specificity at the Youden index (*i.e.*, cut-off at the highest sum of sensitivity and specificity). Sensitivity analyses were performed, for ACT-based control and exacerbations assessment at V1, comparing the total population *versus* subgroups of patients not controlled or with exacerbations at V0, respectively. A complete case strategy was adopted for missing data handling, and a sensitivity analysis was performed to compare the baseline characteristics of the study population with the patients whose V1 was not available because not yet added or lost at follow-up, to check external validity (19). All the analyses were performed with STATA v.15 (StataCorp LLC, Texas, USA).

Results

Study population

A follow-up (V1) visit was conducted after 1 year ± 6 months from V0 in 570 patients, between July 2017 and May 2022. During this timeframe, in addition to omalizumab and mepolizumab, benralizumab and, for a few months, dupilumab became available in Italy. The baseline characteristics are similar to those already published for IRSA patients (14). The mean age was 55.9 ± 13.3, with females accounting for 58.7% and a mean Body Mass Index (BMI) of 26.4 ± 5.0. Regarding education, 15.7% reported a bachelor's degree or higher. Most of them had never smoked (72.1%), while the remaining were ex-smokers (22.8%) or active smokers (5.1%). The majority of patients live in urban areas (84.5%), while only 15.5% reside in rural areas. The mean age at symptoms' onset was 30.4 ± 16.7. Atopic status was recorded in 70.4% of patients, and the median total IgE was 223 kU/L (Interquartile range (IQR): 100, 445). Occupational exposure to potential toxic substances (such as dust or gas at work) was reported by 26.1% of patients, with professional asthma diagnosed in 7.7% of cases. The following frequencies of comorbidities were recorded: sinusitis (53.7%), nasal polyps (47.7%), hypertension (30.6%), osteoporosis (20.3%), diagnosed gastroesophageal reflux disease (dGERD, 19.1%), obesity assessed as BMI > 30 (18.1%), acetylsalicylic acid hypersensitivity (16.1%), bronchiectasis (15.0%), cataract (8.7%), diabetes (7.0%). The other comorbidities had a frequency lower than 5% (*i.e.*, psychological disorders, food allergy, sleep apnea, allergic bronchopulmonary aspergillosis, eosinophilic granulomatosis with polyangiitis, atopic dermatitis). In terms of facility characteristics, the largest medical centers (with ≥ 30 patients followed for SA) recruited 59.2% of patients. Pulmonology centers accounted for 69.3% of patients, compared with allergy units (30.7%). The geographical distribution of the centers was balanced across north (45.7%), center (16.5%), and south/islands (37.8%) of Italy. The other clinical, laboratory, and functional characteristics, at baseline and follow-up, are reported in **table I**. At baseline, the majority of patients were not controlled (ACT < 20 in 60.8% of cases), with at least one exacerbation in the last 12 months (81.2%). The sensitivity analysis did not show significant differences with the characteristics of patients not included in the follow-up study. Most patients showed a T2 phenotype (T2_300 in 77.3% and T2_150 in 86.6% of cases, respectively), and this is reflected by the high baseline eosinophil count (BEC) (> 300/mm^3 in 58.1% of patients). A slightly lower frequency of T2 phenotype was observed in the subgroup of patients (n = 103) without biologic treatments (T2_300 in 68.9% and T2_150 in 84.5% of cases, respectively).

Lung function

Change from baseline (V0) in lung function is shown in **table I**. Overall, the increase of FEV_1 was ≥ 100 ml in 48% of patients and ≥ 15%pred in 30% of patients, at V1. Out of 35 patients with FEV_1/FVC < 50% at V0, 51.4% and 11.4% improved to 50-69% and ≥ 70%, respectively ($p < 0.001$). FEV_1 exceeded the LLN in +15.3% patients at V1, compared to V0 ($p < 0.001$). Baseline characteristics significantly associated with a ≥ 100 ml improvement at V1, accord-

ing to the unadjusted analysis (confirmed by the adjusted analysis), are reported in **table II**. There was a negative correlation with age, with a drop in the mean FEV_1 improvement from 50 years old onwards (+326 ml *versus* +136 ml, respectively; odd ratio (OR) of ≥ 100 ml improvement 0.6 in > 50-year-old patients, p < 0.001). The relationship with T2 phenotype was mainly driven by BEC and FeNO levels, as no significant associations were observed with total IgE. In terms of absolute values of mean FEV_1 improvement, additional variables had an impact. Namely, some differences were observed in smoking status categories (non-smokers +224 ml, ex-smokers +119 ml, active smokers +50 ml, p = 0.06), packs/year > 0 (+101 ml *versus* +226 ml, p = 0.013), professional asthma (+320 ml *versus* +138 ml in non-professional asthma, p = 0.04), BMI > 30 (+64 ml *versus* +219 ml, p = 0.009), osteoporosis (+64 ml *versus* +219 ml, p = 0.006), and cataract (-40 ml *versus* +222 ml, p = 0.001). Osteoporosis and cataract were not confirmed at the adjusted analysis.

Control of asthma

There was a 37.7% increase (95%CI 32.8-42.6; power 100%) of patients reaching ACT ≥ 20 at V1, compared to V0, and 45%

Table I – *Characteristics of the study population at baseline and at follow-up (n = 570).*

	Baseline	Follow-up	P-value
Biological and clinical characteristics			
Median Eosinophils/mm^3 (IQR) [17]	363 (140, 722)	102 (49, 234)	< 0.001
< 150	26.8%	61.9%	< 0.001
150-300	15.1%	18.3%	< 0.001
> 300	58.1%	19.8%	< 0.001
FeNO ppb [297]	42.8 ± 43.0	34.1 ± 31.3	0.004
Phenotype° [15]			
T2_300 ($T2_{high}$)	77.3%	Not applicable	
T2_150 ($T2_{high + low}$)	86.6%	Not applicable	
non-T2	13.4%	Not applicable	
Median ACT score (IQR) [12]	18 (15,21)	22 (20,24)	< 0.001
< 20	60.8%	24.9%	< 0.001
20-24	30.2%	54.2%	< 0.001
25	9.0%	20.9%	< 0.001
Lung function [39]			
FEV_1 L	2.0 ± 0.8	2.2 ± 0.8	< 0.001
FEV_1 %pred	72.5 ± 19.6	80.0 ± 20.4	< 0.001
FEV_1 post-bronchodilator L	2.2 ± 0.8	2.4 ± 0.9	< 0.001
FEV_1 post-bronchodilator %pred	80.4 ± 20.2	84.2 ± 20.8	< 0.001
FEV_1/FVC	69.5 ± 14.3	72.4 ± 14.2	< 0.001
< 50%	8.4%	5.1%	< 0.001
≥ 50 < 70	44.5%	34.6%	
> 70%	47.1%	60.3%	
FEV_1/FVC post-bronchodilator	73.2 ± 15.4	74.9 ± 13.7	< 0.001
< 50%	6.6%	4.0%	0.0183
≥ 50 < 70	35.3%	28.9%	
>70%	58.1%	67.1%	

→

	Baseline	Follow-up	P-value
Exacerbations (last 12 months) [7]			
Median nr of exacerbations (IQR)	2 (1, 4)	0 (0, 1)	< 0.001
Crude exacerbation rate/year	3.3 ± 3.9	0.7 ± 1.4	< 0.001
Patients with ≥1 exacerbations	81.2%	33.2%	< 0.001
Access to Emergency Dept.	21.2%	4.3%	0.0018
Treatments			
Inhaled Corticosteroids[§]			
High dose	66.0%	59.4%	0.0017
Medium dose	34.0%	40.6%	
Long-acting Muscarinic Antagonists	41.4%	40.7%	0.2413
Antileukotrienes	48.9%	45.1%	0.0028
Oral corticosteroids	31.3%	20.7%	< 0.001
Median months of duration (IQR)	5 (1, 12)	3 (1, 12)[^]	Not applicable
Medium equivalent daily mg (IQR)	40 (20, 75)	22.5 (20, 40)	0.0209
Biologics (median months; IQR)			
No	36.6%	17.6%	< 0.001
anti-IgE	29.8% (18.5; 8-37)	29.2%	
anti-IL5(R)	32.9% (6; 1-12)	51.9%	
anti-IL14/IL13	0.7% (3.5; 0.5-15)	1.3%	
Thermoplasty	1.3%	0.2%	0.910

Mean ± standard deviation values are reported, if not otherwise specified [Missing data at follow-up are reported in squared brackets, if any]. ACT: Asthma Control Test; FeNO: Fractional Exhaled Nitric Oxide; FEV_1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; IQR: Interquartile Range. °T2 phenotype defined as T2_300 (IgE > 150 and/or eosinophils > 300 and/or FeNO > 25), T2_150 (IgE > 150 and/or eosinophils > 150 and/or FeNO > 25), and non-T2 (total IgE ≤ 150 and eosinophils ≤ 150 and FeNO ≤ 25). [§]High and medium dose according to GINA 2019. All the patients were taking Inhaled corticosteroids and long-acting beta2 agonists. [^]Duration reported only for the seven patients who started oral corticosteroids after the baseline visit.

of patients reached the MCID in the ACT score. The mean increase in ACT score at V1 was +3.4 points (95%CI 3-3.9; power 100%). Overall, the agreement between control of asthma assessed as per clinical judgement and ACT outcomes was good (89.4%, k = 0.7, p < 0.005). No significant differences were observed between patients with and without biologic treatments.

The unadjusted analysis showed a significant correlation between conversion from uncontrolled (ACT < 20 at V0) to controlled asthma (ACT ≥ 20 at V1) and the following variables: T2 phenotype, nasal polyposis, dGERD, osteoporosis, and rural area of residence (**table II**). Within T2 phenotype, BEC and total IgE were significantly associated with ACT, but not FeNO. In patients with ACT conversion the mean values of BEC and total IgE were +158/mm^3 (p < 0.001) and +70.1 KU/L (p = 0.012), respectively, compared to patients without controlled asthma at V1. Conversely, no correlations between ACT conversion and the other baseline characteristics were observed. After adjusting for confounders, in patients not controlled at baseline, the correlation with ACT conversion was still significant only for T2 phenotype (T2_300: OR 2.8, 95%CI 1.4-5.6, p = 0.003; T2_150: OR 3.6, 95%CI 1.3-8.6, p = 0.012). BEC was a good predictor of ACT improvement. Overall, the linear correlation between absolute eosinophils values (at V0) and ACT score (at V1), in patients not controlled at baseline, was significant but moderate (Spearman's R: 0.19, 95%CI 0.08-0.28, p < 0.001). Namely, the correlation becomes significant at values > 150/mm^3, and even stronger at values > 372/mm^3 (Youden's index). However, the diagnostic accuracy of peripheral eosinophils per se to predict asthma control was poor (AUC 62%, 95%CI 56%-68%).

Exacerbations

The total number of exacerbations decreased from 2,036 to 432 at V1, with a 49% decrease (95%CI 44%-54%; p < 0.001) of the number of patients with at least one exacerbation in the last 12 months, and the exacerbation rate dropped from 3.3 ± 3.9 exacerbations/person-year to 0.7 ± 1.4 (difference: -2.6, 95%CI

Table II *– Significant correlations between baseline characteristics and outcomes at follow-up (overall population).*

	Frequency of patients	Odds ratio (95%CI)	P-value°
Asthma Control Test conversion from < 20 to ≥ 20 at follow-up			
T2 phenotype*	+26.2%	3.1 (1.8 to 5.6)	< 0.001
T2 phenotype_150§	+30.0%	3.6 (1.7 to 7.6)	< 0.001
Nasal polyposis	+14.3%	2.0 (1.2 to 3.2)	0.005
dGERD	-20.6%	0.4 (0.2 to 0.8)	0.003
Osteoporosis	-17.4%	0.5 (0.3 to 0.9)	0.010
Rural area (*vs* urban/ industrial area)	+16.8%	2.3 (1.1 to 5.0)	0.019
Exacerbations at follow-up (at least one in 12 months)			
BMI > 30	+11.7%	1.7 (1.1 to 2.5)	0.017
dGERD	+11.5%	1.6 (1.1 to 2.5)	0.024
FEV_1/FVC < LLN	+9.2%	1.5 (1.1 to 2.1)	0.022
Oral corticosteroid withdrawal at follow-up			
FEV_1 reversibility ≥ 100 ml	-25.1%	0.3 (0.1 to 0.6)	0.001
FEV_1 improvement at follow-up			
Age > 50 years	-12.0%	0.6 (0.4 to 0.9)	0.022
T2 phenotype*	+17.3%	2.0 (1.3 to 3.3)	0.003
T2 phenotype_150§	+15.5%	1.9 (1.0 to 3.4)	0.034

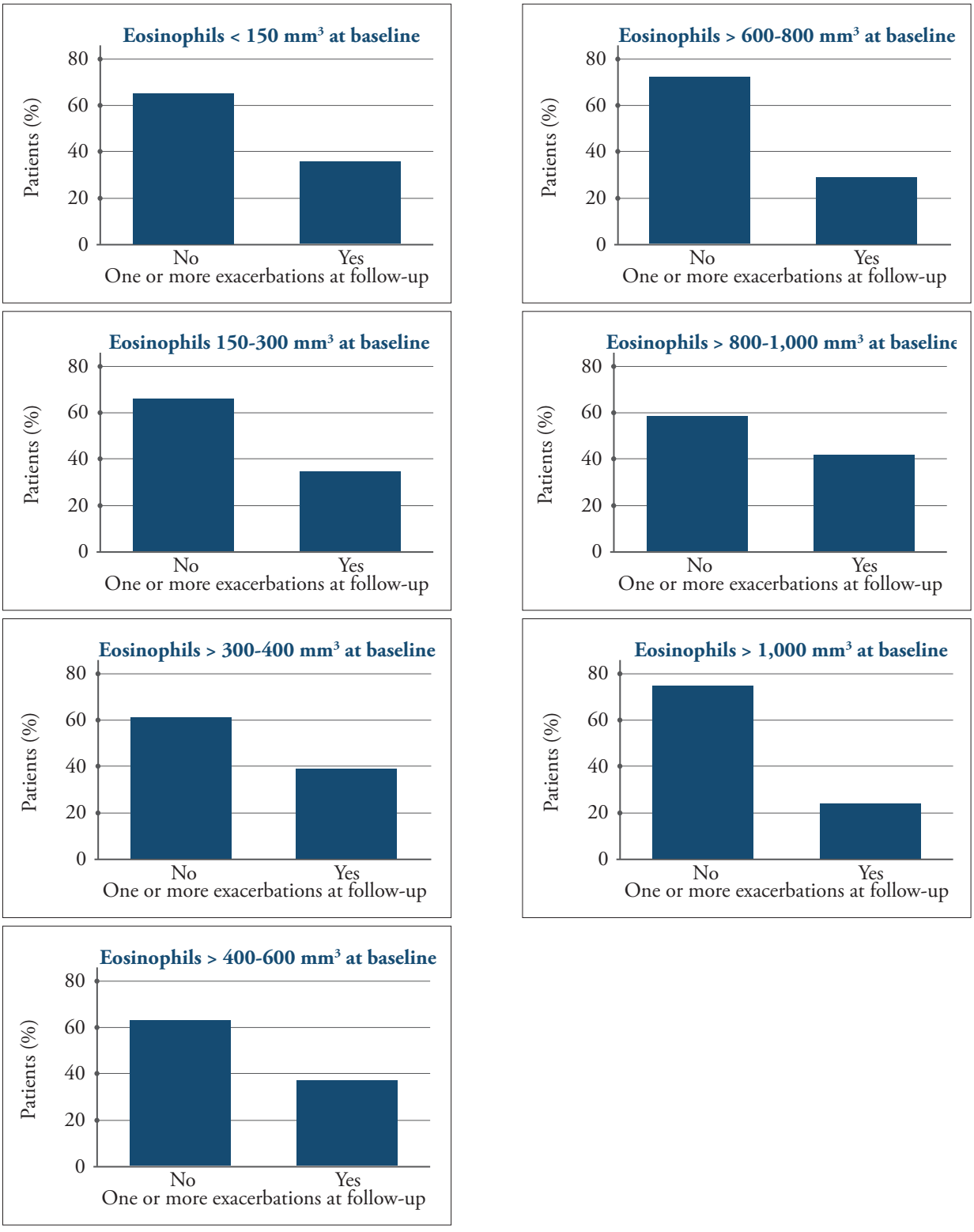
BMI: Body Mass Index; CI: confidence interval; FEV_1: Forced Expiratory Volume in 1 second; dGERD: diagnosed gastroesophageal reflux disease; LLN: Lower Limit of Normal FEV_1/FVC; °Simple logistic regression; *IgE >150 and/or Eos > 300 and/or FeNO > 25; §IgE > 150 and/or Eos > 150 and/or FeNO > 25.

-2.9 to -2.3; p < 0.001). Similar improvements were observed in patients with or without biologic treatment (patients with at least one exacerbation in the last 12 months, in patients without biologic treatments: from 90.1% of V0 to 42.7% of V1, IR from 3.9 to 0.97/person-year, respectively). Obesity, dGERD, and FEV_1/FVC<LLN were significantly associated with exacerbations at V1, according to the unadjusted analysis (**table II**), and they were confirmed by the adjusted analysis. T2 phenotype did not show a significant correlation with exacerbations. However, even if a linear relationship with BEC was not found, patients with BEC > 1000/mm^3 tended to experience exacerbations less frequently at V1, compared to patients with lower BEC (-11%, OR 0.6, 95%CI 0.3-1.0, p = 0.06) (**figure 1**). This trend is supported by the lower IRR in patients with BEC > 1,000/mm^3 (IRR 0.6, 95%CI 0.4-1.0, p = 0.05). There was a clear correlation between BMI and annual rate of exacerbations with an IRR of 1.8 (95%CI 1.2-2.6, p = 0.004) in patients with BMI > 30, compared to lower BMI values. In the BMI > 30 group, 43% of patients had at least one exacerbation at V1, compared with 29% and 35% of the < 25 and 25-30 BMI groups, respectively. Concerning lung function, no linear relationships were observed between FEV_1 or FEV_1/FVC and exacerbations. However, in case of FEV_1/FVC < LLN at V0, an increase at V1 was recorded of both the number of patients with at least one exacerbation (+9.2%, OR 1.5, 95%CI 1.1-2.1, p = 0.02) and exacerbation rate (IRR 1.4, 95%CI 1.1-2.0, p = 0.02).

Treatments

Overall, the frequency of patients taking maintenance OCS decreased from 31% to 21% at V1 (**table I**), and 91% of the patients managed to reach at least a 50% dose reduction. This was mostly due to the OCS sparing effect observed after the initiation of biologic therapy. In addition, low baseline FEV_1 reversibility was identified as an independent factor associated with OCS withdrawal/reduction, *i.e.*, in case of ≥ 100 ml reversibility, -25.1% of patients were able to withdraw OCS (OR 0.3, p = 0.001; **table II**). On the contrary, the use of biologics increased from 63% to 82%, and 11% of patients switched to a different biologic at V1 (**figure 2**). No significant differences were observed in inhaled treatments from V0 to V1. Patients taking high ICS dose (as per GINA 2019 (20) classification) slightly decreased from 66.0% to 59.4%. No difference in the frequency of Long-Acting Muscarinic Antagonists and LTRA was observed, with a similar distribution between patients in and out of biologic treatment. However, in the subgroup of patients not treated with biologics, the maintenance OCS therapy did not change significantly from V0 (47.6%) to V1 (42.7%).
Good response to biologics was recorded in 69.9% of patients, namely in 81.1% and 64.7% of OCS and non-OCS-dependent patients, respectively. Their characteristics are shown in **table III**. The adjusted analysis confirmed the negative association between good response and atopic status (OR 0.5, 95%CI 0.2-0.9, p = 0.038), and the positive association with high BEC (OR 2.3, 95%CI 1.2-4.3, p = 0.011 for BEC > 600/mm^3) and education (OR 3.5, 95%CI 1.4-9.1, p = 0.010 for bachelor or higher degree), but not the relationship with ASA hypersensitivity. Good responders were more frequently treated with OCS (OR 2.3, 95%CI 1.3-4.2, p = 0.005), compared to poor responders. The ROC analysis showed an AUC = 59% (95%CI 53%-66%) in predicting good

Figure 1 *- Frequency of patients with at least one exacerbation at follow-up, per categories of baseline peripheral eosinophils (n = 553).*



response to biologics, with 84% specificity and 35% sensitivity at the BEC cut-off of 635/mm^3 (Youden index).

Discussion

The results of this study provide insights into various aspects of the real-world management of SA after 1 year of follow-up, in Italy, concerning the feature of patients, the effectiveness of the therapy, the predictors of efficacy, the features of non-responders, and finally the homogeneity of therapeutic outcomes across the country, despite different regional health services and different healthcare providers.

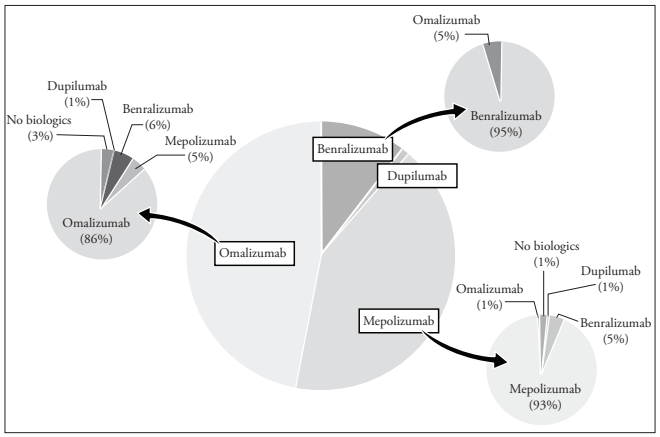
Patients' characteristics

In general, the baseline characteristics of the patients were similar to the ones previously reported by IRSA (14). Most of the patients showed a T2 phenotype (77.3% and 86.6% for T2_300 and T2_150, respectively). Our prevalence of patients with non-T2 phenotype (13.4%) is consistent with the one resulted from Ricciardolo *et al.* (21) (19.5%), where similar cut-off values for T2 were used, specifically focused on phenotyping of SA in Italy, using non-invasive parameters. The slight mismatch between the two figures is probably due to patients with BEC between 150 and 300, that are included in the T2 phenotype in our study (within the T2_150 group) because they are eligible for mepolizumab and dupilumab, but who are excluded from T2 phenotype by Ricciardolo *et al.*

Asthma control and lung function

In terms of ACT-based control, notwithstanding the intrinsic limitation of this self-reported tool due to the short 4-week timeframe considered, asthma was uncontrolled in 60.8% of patients. A significant improvement was observed, as evidenced by a 37.7% increase in the number of patients reaching an ACT score ≥ 20 at V1. Moreover, 45% of patients achieved the MCID in the ACT score.

Figure 2 *- Change in biologic treatment from baseline (large chart) to follow-up (small charts).*



These results demonstrate the effectiveness of the management of patients adhering to a registry in terms of interventions and treatments employed during the follow-up period in enhancing asthma control, as already reported by the literature (10). T2 phenotype – in particular high BEC and, to a lesser extent, total IgE – was a good predictor of control (OR 3.1 and 3.6 for T2_300 and T2_150, respectively), as well as nasal polyposis (OR 2.0). Numerous findings show close links between chronic rhinosinusitis with nasal polyps and asthma: both conditions are linked through the underlying T2 inflammation. Indeed, a clear relationship has been reported between control of upper airway disease and control of lower airway disease in patients with nasal polyps and asthma (22). Diagnosed dGERD was confirmed to be a troublesome comorbidity in asthma (OR for control 0.4) (23, 24). In addition, osteoporosis was related to poor asthma control (OR 0.5), possibly due to the consequent low quality of life in all aspects of the daily life of these patients or to the association with OCS consumption, and therefore to severity of asthma. Interestingly, patients living in rural areas obtained better control than the ones in industrial/urban areas (OR 2.3), supporting the detrimental effect of pollution on asthma (25).

The study outcomes from IRSA demonstrated a substantial decrease in the number of patients experiencing at least one exacerbation in the last 12 months. The exacerbation rate dropped significantly too, indicating a notable improvement in exacerbation control. Obesity and dGERD were confirmed as strong predictor of poor control in terms of exacerbations (26, 27) at follow-up (OR 1.7 and 1.6, respectively), followed by airflow obstruction assessed as $FEV_1/FVC < LLN$ (OR 1.5). Interestingly, other parameters of lung function, including absolute and predicted percent values of FEV_1 or FEV_1/FVC, did not show significant correlations with risk of exacerbations. T2 phenotype did not show a significant role as a predictor of exacerbations at follow-up. Conversely, BEC was the main driver for exacerbation, within the considered biomarkers (**figure 1**), highlighting the role of eosinophilic inflammation in exacerbation and as a marker of response to treatments.

Overall, lung function improved both in terms of FEV_1 and FEV_1/FVC over the follow-up period. Improvement in FEV_1 (frequency of $FEV_1 \geq 100$ ml and/or increase of absolute FEV_1 at V1) was hampered by older age, exposure to smoke, and obesity. Conversely, T2 phenotype and professional asthma were predictors of FEV_1 improvement. These data confirm that there is a complex relationship between inflammation and lung function in SA, and lung function may be associated with other factors (28, 29).

Effectiveness of therapy at follow-up

The change in treatments recorded at V1 reflected the better control of asthma, compared to V0. In fact, a significant decrease in use of OCS was observed at follow-up, and only few patients switched to different biologics. The switch to different biologics in 11% of patients was consequent to the progressive marketing authorization

Table III – *Baseline characteristics of good and poor responders to biologics at follow-up in patients on biologic treatment (n = 322).*

	Poor responders n = 99 (30.8%)	Good responders n = 223 (69.2%)	P-value
General characteristics			
Females	56.6%	58.3%	0.772
Age	56.2 ± 1.3	56.7 ± 0.8	0.692
BMI	26.6 ± 0.5	26.8 ± 0.4	0.758
Smoking status			
Active	4.0%	5.4%	0.729
Former	27.3%	23.8%	
Never	68.7%	70.9%	
Age at symptom's onset	30.5 ± 1.7	30.5 ± 1.1	0.977
Atopy	85.7%	71.3%	**0.006**
Occupational exposure at risk	28.4%	33.3%	0.420
Professional asthma	8.1%	11.8%	0.365
Rural area of residence	11.4%	16.4%	0.272
Bachelor or higher education	7.1%	18.4%	**0.001**
Biological and functional characteristics			
Median total IgE kU/L (IQR)	263 (155, 527)	225 (125, 450)	0.409
Median Eosinophils/mm^3 (IQR)	266.1 (80.3, 508)	335 (132.3, 814.3)	**0.008**
< 150	39.2%	27.4%	**0.038**
150-300	13.4%	16.7%	0.457
> 300	47.4%	55.8%	0.169
Median FeNO ppb	26 (15, 65)	25.5 (20.7, 42)	0.892
Phenotype T2_300°			
T2_300	78.4%	76.4%	0.754
non-T2	21.6%	23.6%	0.754
Phenotype T2_150°			
T2_150	84.5%	87.4%	0.486
non-T2_150	15.5%	12.6%	0.486
Median ACT score (IQR)	20 (16, 23)	18 (15, 21)	**0.018**
ACT score ≥ 20	51.5%	38.1%	**0.025**
Lung function			
FEV_1 %pred	70.4 ± 1.9	72.2 ± 1.4	0.444
FEV_1 post-bronchodilator %pred	79.5 ± 1.8	81.1 ± 1.4	0.503
FVC %pred	88.3 ± 1.9	87.9 ± 1.2	0.870
FVC post-bronchodilator %pred	95.7 ± 1.7	93.5 ± 1.2	0.295
FEV_1/FVC	69 ± 1.8	69.6 ± 1.1	0.434
FEV_1/FVC post-bronchodilator	70.7 ± 1.6	73.2 ± 1.1	0.187

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Exacerbations (last 12 months)			
Rate/person-year	1.9 0.2	3.8 0.2	**< 0.001**
Patients with ≥ 1 exacerbations	78.6%	100%	**< 0.001**
Access to Emergency Department	18.4%	18.8%	0.957
Hospitalizations	13.3%	15.3%	0.644
Comorbidities*			
Sinusitis	57%	55.1%	0.764
Nasal polyps	52.2%	49.3%	0.645
Hypertension	24.7%	31.7%	0.212
Osteoporosis	23%	19.7%	0.527
Diagnosed GERD	27.2%	20.3%	0.190
BMI > 30	22.2%	20.2%	0.677
ASA hypers	21.1%	11.9%	**0.037**
Bronchiectasis	22.2%	14.8%	0.315
Cataract	7.5%	8.9%	0.696
Diabetes	8.3%	7.8%	0.883
Treatments			
Inhaled Corticosteroids[§]			
High dose	63.3%	62.2%	0.225
Medium dose	36.7%	37.9%	
Long-acting Muscarinic Antagonists	46.9%	36.8%	0.093
Antileukotrienes	43.9%	51.6%	0.204
Oral corticosteroids	17.2%	32.7%	**0.004**
Biologics			
anti-IgE	59.80%	39.70%	**0.005**
anti-IL5(R)	39.4%	58.3%	
anti-IL4/IL13	0%	1.80%	
Thermoplasty	1.0%	1.4%	0.802

ACT: Asthma Control Test; BMI: Body Mass Index; FeNO: Fractional Exhaled Nitric Oxide; FEV_1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; IQR: Interquartile Range; LCA: Latent Class Analysis. Mean ± standard deviation values are reported, if not otherwise specified. °T2_300 phenotype: IgE > 150 and/or Eos > 300 and/or FeNO > 25; T2_150 phenotype: IgE > 150 and/or Eos > 150 and/or FeNO > 25. [§]High and medium dose according to GINA 2019. *Not reported and not included in the analyses when < 5% of the study population (*i.e.* psychological disorders, food allergy, sleep apnea, ABPA, vasculitis, atopic dermatitis).

of new biologics, and is similar to the switching frequency reported by the UKSAR (12.1%) (9), as well as the trend of the decision making about the first biologic to use among dual eligible patients. The slight differences in the choice of second-line treatment after switching, between IRSA and UKSAR, can be justified by the different characteristics of SA in UKSAR, compared with SA in IRSA, *e.g.*, higher frequency of OCS maintenance therapy (55.2%) and exacerbations (median number in the last 12 months: 5), lower frequency of atopy (52.9%) (9). Conversely, no withdrawals of biologic therapy were observed in IRSA over one year of follow-up, suggesting the possibility to catch a late therapeutic efficacy (30). A significant improvement of asthma outcomes was also observed in patients not treated with biologics. However, this was likely due to the high frequency of maintenance OCS, administered before and during the follow-up period in almost half of these patients, suggesting room for optimization of asthma management. In addition, the frequency of thermoplasty was also higher in patients not treated with biologics (3.9%). The more frequent use of maintenance OCS in patients not treated with biologics is confirmed by RItA (10).

The significant improvement over the follow-up period was probably due to the increasing availability of biologics over the last years, also considering the high frequency of T2 phenotype in the registry, that is

the current main target of these therapies. In addition, the closer follow-up of patients enrolled in any study or registry with the possibility of modifying and optimizing the treatment might help the management of asthma. These results are in line with the data from RItA (10), where the quite high frequency of persistence/worsening asthma after a 1-year follow-up (53.9%) was justified with the availability of just one anti-IgE biologic, compared to other studies/registries where anti-IL5(R) treatments were already authorized. In fact, RItA showed that, at baseline, patients with controlled asthma on omalizumab were about twice as numerous as those treated with ICS-LABA only, but in the absence of other biological agents (which were not available at the time of the study), this result remained stable over one year of follow-up. This apparent stability is a result of a complex migration of patients through the different levels of asthma severity (controlled, severe, very severe) throughout the year, due to the interplay between spontaneous fluctuation of severity and the effect of the periodic therapy reviews conducted by doctors participating in the registry. On the other hand, if there are many therapeutic options available, there may be potential for further improvement. In our registry, the case-by-case selection process, conducted by physicians, to differentiate between responders and non-responders to ongoing treatments, applied to both patients receiving biologic and non-biologic drugs (approximately half of these patients switched to biologics between V0 and V1), and the consequent switching within biologics, when necessary (*i.e.*, 11% of cases), contributed to enhancing the overall outcomes of our patients. Moreover, our results confirm the trend observed in RItA (10) concerning obesity, dGERD, and, to a lesser extent, smoking as risk factors for persistence/worsening of asthma, but we did not find association with older age of asthma diagnosis.

After one year from enrolment in IRSA, the improvement of the key outcomes of SA treatment (improvement in asthma control and lung function, decrease of exacerbations, decrease/discontinuation of add-on OCS) was documented in 69% of subjects on biologic treatment (**table III**), which is greater than the average effect obtained in the registrational trials (50%) (31). This is consistent with the known positive effects of entering a disease registry, which include standardized follow-up and fine-tuning of therapy by doctors involved in the registry (32). Additionally, the availability of a broader range of therapeutic options is essential for improvement of SA.

Poor responders to biologics

Poor responders to biologic therapy (30.8%) present less severe symptoms at baseline, compared to responders, in terms of symptom control, number of exacerbations per year, and OCS consumption, although the prevalence of emergency department visits and hospitalizations is similar. In terms of objective disease indicators, there is a substantial homogeneity in the prevalence of the T2 and non-T2 phenotypes, comorbidities, and level of respiratory function, although in poor responders there is an increased prevalence of atopy and lower BEC. In fact, BEC seems to play a major role in predicting good response (*i.e.*, the higher the better, OR 2.3 in BEC > 600/mm^3), but the accuracy when used as a single biomarker was too low to be used in clinical practice (AUC < 60%). The multivariate analysis aiming to assess the balance between factors favoring and hindering the effectiveness of therapy shows that the presence of T2 inflammation is the best positive prognostic factor for improving symptom control and respiratory function. Conversely, the presence of comorbidities, particularly dGERD, BMI > 30, and a LLN of FEV_1/FVC, counteract clinical improvement. Furthermore, our results confirm that people treated with biologics with higher levels of education are more likely to have their asthma controlled than people with lower levels of education. This is in line with the higher mortality in case of low education, in asthma and other diseases (33, 34), and it is likely due to a better understanding of asthma and therapeutic options, with consequent higher adherence to treatments and to necessary lifestyle changes (35-37).

Homogeneity of outcomes

No significant difference in exacerbations was observed among centers, suggesting that the size of the facility (*i.e.*, large *versus* medium-small centers), within the IRSA centers, was not a predictive factor. The organizational models for managing SA vary from country to country. For instance, the UKSAR (9) presents the results of biologic therapy from 10 SA specialized centers, while in Italy, the national health service is structured into 21 regional health services, some of which may have specialized centers for SA and others may not. The only element of homogeneity lies in the eligibility criteria for individual biologics, which regulate the prescription of biologics throughout the country. The effectiveness of biologic therapy is similar between the two registries and is not influenced by geographic variations or the number of patients/centers involved. However, in line with the higher burden of asthma in the UK, some data suggest that the average severity of asthma symptoms in patients with SA in Italy is lower than what is observed in UK cases (9).

Weaknesses and strengths

The limitations of studies based on routine data, such as potential selection bias (*e.g.*, drop out at follow-up) or hidden confounders related to real-world populations, are well-known. However, the large sample size, consecutive enrolment of all the eligible patients, the homogeneous distribution of the IRSA sites, and the sensitivity analysis help to mitigate these potential biases in our study, providing a representative sample of Italian patients with SA. Another limitation of the study is that the change in biologics during the observation time is not the result of a head-to-head comparison of biologics, but rather the outcome of physician decision-making in accordance with patients' unmet needs and the different dates of availability of biologics in the market. Further accrual of data in the registry, over a follow-up period longer than 1 year, will probably help in better understanding the natural history of SA and the long-term effect of biologic treatments.

In conclusion the enrolment in the IRSA registry documented, just after one year, the improvement of the key outcomes of SA treatment in the majority of patients, highlighting the role of this tool in improving the management of the disease, possibly by strengthening the specialist-patient relationship.
Moreover, results from the IRSA Registry confirm the high effectiveness of biologic therapy targeting T2 inflammation, when implemented as part of a planned follow-up strategy aimed at optimizing and fine-tuning the therapy. However, despite this excellent result, effective treatment of SA remains an unmet need for approximately one-third of these patients. Furthermore, the study identifies potential biomarkers and factors associated with treatment response, highlighting the importance of personalized approaches in managing SA.

Fundings

None.

Contributions

MBB, MM, LA, FDM, AV, AM, CM: writing - original draft. MM: statistical analysis. All authors: writing - review & editing, patients enrollment.

Conflict of interests

The authors declare that they have no conflict of interests related to this work.

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References

1. Song P, Adeloye D, Salim H, Dos Santos JP, Campbell H, Sheikh A, et al. Global, regional, and national prevalence of asthma in 2019: a systematic analysis and modelling study. J Glob Health. 2022;12:4052. doi: 10.7189/jogh.12.04052.
2. Nunes C, Pereira AM, Morais-Almeida M. Asthma costs and social impact. Asthma Res Pract. 2017;3:1. doi: 10.1186/s40733-016-0029-3.
3. GDB 2017. Global Burden of Disease Study 2017. Available at: https://vizhub.healthdata.org/gbd-compare. Last access date: 07/03/2023.
4. Engelkes M, de Ridder MA, Svensson E, Berencsi K, Prieto-Alhambra D, Lapi F, et al. Multinational cohort study of mortality in patients with asthma and severe asthma. Respir Med. 2020;165:105919. doi: 10.1016/j.rmed.2020.105919.
5. Global Initiative for Asthma (GINA). Difficult-to-treat and severe asthma in adolescent and adult patients. Diagnosis and management. A GINA pocket guide for health professionals. 2019. Available at: https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf. Last access date: 07/03/2023.
6. Wenzel SE. Severe Adult Asthmas: Integrating Clinical Features, Biology, and Therapeutics to Improve Outcomes. Am J Respir Crit Care Med. 2021;203(7):809-821. doi: 10.1164/rccm.202009-3631CI.
7. Couillard S, Pavord ID, Heaney LG, Petousi N, Hinks TSC. Sub-stratification of type-2 high airway disease for therapeutic decision-making: A 'bomb' (blood eosinophils) meets 'magnet' (FeNO) framework. Respirology. 2022;27(8):573-7. doi: 10.1111/resp.14294.
8. Burn J, Sims AJ, Patrick H, Heaney LG, Niven RM. Efficacy and safety of bronchial thermoplasty in clinical practice: a prospective, longitudinal, cohort study using evidence from the UK Severe Asthma Registry. BMJ Open. 2019;9(6):e026742. doi: 10.1136/bmjopen-2018-026742.
9. Mansur AH, Gonem S, Brown T, Burhan H, Chaudhuri R, Dodd JW, et al. Biologic therapy practices in severe asthma; outcomes from the UK Severe Asthma Registry and survey of specialist opinion. Clin Exp Allergy. 2022. doi: 10.1111/cea.14222. Epub ahead of print.
10. Maio S, Murgia N, Tagliaferro S, Angino A, Sarno G, Carrozzi L, et al. The Italian severe/uncontrolled asthma registry (RItA): A 12-month clinical follow-up. Respir Med. 2022;205:107030. doi: 10.1016/j.rmed.2022.107030.
11. Solidoro P, Nicola S, Ridolfi I, Canonica GW, Blasi F, Paggiaro P, et al. Biologics in Severe Eosinophilic Asthma: Three-Year Follow-Up in a SANI Single Center. Biomedicines. 2022;10(2):200. doi: 10.3390/biomedicines10020200.
12. Graff S, Brusselle G, Hanon S, Sohy C, Dupont L, Peche R, et al. Anti-Interleukin-5 Therapy Is Associated with Attenuated Lung Function Decline in Severe Eosinophilic Asthma Patients From the Belgian Severe Asthma Registry. J allergy Clin Immunol Pract. 2022;10(2):467-77. doi: 10.1016/j.jaip.2021.09.023.
13. Micheletto C, Bilò MB, Antonicelli L, Bresciani M, D'Amato G, De Benedictis E, et al. Severe asthma in adolescents and adults: a national, multicenter registry in real life. Eur Ann Allergy Clin Immunol. 2018;50(5):196-201. doi: 10.23822/EurAnnACI.1764-1489.69.
14. Bilò MB, Antonicelli L, Carone M, De Michele F, Menzella F, Musarra A, et al. Severe asthma management in the era of biologics: insights of the Italian Registry on Severe Asthma (IRSA). Eur Ann Allergy Clin Immunol. 2021;53(3):103-14. doi: 10.23822/EurAnnACI.1764-1489.196.
15. Senna G, Latorre M, Bugiani M, Caminati M, Heffler E, Morrone D, et al. Sex Differences in Severe Asthma: Results From Severe Asthma Network in Italy-SANI. Allergy Asthma Immunol Res. 2021;13(2):219-28. doi: 10.4168/aair.2021.13.2.219.
16. Menzies-Gow A, Hoyte FL, Price DB, Cohen D, Barker P, Kreindler J, et al. Clinical Remission in Severe Asthma: A Pooled Post Hoc Analysis of the Patient Journey with Benralizumab. Adv Ther. 2022;39(5):2065-84. doi: 10.1007/s12325-022-02098-1.
17. Bonini M, Di Paolo M, Bagnasco D, Baiardini I, Braido F, Caminati M, et al. Minimal clinically important difference for asthma endpoints: an expert consensus report. Eur Respir Rev. 2020;29(156):190137. doi: 10.1183/16000617.0137-2019.
18. Brusselle GG, Koppelman GH. Biologic Therapies for Severe Asthma. N Engl J Med. 2022;386(2):157-171. doi: 10.1056/NEJMra2032506.
19. European Medicines Agency (EMA). Guideline on registry-based studies. EMA/426390/2021. 2021. Available at: https://www.ema.europa.eu/en/guideline-registry-based-studies-scientific-guideline. Last access date: 07/03/2023.

20. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention - 2019 update. 2019. Available at: https://ginasthma.org/reports. Last access date: 07/03/2023.
21. Ricciardolo FLM, Sprio AE, Baroso A, Gallo F, Riccardi E, Bertolini F, et al. Characterization of T2-Low and T2-High Asthma Phenotypes in Real-Life. Biomedicines. 2021;9(11):1684. doi: 10.3390/biomedicines9111684.
22. Laidlaw TM, Mullol J, Woessner KM, Amin N, Mannent LP. Chronic Rhinosinusitis with Nasal Polyps and Asthma. J Allergy Clin Immunol Pract. 2021;9(3):1133-41. doi: 10.1016/j.jaip.2020.09.063.
23. Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. Am J Respir Crit Care Med. 2010;181(4):315-23. doi: 10.1164/rccm.200906-0896OC.
24. Shaw DE, Sousa AR, Fowler SJ, Fleming LJ, Roberts G, Corfield J, et al. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. Eur Respir J. 2015;46(5):1308-21. doi: 10.1183/13993003.00779-2015.
25. Tiotiu AI, Novakova P, Nedeva D, Chong-Neto HJ, Novakova S, Steiropoulos P, et al. Impact of Air Pollution on Asthma Outcomes. Int J Environ Res Public Health. 2020;17(17):6212. doi: 10.3390/ijerph17176212.
26. Porsbjerg C, Menzies-Gow A. Co-morbidities in severe asthma: Clinical impact and management. Respirology. 2017;22(4):651-61. doi: 10.1111/resp.13026.
27. McDonald VM, Hiles SA, Godbout K, Harvey ES, Marks GB, Hew M, et al. Treatable traits can be identified in a severe asthma registry and predict future exacerbations. Respirology. 2019;24(1):37-47. doi: 10.1111/resp.13389.
28. Moore WC, Fitzpatrick AM, Li X, Hastie AT, Li H, Meyers DA, et al. Clinical heterogeneity in the severe asthma research program. Ann Am Thorac Soc. 2013 Dec;10 Suppl(Suppl):S118-24. doi: 10.1513/AnnalsATS.201309-307AW.
29. Manni ML, Trudeau JB, Scheller E V, Mandalapu S, Elloso MM, Kolls JK, et al. The complex relationship between inflammation and lung function in severe asthma. Mucosal Immunol. 2014;7(5):1186-98. doi: 10.1038/mi.2014.8.
30. Khaleva E, Rattu A, Brightling C, Bush A, Bourdin A, Bossios A, et al. Definitions of non-response and response to biological therapy for severe asthma: a systematic review. ERJ Open Res. 2023;9(3):00444-2022. doi: 10.1183/23120541.00444-2022.
31. Agache I, Beltran J, Akdis C, Akdis M, Canelo-Aybar C, Canonica GW, et al. Efficacy and safety of treatment with biologicals (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) for severe eosinophilic asthma. A systematic review for the EAACI Guidelines - recommendations on the use of biologicals in severe asthma. Allergy. 2020;75(5):1023-42. doi: 10.1111/all.14221.
32. Gibeon D, Heaney LG, Brightling CE, Niven R, Mansur AH, Chaudhuri R, et al. Dedicated severe asthma services improve health-care use and quality of life. Chest. 2015;148(4):870-6. doi: 10.1378/chest.14-3056.
33. Alicandro G, Frova L, Sebastiani G, Boffetta P, La Vecchia C. Differences in education and premature mortality: a record linkage study of over 35 million Italians. Eur J Public Health. 2018;28(2):231-7. doi: 10.1093/eurpub/ckx125.
34. Serrano-Pariente J, Rodrigo G, Fiz JA, Crespo A, Plaza V. Identification and characterization of near-fatal asthma phenotypes by cluster analysis. Allergy. 2015;70(9):1139-47. doi: 10.1111/all.12654.
35. Ilmarinen P, Stridsman C, Bashir M, Tuomisto LE, Vähätalo I, Goksör E, et al. Level of education and asthma control in adult-onset asthma. J asthma Off J Assoc Care Asthma. 2022;59(4):840-9. doi: 10.1080/02770903.2021.1871742.
36. Cope SF, Ungar WJ, Glazier RH. Socioeconomic factors and asthma control in children. Pediatr Pulmonol. 2008;43(8):745-52. doi: 10.1002/ppul.20847.
37. Redmond C, Akinoso-Imran AQ, Heaney LG, Sheikh A, Kee F, Busby J. Socioeconomic disparities in asthma health care utilization, exacerbations, and mortality: A systematic review and meta-analysis. J Allergy Clin Immunol. 2022;149(5):1617-27. doi: 10.1016/j.jaci.2021.10.007.