The Severe Asthma Network in Italy: Findings and Perspectives

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

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Running title: Severe asthma registry data in Italy

The SANI Project was supported by GINA Italy / Federasma/ SIAAIC / SIP-IRS through Unrestricted support from: AstraZeneca, Glaxo-Smith & Kline, Novartis, Sanofi and Teva

No conflict of interest to declare.

Article words count: 2736

Abstract words count: 247

Figures: 1

Tables: 5

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ABSTRACT

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

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

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

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

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

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

ABBREVIATIONS LIST:

ACQ: Asthma Control Questionnaire

ACT: Asthma Control Test

AHRQ: Agency for Healthcare Research and Quality

CRSwNP: chronic rhinosinusitis with nasal polyps

ERS/ATS (European Respiratory Society/American Thoracic Society

FENO: Fractional Exhaled Nitric Oxide

GINA: Global Initiative for Asthma

ICS: Inhaled CorticoSteroids

LABA: long-acting beta agonists

OCS: Oral CorticoSteroids

RItA: Italian registry of severe/uncontrolled asthma

SA: Severe Asthma

SANI: Severe Asthma Network in Italy

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

SIP/IRS (Italian Respiratory Society

HIGHLIGHTS BOX

1. What is already known about this topic?

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

2. What does this article add to our knowledge?

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

3. How does this study impact current management guidelines?

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

Introduction

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

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

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

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

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

Methods

Severe Asthma Network in Italy (SANI) and data collection

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

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

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

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

Study population

Patients aged >12 years with a diagnosis of SA according to the ERS/ATS criteria [1] were eligible for inclusion into the study. Briefly, ERS/ATS recommendations define as severe asthmatic a patient that, despite high doses of inhaled corticosteroids (ICS) plus another controller or chronic oral corticosteroid therapy for at least 6 months in the previous year, is still clinically uncontrolled (altered Asthma Control Test and/or Asthma Control Questionnaire), or experiencing at least 2 acute asthma exacerbations per year (or at least one severe exacerbation requiring emergency department admission, or hospitalization or intubation), or is still having a compromised lung function (FEV_1<80% predicted value) [1]. Exclusion criteria have not been considered in order to have a realistic view of SA in real life. For each participant the following information has been collected: demographic data (age, sex , height, weight, body mass index - BMI), clinical features (age of onset of asthma, presence of allergies and other comorbidity, lung function, exacerbations, unscheduled visits), asthma control in the previous month according to the GINA (Global INitiative for Asthma) Guidelines [17] and standardized questionnaires (asthma control test - ACT, asthma control questionnaire ACQ), concomitant regular and on demand treatments (including biologic agents) and inflammatory markers (fractional exhaled nitric oxide - FE_{NO}, eosinophils in the blood and/or in the sputum).

Ethical issues

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

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

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

Statistical analysis

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

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

RESULTS:

Demographic data

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

Comorbidities

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

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

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

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

Functional and biological data

Functional and biological parameters are shown in Table 3. An ACT value less than 20 was observed in one third of cases (36.2%). Mean FEV_1 and FVC values (% predicted) were 71.4 and 85.7, respectively, with a mean value of FEV_1/FVC ratio of 65.3. Mean blood eosinophils count was 536.7/mm^3 and FE_{NO} was 48.9 ppb. Total IgE average value was 470.3 Ku/L.

Concomitant treatments

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

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

Age of asthma onset

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

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

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

ACKNOWLEDGEMENTS

We sincerely thank Dr.Piero Zucchi (Medical Writer) and Dr. Concetta Sirena (SANI Project Manager).

REFERENCES

1. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, Adcock IM, Bateman ED, Bel EH, Bleecker ER, Boulet LP, Brightling C, Chanez P, Dahlen SE, Djukanovic R, Frey U, Gaga M, Gibson P, Hamid Q, Jajour NN, Mauad T, Sorkness RL, Teague WG. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Resp J 2014; 43: 343-73
2. Accordini S, Corsico A, Cerveri I, Gislason D, Gulsvik A, Janson C, Jarvis D, Marcon A, Pin I, Vermeire P, Almar E, Bugiani M, Cazzoletti L, Duran-Tauleria E, Jõgi R, Marinoni A, Martínez-Moratalla J, Leynaert B, de Marco R; Therapy and Health Economics Working Group of the European Community Respiratory Health Survey II. The socio-economic burden of asthma is substantial in Europe. Allergy 2008 J;63(1):116-24
3. Heaney LG, Bel EH, Park HS, Wenzel S. Severe Asthma In: Pawankar R, Canonica GW, Holgate ST, Lockey RF, Blaiss MS, eds. World Allergy Organization (WAO). White Book on Allergy: Update 2013. 2013 World Allergy Organization (WAO), pp. 39-43
4. Schleich F, Brusselle G, Louis R, Vandenplas O, Michils A, Pilette C, Peche R, Manise M, Joos G. Heterogeneity of phenotypes in severe asthmatics. The Belgian Severe Asthma Registry (BSAR). Resp Med 2014; 108: 1723-32
5. Vennera Mdel C, Pérez De Llano L, Bardagí S, Ausin P, Sanjuas C, González H, Gullón JA, Martínez-Moragón E, Carretero JA, Vera E, Medina JF, Alvarez FJ, Entrenas LM, Padilla A, Irigaray R, Picado C; Spanish Registry. Omalizumab therapy in severe asthma :experience from the Spanish Registry-Some new approaches. J Asthma 2012; 49: 416-22

6. de Llano LP, Vennera Mdel C, Álvarez FJ, Medina JF, Borderías L, Pellicer C, González H, Gullón JA, Martínez-Moragón E, Sabadell C, Zamarro S, Picado C; Spanish Registry. Effects of omalizumab in non atopic asthma : results from a Spanish Multicentre Registry. J Asthma 2013; 50: 296-301
7. Caminati M, Senna G, Chieco Bianchi F, Marchi MR, Vianello A, Micheletto C, Pomari C, Tognella S, Savoia F, Mirisola V, Rossi A; NEONET Study Group. Omalizumab management beyond clinical trials: the added value of a network model. Pulm Pharmacol Ther 2014; 29: 74-9
8. Smith JR, Noble MJ, Musgrave S, Murdoch J, Price GM, Barton GR, Windley J, Holland R, Harrison BD, Howe A, Price DB, Harvey I, Wilson AM. The at risk registers in severe asthma (ARRISA) study: a cluster-randomized controlled trial examining effectiveness and costs in primary care. Thorax 2012; 67: 1052-60
9. Sweeney J, Brightling CE, Menzies-Gow A, Niven R, Patterson CC, Heaney LG; British Thoracic Society Difficult Asthma Network. Clinical management and outcome of refractory asthma in the UK from the British Thoracic Society Difficult Asthma Registry. Thorax 2012; 67: 754-6
10. Newby C, Heaney LG, Menzies-Gow A, Niven RM, Mansur A, Bucknall C, Chaudhuri R, Thompson J, Burton P, Brightling C; British Thoracic Society Severe Refractory Asthma Network. Statistical cluster analysis of the British Thoracic Society Severe Refractory Asthma Registry: clinical outcome and phenotype stability. Plos One 2014; 9 (7): e102987
11. O'Neill S, Sweeney J, Patterson CC, Menzies-Gow A, Niven R, Mansur AH, Bucknall C, Chaudhuri R, Thomson NC, Brightling CE, O'Neill C, Heaney LG; British Thoracic Society Difficult Asthma Network. The cost of treating severe refractory asthma in the UK: an economic analysis from the British Thoracic Society Difficult Asthma Registry. Thorax 2015; 70: 376-8

12. Sweeney J, Patterson CC, Menzies-Gow A, Niven RM, Mansur AH, Bucknall C, Chaudhuri R, Price D, Brightling CE, Heaney LG; British Thoracic Society Difficult Asthma Network. Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry. Thorax 2016; 71 :339-46
13. Pretolani M, Soussan D, Poirir I, Thabut G, Aubier M, on behalf of the COBRA study group. Clinical and biological characteristics of the French COBRA cohort of adult subjects with asthma. Eur Respir J. 2017 Aug 24;50(2). pii: 1700019
14. Maio S, Baldacci S, Bresciani M, Simoni M, Latorre M, Murgia N, Spinozzi F, Braschi M, Antonicelli L, Brunetto B, Iacovacci P, Roazzi P, Pini C, Pata M, La Grasta L, Paggiaro P, Viegi G; AGAVE group. RItA: The Italian severe/uncontrolled asthma registry. Allergy. 2018 Mar;73(3):683-695. doi: 10.1111/all.13342.
15. Senna G, Guerriero M, Paggiaro PL, Blasi F, Caminati M, Heffler E, Latorre M, Canonica GW on Behalf of SANI. SANI-Severe Asthma Network in Italy: a way forward to monitor severe asthma. Clin Mol Allergy 2017; 15: 9
16. Price D, Hiller EV, van der Molen T. Efficacy vs effectiveness trials: informing guidelines for asthma management. Curr Opin Allergy Clin Immunol 2013; 13: 50-7
17. www.ginasthma.org - Accessed the 30th May 2018
18. Chipps BE, Haselkorn T, Paknis B, Ortiz B, Bleecker ER, Kianifard F, Foreman AJ, Szefler SJ, Zeiger RS; Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens Study Group. More than a decade follow-up in patients with severe or difficult-to-treat asthma: The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) II. J Allergy Clin Immunol. 2018;141(5):1590-1597
19. Hanania NA, King MJ, Braman SS, Saltoun C, Wise RA, Enright P, Falsey AR, Mathur SK, Ramsdell JW, Rogers L, Stempel DA, Lima JJ, Fish JE, Wilson SR,

Boyd C, Patel KV, Irvin CG, Yawn BP, Halm EA, Wasserman SI, Sands MF, Ershler WB, Ledford DK; Asthma in Elderly workshop participants. Asthma in the elderly: Current understanding and future research needs--a report of a National Institute on Aging (NIA) workshop. J Allergy Clin Immunol. 2011;128(3 Suppl):S4-24

20. Hirano T, Matsunaga K. Late-onset asthma: current perspectives. J Asthma Allergy. 2018;11:19-27.
21. Bagnasco D, Ferrando M, Varricchi G, Puggioni F, Passalacqua G, Canonica GW. Anti-Interleukin 5 (IL-5) and IL-5Ra Biological Drugs: Efficacy, Safety, and Future Perspectives in Severe Eosinophilic Asthma. Front Med (Lausanne). 2017;4:135.
22. Bachert C, Gevaert P, Hellings P. Biotherapeutics in Chronic Rhinosinusitis with and without Nasal Polyps. J Allergy Clin Immunol Pract. 2017;5(6):1512-1516.
23. Mansur AH, Srivastava S, Mitchell V, Sullivan J, Kasujee I. Longterm clinical outcomes of omalizumab therapy in severe allergic asthma: Study of efficacy and safety. Respir Med. 2017;124:36-43.
24. Roche N, Reddel HK, Agusti A, Bateman ED, Krishnan JA, Martin RJ, Papi A, Postma D, Thomas M, Brusselle G, Israel E, Rand C, Chisholm A, Price D; Respiratory Effectiveness Group. Integrating real-life studies in the global therapeutic research framework. Lancet Respir Med. 2013;1(10):e29-30.
25. Berger ML, Sox H, Willke RJ, Brixner DL, Eichler HG, Goettsch W, Madigan D, Makady A, Schneeweiss S, Tarricone R, Wang SV, Watkins J, Mullins CD. Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making. Value Health. 2017 Sep;20(8):1003-1008
26. Irving E, van den Bor R, Welsing P, Walsh V, Alfonso-Cristancho R, Harvey C, Garman N, Grobbee DE; GetReal Work Package 3. Series: Pragmatic trials and

real world evidence: Paper 7. Safety, quality and monitoring. J Clin Epidemiol. 2017 Nov; 91: 6-12

27. Makady A, de Boer A, Hillege H, Klungel O, Goettsch W; (on behalf of GetReal Work Package 1). What Is Real-World Data? A Review of Definitions Based on Literature and Stakeholder Interviews. Value Health. 2017 Jul - Aug;20(7):858-865.
28. Battaglia S, Basile M, Spatafora M, Scichilone N. Are asthmatics enrolled in randomized trials representative of real-life outpatients? Respiration. 2015;89(5):383-9.
29. Diver S, Brightling CE. Big asthma data: getting bigger and more beautiful? Thorax. 2018;73(4):311-312.
30. Bloom CI, Nissen F, Douglas IJ, Smeeth L, Cullinan P, Quint JK. Exacerbation risk and characterisation of the UK's asthma population from infants to old age. Thorax. 2018;73(4):313-320.

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

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

SD, standard deviation; BMI, body mass index

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%

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 20-24 25	 36.2% 19.6% 44.2%
Exhaled nitric oxide (FENO) ppb (mean, SD) Distribution of patients according to FENO: - ≤ 25 ppb - 25 – 40 ppb - > 40 ppb	48.0 ± 46.3 40.9% 18.2% 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) Distribution of patients according to blood eosinophils: - ≤ 150 / mm^3 - >150 / mm^3 - >300 / mm^3	536.7 ± 650.9 - 20.2% - 79.8% - 58.8%
Total IgE, Ku/L (mean, SD)	470.3 ± 812.9

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

493 **Table 4. Concomitant treatments**

Patients chronically taking OCS Mean OCS dose (Prednisone equivalents), (mg, SD)	64.1% 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%	
18,5 – 24,9	46.7%	38.3%	0.327
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) Distribution of patients according to FENO: - ≤ 25 ppb - 25 – 40 ppb - > 40 ppb	47.1 ± 42.5 37.3% 18.7% 44.0%	48.4 ± 45.1 44.7% 17.0% 38.3%	0.873 0.584
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) Distribution of patients according to blood eosinophils: - ≤ 150 / mm^3 - >150 / mm^3 - >300 / mm^3	514.7 ± 615.9 20.6% 79.4% 59.6%	539.8 ± 523.9 23.3% 76.7% 58.9%	0.769 0.882
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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FIGURE LEGENDS:

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