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The Severe Asthma Network in Italy (SANI): findings and perspectives

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49 **ABSTRACT**

50

51 **Background:** Severe Asthma Network in Italy (SANI) is a registry of patients recruited by
52 accredited centers on severe asthma.

53

54 **Objective:** to analyze epidemiological, clinical, inflammatory, functional and treatment
55 characteristics of severe asthmatics from the SANI registry

56

57 **Methods:** All consecutive patients with severe asthma were included into the registry,
58 without exclusion criteria in order to have real-life data on demographics, asthma control,
59 treatments (including biologics), inflammatory biomarkers and comorbidities.

60

61 **Results:** 437 patients (mean age: 54.1 years, 57.2% females, 70.7% atopics, 94.5% in GINA
62 severity step 5) were enrolled into the study. Mean annual exacerbation rate was 3.75. Mean
63 blood eosinophil level was 536.7 cells/mcl and average serum total IgE was 470.3 kU/l. About
64 64% of patients were on regular oral corticosteroid treatment, 57% with omalizumab and
65 11.2% with mepolizumab. Most common comorbidities were rhinitis, nasal polyposis and
66 bronchiectasis. Patients with nasal polyposis had higher age of disease onset, higher blood
67 eosinophil count and lower frequency of atopy and atopic eczema. Bronchiectasis was
68 associated with more frequent severe exacerbations, higher blood eosinophils and total IgE.
69 Stratifying patients,, those with late-onset asthma were less frequently atopic (with less
70 frequent allergic rhinitis and food allergy), and more frequently with nasal polyposis and
71 higher serum total IgE levels.

72

73 **Conclusions:** This study revealed a high frequency of relevant comorbidities and that a
74 substantial proportion of patients have a late-onset asthma; all these features define specific
75 different disease phenotypes. Severe asthma complexity and comorbidities require
76 multidisciplinary approaches, led by specifically trained Pulmonologists and Allergists.

77

78

79 **Keywords:** Severe Asthma; Registry; Comorbidities; Nasal polyps; Bronchiectasis; Late-onset
80 asthma; SANI

81

82 **ABBREVIATIONS LIST:**

83 ACQ: Asthma Control Questionnaire

84 ACT: Asthma Control Test

85 AHRQ: Agency for Healthcare Research and Quality

86 CRSwNP: chronic rhinosinusitis with nasal polyps

87 ERS/ATS (European Respiratory Society/American Thoracic Society)

88 FENO: Fractional Exhaled Nitric Oxide

89 GINA: Global Initiative for Asthma

90 ICS: Inhaled CorticoSteroids

91 LABA: long-acting beta agonists

92 OCS: Oral CorticoSteroids

93 RItA: Italian registry of severe/uncontrolled asthma

94 SA: Severe Asthma

95 SANI: Severe Asthma Network in Italy

96 SIAAIC: Italian Society of Allergy, Asthma and Clinical Immunology)

97 SIP/IRS (Italian Respiratory Society)

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101

102 **HIGHLIGHTS BOX**

103

104 1. What is already known about this topic?

105 Severe asthma is a complex and heterogeneous disease, with different phenotypic and
106 endotypic expressions.

107

108 2. What does this article add to our knowledge?

109 This is a real-life snapshot on severe asthmatics enrolled for a clinical registry: real life data
110 are important to identify most relevant clinical characteristics of severe asthma

111

112 3. How does this study impact current management guidelines?

113 In this real-life study, patients with severe asthma are characterized by high expression of
114 inflammatory biomarkers (despite frequent chronic treatment with oral corticosteroids),
115 have different clinical phenotypes, and are associated with comorbidities (especially
116 bronchiectasis and nasal polyposis)

117 **Introduction**

118

119 Severe asthma (SA) is currently attracting a lot of interest, since quite a few unmet needs are
120 still to be answered. In fact, though most patients with asthma can be successfully controlled
121 with the current therapies, 5-10% of them remain uncontrolled despite standard treatment,
122 suffer from frequent exacerbations, require Emergency Room visits and hospitalizations, and
123 receive oral steroids on a regular or intermittent basis [1]. Severe asthma has a high social
124 and economic burden, as severe asthma accounts for 50% of global costs of the disease due to
125 high healthcare utilization, drugs used, hospital admissions and days lost from work [2-3].

126

127 In order to address this problem, several European networks, including the Italian Registry
128 RiTA (Italian registry of severe/uncontrolled asthma), whose data were recently published,
129 have been carried out in Europe in order to recruit the highest number of cases, to share
130 common diagnostic workups and to address different aspects of the disease [4-14]

131

132 In Italy, SANI (Severe Asthma Network in Italy), an Italian National observatory supported by
133 GINA (Global Initiative for Asthma) Italy—SIAAIC (Italian Society of Allergy, Asthma and
134 Clinical Immunology), SIP/IRS (Italian Respiratory Society) and Federasma (an asthma
135 patients' association), has been recently promoted and set up [15].

136

137 The aim of this network is to recruit patients with severe asthma, defined according to the
138 ERS/ATS (European Respiratory Society/American Thoracic Society) classification, enroll
139 them in a real life setting in accredited centers, and follow them over time using a database
140 management system [16] The present cross-sectional analysis focuses on the first available

141 baseline epidemiological, clinical, inflammatory, functional and treatment characteristics of a
142 large Italian population of SA patients from the SANI registry.

143

144 **Methods**

145

146 **Severe Asthma Network in Italy (SANI) and data collection**

147 The Italian asthma network SANI is a web-based observatory collecting demographic, clinical,
148 functional and inflammatory data of SA patients, recruited in Italian reference centers for
149 severe asthma, according to the ERS/ATS classification [1].

150 Each reference center (Allergy and/or Respiratory Disease Units) was accredited based upon
151 criteria: enough trained personnel dedicated to asthma (at least one specialist and one
152 nurse), population of treated asthmatic patients per year (at least 1000 patients per year),
153 availability of lung function equipment (spirometry, bronchodilation test, methacholine
154 challenge) and other clinical procedures (exhaled nitric oxide), availability of biologic
155 treatments among prescribable drugs and number and quality of scientific publications on
156 asthma and severe asthma. Each item, together with a relevant documentation, was evaluated
157 through a scoring system validated by the Scientific Committee (maximum score: 100 points).
158 To be eligible, each center must achieve a minimum score of 75. To date , 66 applicants have
159 reached the minimum threshold , distributed throughout the Italian territory (Figure 1).

160

161 The patient enrollment protocol has been approved by the Central Ethics Committee
162 (Comitato Etico Area Vasta Nord-Ovest Toscana; protocol number: study number 1245/2016,
163 protocol number: 73714) and the enrollment in the other Centers started upon approval of
164 each local Ethics Committee; to date , 21 Centers are enrolling patients.

165 Each participant center, after having obtained the approval of the local Ethics Committee, was
166 provided with the access code for anonymously entering patient's data into a web-based
167 platform (Eidos Infostat S.a.S. – Verona, Italy). For each patient, the investigators were invited
168 to collect baseline (at enrollment) and follow-up (at every visit or at least every 3 months)
169 data.

170

171 **Study population**

172 Patients aged >12 years with a diagnosis of SA according to the ERS/ATS criteria [1] were
173 eligible for inclusion into the study. Briefly, ERS/ATS recommendations define as severe
174 asthmatic a patient that, despite high doses of inhaled corticosteroids (ICS) plus another
175 controller or chronic oral corticosteroid therapy for at least 6 months in the previous year, is
176 still clinically uncontrolled (altered Asthma Control Test and/or Asthma Control
177 Questionnaire), or experiencing at least 2 acute asthma exacerbations per year (or at least one
178 severe exacerbation requiring emergency department admission, or hospitalization or
179 intubation), or is still having a compromised lung function ($FEV_1 < 80\%$ predicted value) [1].

180 Exclusion criteria have not been considered in order to have a realistic view of SA in real life.

181 For each participant the following information has been collected: demographic data (age,
182 sex, height, weight, body mass index - BMI), clinical features (age of onset of asthma,
183 presence of allergies and other comorbidity, lung function, exacerbations, unscheduled
184 visits), asthma control in the previous month according to the GINA (Global Initiative for
185 Asthma) Guidelines [17] and standardized questionnaires (asthma control test - ACT, asthma
186 control questionnaire ACQ), concomitant regular and on demand treatments (including
187 biologic agents) and inflammatory markers (fractional exhaled nitric oxide - FE_{NO} , eosinophils
188 in the blood and/or in the sputum).

189

190 **Ethical issues**

191 The observatory was carried out according to the declarations of Helsinki and Oviedo.

192 The SANI registry was set-up according to the 3rd Edition Recommendation on registries for
193 evaluating patients outcomes published by the Effective Health Care Program of the Agency
194 for Healthcare Research and Quality (AHRQ -
195 <https://effectivehealthcare.ahrq.gov/topics/registries-guide-3rd-edition/research/>) The
196 protocol has been performed according to the principles and procedures of the Good Clinical
197 Practice (ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996; Directive
198 91/507. EEC, The Rules Governing Medical Products in the European Community) and in
199 accordance with the Italian laws (D.L.vo n.211 del 24 Giugno 2003; D.L.n.200 del 6 Novembre
200 2007; MD del 21 Dicembre 2007).

201 The SANI initiative is supported by several pharmaceutical companies, listed in the
202 acknowledgement, which provided unrestricted grants and had no role in study design and
203 planned analysis.

204

205 **Statistical analysis**

206 Statistical analysis was performed using SPSS 21.0 software (SPSS, Chicago, IL, USA). The
207 Kolmogorov-Smirnov test was used to evaluate the normality of distribution of each
208 continuous variable, and depending on the result of this test, the Student t-test or Mann-
209 Whitney test was used to compare variables. Categorical variables were compared with the
210 Fisher exact test.

211 A p-value of < 0.05 was considered statistically significant.

212

213

214 **RESULTS:**

215 **Demographic data**

216 The data of 437 eligible patients were analyzed: almost all the patients (413, 94.5%) can be
217 classified as GINA therapeutic step V [17]. In the study population, more than half of patients
218 was females (57.2%) and the mean age was 54.1 years (Table 1). About 70% of patients were
219 sensitized to at least one airborne allergen and were defined as “atopic”. Forty-five percent
220 (45.1%) of patients had a normal BMI value whereas 35% and 19.9% of patients were
221 overweight and obese respectively. Furthermore 167 (38.2%) had a late onset of the disease
222 (defined as age of diagnosis > 40 years). The mean number of asthma exacerbations/year was
223 3.75 (Table 1).

224 **Comorbidities**

225 Several comorbidities were identified in our study population (Table 2). Concomitant upper
226 airways involvement was frequent: Nearly 70% had rhinitis, and chronic rhinosinusitis with
227 nasal polyps (CRSwNP) was observed in 42.6% of patients. Atopic eczema and confirmed
228 bronchiectasis were reported in 42 (9.6%) and 70 (16%) patients, respectively.

229 Patients with bronchiectasis, mainly present in GINA V patients, had worse disease control
230 (ACT: 16.2 vs 18.1, $p = 0.035$), higher number of severe exacerbations (admission to
231 Emergency Unit/year: 1.0 vs 0.4, $p < 0.001$; hospitalization per asthma/year: 0.44 vs 0.21, $p =$
232 0.038), higher peripheral count of eosinophils (763.2 vs 510.3, $p=0.045$) and higher level of
233 total IgE (1021.1 vs 374.2, $p<0.001$).

234 Patients with nasal polyposis had lower BMI (25.6 vs 27.3, $p = 0.048$), more elevated age of
235 disease onset (38.5 vs 32.4 years, $p = 0.047$; late-onset asthma: 51.7% vs 31.9%, $p = 0.023$)
236 and higher peripheral count of eosinophils (594.5 vs 425.4, $p = 0.042$); furthermore, they

237 were less frequently atopic (55.1% vs 86.0%, $p < 0.001$) and with lower prevalence of
238 associated atopic eczema (5.9% vs 23.6%, $p = 0.002$).

239

240 **Functional and biological data**

241 Functional and biological parameters are shown in Table 3. An ACT value less than 20 was
242 observed in one third of cases (36.2%). Mean FEV₁ and FVC values (% predicted) were 71.4
243 and 85.7, respectively, with a mean value of FEV₁/FVC ratio of 65.3. Mean blood eosinophils
244 count was 536.7/mm³ and FE_{NO} was 48.9 ppb. Total IgE average value was 470.3 Ku/L.

245

246 **Concomitant treatments**

247 All patients were on regular treatment with a combination of inhaled corticosteroids (ICS)
248 (mean dose: 1084.3 +/- 489.0 mg of fluticasone propionate equivalents) plus long-acting beta
249 agonists (LABA). Furthermore, 46.4% of patients received leukotriene receptor antagonist
250 and 35.7% a long-acting muscarinic antagonist in addition to the abovementioned treatment.
251 Omalizumab was used in more than 50% of cases. Finally, it is noteworthy that oral steroids
252 were administered to 64.1% of the study population (Table 4) (mean prednisone equivalent
253 dose: 11.4 +/- 8.0 mg)

254 When considering the eligibility for anti-IL5 and/or anti-IgE treatment, 257 (58.9%) patients
255 had blood eosinophil levels higher than 300/mcl (required for anti-IL5 eligibility), while 285
256 (65.0%) had serum IgE levels between 30 and 1500 IU/ml, at least one perennial allergen
257 sensitization and FEV₁<80% of predicted value (required for prescribing anti-IgE monoclonal
258 antibody omalizumab). About 35% (153) patients were potentially eligible for both biologic
259 agents classes.

260

261 **Age of asthma onset**

262 Mean age of asthma onset was 32.4 ± 17.1 years, but in 167 (38.2%) patients the disease
263 onset later than age 40 . and these patients were classified as “late onset” asthmatics.

264 Patients with late-onset asthma were less frequently atopic (at least one sensitization: 62.9%
265 vs 75.5%, $p=0.03$; perennial allergens sensitization: 53.3% vs 67.8%, $p=0.025$) and with less
266 frequent allergic comorbidities (allergic rhinitis: 35.9% vs 50.0%, $p=0.034$; food allergy: 1.8%
267 vs 13.0%, $p=0.006$), but they were characterized by higher prevalence of CRSwNP(56.3% vs
268 34.1%, $p=0.023$) and for having higher levels of serum total IgE (550.1 ± 1038.3 Ku/L vs
269 325.2 ± 289.9 Ku/L, $p = 0.049$).

270 A greater proportion of late-onset asthmatics were receiving treatment with omalizumab
271 (65.5% vs 43.1%, $p = 0.019$). (Table 5).

272

273 **Discussion**

274 This study is the report of the first available data collected in the context of the SANI registry
275 of patients with severe asthma. The great majority of patients had clinical, functional and
276 therapy-related features consistent with GINA V step severity classification. In fact, by
277 definition according to ERS/ATS recommendations [1] all of them were taking high-dose of
278 ICS plus another controller agent and, despite that, more than one-third of them had
279 suboptimal ACT values, 73% had FEV1 value below the normal limit, more than 60% were
280 chronically taking OCS and the great majority had more than two exacerbations/year.

281 From a demographic point of view, the mean age of patients was 57 years, with a higher
282 prevalence of females and overweight patients. In most of the patients Th-2 systemic and
283 airway inflammation was revealed by high levels of blood eosinophils and FE_{NO}.

284 The most prevalent comorbidities were rhinitis, observed in 70% of patients, followed by
285 nasal polyps and bronchiectasis. The latter two appeared to define two specific and different
286 phenotypes of patients: those with nasal polyps were less frequently atopic, with older age of
287 disease onset and higher blood eosinophils count, while those with associated bronchiectasis
288 had clinical and functional features of extremely severe asthma, presenting with worse
289 disease control and higher number of severe exacerbations (defined as admissions to
290 Emergency Unit and hospitalization for asthma attacks). Patients with associated
291 bronchiectasis were also characterized by very high levels of blood eosinophils and serum
292 IgE, suggesting a chronic persistent severe systemic Th2-inflammation.

293 This persistent degree of inflammation was present even in those patients regularly taking
294 OCS, suggesting that most of them are probably only partially sensitive to corticosteroids. The
295 frequent use of oral corticosteroids observed in our study can have a clinical impact on
296 patients in terms of clinical outcome and adverse events [12].

297 Moreover, about 70% of patients were sensitized to at least one airborne allergen, and 62% to
298 at least one perennial allergen, in line with literature data on high prevalence of severe
299 allergic asthma [18].

300 When considering the age of onset of asthma, about one third of our patients can be classified
301 as "late-onset" asthmatics [19] which has been described as a possible distinct phenotype of
302 severe asthma [20]. In our population, , those with late disease-onset were characterized by a
303 lower frequency of atopy (sensitization to both any allergen and perennial allergens), and
304 atopic diseases, reduced serum IgE levels and a higher prevalence of CRSwNP. In these

305 patients, blood eosinophil levels were not different compared to early-onset asthmatics, and
306 usually higher than 300 cells/mcl, the common cut-off value suggested to consider a possible
307 anti-IL5 biologic strategies in severe asthmatics [21].

308 Taking together the findings of high frequency of sensitization to perennial airborne
309 allergens, high blood eosinophils and serum IgE levels, it is possible to speculate that the
310 majority of patients are eligible to be treated by at least one of the available biologics (anti-
311 IgE or anti-IL5 drugs), with 35% of the entire population being eligible for both types of
312 biologic therapy . In actuality., nearly 70% of enrolled patients are being treated with
313 mepolizumab or omalizumab (the only two available biologic agents so far in Italy).

314

315 Recently, data from another Italian registry (the RiTA Registry) of about 500 uncontrolled
316 asthmatics have been published [14]. Based on a comparison of the results of the two registry
317 reports , patients included had similar characteristics in terms of mean age (range 54 – 57
318 years), sex (female prevalent) and BMI (overweight prevalent). Comorbidities and rates
319 observed in our study were similar to those reported in the RiTA Registry, particularly
320 regarding a high prevalence of upper airways involvement (rhinitis, CRSwNP). These findings
321 highlight the need for a prompt change of the diagnostic procedures and a different diagnostic
322 approach, involving other medical professionals such as ENT specialists. For example, nasal
323 endoscopy could be a recommended step in asthma diagnosis, not only due to the high
324 incidence of nasal polyps but also for their potential role in responsiveness to the biologic
325 drugs [22]. Furthermore, the relatively high incidence of bronchiectasis suggests that a high
326 resolution computerized tomography of the thorax should be added to the routine SA
327 diagnostic tools, at least in patients with GINA V severe asthma. Together, these observations
328 underline the need for a multidisciplinary approach to SA patients.

329 The therapeutic step V of GINA Guidelines recommends the use of medium to high dose
330 ICS/LABA combination therapy plus other drugs (tiotropium, anti-IgE, anti-IL5, low dose oral
331 corticosteroids for uncontrolled cases) for the treatment of SA patients.[17] Another major
332 difference between the two Italian Registries was the administration of oral corticosteroids,
333 almost 4 times higher in the SANI Registry than in the RiTA Registry.. There are two possible
334 explanations for the limited use of oral corticosteroids in the RiTA Registry. : The first is that
335 patients using anti-IgE monoclonal antibody reduced the intake of oral corticosteroids for the
336 management of uncontrolled asthma [23]. However, 57% of the patients in the SANI registry
337 also used omalizumab. The second more likely explanation is the higher prevalence of GINA
338 IV patients in the RiTA study, whereas in SANI, 94.5% of patients were stratified as GINA V,
339 and therefore more severe than in RiTA. The different characteristics of our registry can be
340 possibly explained by the fact that reference centers for severe asthma tend to manage the
341 most severe patients (i.e.: those requiring chronic OCS and/or those with indication for
342 biologic treatment).

343

344 Real-world evidence, which refers to epidemiological and clinical data derived from non-
345 clinical trial sources (electronic health records, disease or product registries and
346 observational trials), is an important current topic. While randomized controlled trials still
347 remain the gold standard of clinical research in order to minimize bias and to evaluate
348 efficacy and safety of a clinical intervention in experimental conditions, real world studies
349 evaluates the 'effectiveness' of a drug in a real-life context [24]. These studies consider the
350 common issues of the normal clinical practice (elderly or comorbid patients, unavailability of
351 diagnostic or monitoring tests, poor adherence to treatment, different schedules of dosing or
352 administration) and are able to provide a more realistic picture of what can be achieved with
353 a new treatment in normal clinical practice [25-27]. Our SANI Registry, as well as the other

354 national and international Asthma Registries, can offer the possibility to monitor the
355 epidemiology and the clinical response to the different treatments, including biologic drugs, of
356 SA patients in a real-life context, can improve healthcare decision making, and can be
357 considered a useful tool to confirm data collected for regulatory purposes [28].

358 Finally, we wish to mention the need and the relevance of the “Big Data” in asthma, as
359 recently highlighted by Diver and Brightling [29] and Bloom et al. [30].: The SANI project
360 perfectly fits in this context.

361

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365

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Table 1. Demographic and clinical characteristics of 437 SA patients

Parameter	Value
Age, years (mean, SD)	54.1 ± 13.7
Sex (females, %)	57.2%
Atopics	70.7%
Sensitized to perennial allergens	62.2%
Active smokers	2.7%
Past smokers	20.1%
BMI (mean, SD)	26.2 ± 5.0
BMI classes	
<18,5	1.6%
18,5 – 24,9	43.5%
25 – 29,9	35.0%
≥ 30	19.9%
Age of onset, years (mean, SD)	32.4 ± 17.1
Late onset* (n, %)	167 (38.2%)
Exacerbations/year (mean, SD)	3.75 ± 7.2
Exacerbations in the last 12 months:	
- 0	17.4%
- 1	11.2%
- 2	22.7%
- >2	48.7%
Emergency Dept/year (mean, SD)	0.49 ± 0,97
Hospitalizations/year (mean, SD)	0.25 ± 0.70
Intubation or mechanical ventilation /year (mean, SD)	0.06 ± 0.39

485 * Late onset is defined as age of diagnosis > 40 years.

486 SD, standard deviation; BMI, body mass index

487 **Table 2. Comorbidities of 437 SA patients**

Comorbidity	
Atopics	70.7%
Sensitized to perennial allergens	62.2%
Any kind of rhinitis	68.2%
Allergic rhinitis	44.6%
Food allergy	8.7%
CRSwNP	42.6%
Atopic eczema	9.6%
Bronchiectasis	16.0%

488 CRSwNP, chronic rhinosinusitis with nasal polyps

Table 3. Functional and biological features of SA patients

Parameter	
ACT (mean, SD)	17.2 ± 5.4
ACT classes	
<20	36.2%
20-24	19.6%
25	44.2%
Exhaled nitric oxide (FENO) ppb (mean, SD)	48.0 ± 46.3
Distribution of patients according to FENO:	
- ≤ 25 ppb	40.9%
- 25 – 40 ppb	18.2%
- > 40 ppb	40.9%
FEV ₁ % predicted (mean, SD)	71.4 ± 20.2
FVC % predicted (mean, SD)	85.7 ± 21.1
FEV ₁ /FVC (mean, SD)	65.3 ± 14.2
Blood eosinophils, mm ³ (mean, SD)	536.7 ± 650.9
Distribution of patients according to blood eosinophils:	
- ≤ 150 / mm ³	- 20.2%
- >150 / mm ³	- 79.8%
- >300 / mm ³	- 58.8%
Total IgE, Ku/L (mean, SD)	470.3 ± 812.9

490 SD, standard deviation; ACT, asthma control test; FeNO, fractional exhaled nitric oxide; FEV₁,
491 forced expiratory volume in the 1st second; FVC, forced vital capacity

493 **Table 4. Concomitant treatments**

Patients chronically taking OCS	64.1%
Mean OCS dose (Prednisone equivalents), (mg, SD)	10.7 ± 8.3
Patients taking LTRA	46.4%
Patients taking LAMA	35.7%
Patients taking Omalizumab	57.0%
Patients taking Mepolizumab	11.2%

494 OCS, oral steroid; LTRA, leukotriene receptor antagonist; LAMA, long-acting muscarinic antagonist

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Table 5. Demographic and clinical characteristics of SA patients according to the disease onset (early or late)

	Early onset (n=270)	Late onset* (n=167)	p value
Age, years (mean, SD)	50.0 ± 13.3	65.0 ± 9.0	<0.001
Gender (females, %)	63.7%	46.7%	0.253
Active smokers	3.3%	1.8%	0.894
Past smokers	17.4	24.5%	0.101
BMI (mean, SD)	25.7 ± 4.8	26.8 ± 5.1	0.750
BMI classes			
<18,5	1.8%	1.2%	0.327
18,5 – 24,9	46.7%	38.3%	
25 – 29,9	34.1%	36.5%	
≥ 30	17.4%	24.0%	
Atopics	75.5%	62.9%	0.030
Age of onset, years (mean, SD)	23.3 ± 10.8	52.3 ± 7.9	<0.001
ACT (mean, SD)	17.8 ± 5.5	17.3 ± 4.9	0.464
ACT classes			
<20	97 (35.9%)	61 (36.5%)	0.149
20-24	45 (16.7%)	41 (24.5%)	
25	128 (47.4%)	65 (39.0%)	
Exacerbations/year (mean, SD)	3.91 ± 8.8	3.41 ± 3.6	0.538
Emergency Dept/year (mean, SD)	0.53 ± 0.97	0.42 ± 0.89	0.376
Hospitalizations/year (mean, SD)	0.27 ± 0.82	0.21 ± 0.48	0.481
Intubation or mechanical	0.08 ± 0.49	0.05 ± 0.26	0.566

ventilation /year (mean, SD)			
Exhaled nitric oxide (FENO), ppb (mean, SD)	47.1 ± 42.5	48.4 ± 45.1	0.873
Distribution of patients according to FENO:			0.584
- ≤ 25 ppb			
- 25 – 40 ppb	37.3%	44.7%	
- > 40 ppb	18.7%	17.0%	
	44.0%	38.3%	
FEV1 % predicted (mean, SD)	71.1 ± 21.1	71.7 ± 20.0	0.811
FVC % predicted (mean, SD)	85.6 ± 22.3	87.9 ± 21.0	0.566
FEV1/FVC (mean, SD)	65.7 ± 13.7	65.0 ± 13.7	0.691
Blood eosinophils, mm ³ (mean, SD)	514.7 ± 615.9	539.8 ± 523.9	0.769
Distribution of patients according to blood eosinophils:			0.882
- ≤ 150 / mm ³			
- >150 / mm ³	20.6%	23.3%	
- >300 / mm ³	79.4%	76.7%	
	59.6%	58.9%	
Total IgE, Ku/L (mean, SD)	550.1 ± 1038.3	325.2 ± 289.9	0.049
Sensitized to perennial allergens	67.8%	53.3%	0.025
Any kind of rhinitis	70.0%	65.3%	0.254
Allergic rhinitis	50.0%	35.9%	0.034
Food allergy	13.0%	1.8%	0.006
CRSwNP	34.1%	56.3%	0.023
Atopic eczema	11,8%	6.0%	0.104

Bronchiectasis	17.0%	14.4%	0.543
Patients taking OCS	64.8%	62.9%	0.551
Patients taking LTRA	47.4%	44.9%	0.956
Patients taking LAMA	34.8%	37.1%	0.669
Patients taking Omalizumab	65.5%	43.1%	0.019
Patients taking Mepolizumab	11.8%	10.2%	0.369

498 * Late onset is defined as age of diagnosis > 40 years

499 SD, standard deviation; BMI, body mass index; CRSwNP, chronic rhinosinusitis with nasal polyps;

500 ACT, asthma control test; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in

501 the 1st second; FVC, forced vital capacity; OCS, oral steroid; LTRA, leukotriene receptor

502 antagonist; LAMA, long-acting muscarinic antagonist

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504 FIGURE LEGENDS:

505 **Figure 1.** Reference centers of the Severe Asthma Network in Italy (SANI). In green, the centers
506 already enrolling patients; in yellow, the centers who recently obtained the Ethic Committee
507 approval but still without any enrolled patient; in red, the centers still waiting for Ethic Committee
508 approval for enrolling patients.

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