RItA: The Italian severe/uncontrolled asthma registry

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Short title: the RItA Italian registry

Abstract

Background: The Italian severe/uncontrolled asthma (SUA) web-based registry encompasses demographic, clinical, functional, inflammatory data; it aims to raise SUA awareness, identifying specific phenotypes and promoting optimal care.

Methods: 493 adult patients from 27 Italian centres (recruited in 2011-2014) were analyzed.

Results: Mean age was 53.8yrs. SUA patients were more frequently female (60.6%), with allergic asthma (83.1%). About 30% showed late onset of asthma diagnosis/symptoms (>40yrs); the mean age for asthma symptoms onset was 30.2yrs and for asthma diagnosis 34.4yrs. 97.1% used ICS (dose 2000 BDP), 93.6% LABA in association with ICS, 53.3% LTRAs, 64.1% anti-IgE, 10.7% theophylline, 16.0% oral corticosteroids.

Mean FEV_1% pred of 75.1%, median values of 300/mm^3 of blood eosinophil count, 323 kU/l of serum total IgE, 24 ppb of FENO were shown.

Most common comorbidities were allergic rhinitis (62.4%), gastroesophageal reflux (42.1%), sinusitis (37.9%), nasal polyposis (30.2%), allergic conjunctivitis (30.2%).

55.7% of SUA patients had exacerbations in the last 12 months, 9.7% emergency department visits, 7.3% hospitalizations.

Factors associated with exacerbation risk were: obesity (OR, 95%CI 2.46, 1.11-5.41), psychic disorders (2.87, 0.89-9.30 - borderline), nasal polyps (1.86, 0.88-3.89 - borderline), partial/poor asthma treatment adherence (2.54, 0.97-6.67 - borderline), anti-IgE use in a protective way (0.26, 0.12-0.53).

Comparisons to severe asthma multicentre studies and available registries showed data consistency across European and American populations.

Conclusions: An international effort in the implementation of SUA patients registries could help to better understand the clinical features and to manage severe asthma, representing a non negligible socio-economic burden for health services.

Introduction

Severe asthma is of remarkable interest for the scientific community, as documented by the work of some research groups in US (1,2) and Europe (3-5).

The reasons of this large interest are many. First of all, around 10% of asthmatic patients are uncontrolled or refractory to the treatment. These patients with severe asthma are responsible for a relevant socio-economic burden, in terms of direct costs related to out/in-patient treatments, and indirect costs related to quality of life worsening and work disability. These patients account for 50% of asthma total costs (6,7).

Another reason lies in the pathogenesis of severe asthma: there is need for a better understanding since most mechanisms underlying asthma severity and therapy resistance are still unclear. To collect elements for characterizing the disease (clinical, epidemiological, functional, inflammatory features) may help to define the severe asthma phenotypes and to improve treatment (8).

The third reason is that patients with severe/uncontrolled asthma (SUA) poorly respond to standard therapy and often an acceptable symptom control is achieved only through regular intake of oral corticosteroids (OCS) (9). Introduction of new biological drugs might help controlling the disease, a goal not achievable with the available therapy.

In spite of the socio-economic burden, an estimate of the real impact of SUA has been obtained so far only from selected centres in Italy (10) and an evaluation of the disease burden throughout all Italian regions is not available. Few experiences have been developed in other countries. A need remains for a better understanding and management of difficult-to-treat asthmatic patients (1-5).

Within this framework, the Italian Medicines Agency (AIFA) funded the AGAVE project (*Severe Asthma: epidemiological and clinical cohorts follow up by registry and questionnaires; therapeutic appropriateness and outcome assessment, according to GINA guidelines*) aimed at assessing the effectiveness of therapeutic strategies for SUA patients, according to GINA guidelines (11), in epidemiological and clinical samples, through the implementation of an on-line Registry.

RItA (acronym from the Italian words standing for Italian Registry of SUA) is a database containing information on patients' general characteristics, clinical data, risk factors, asthma exacerbations. Currently, it contains information on 916 SUA adult subjects (n=423 from the epidemiological sample, n=493 from the clinical sample).

This manuscript focuses on increasing the knowledge regarding the Italian scenario of SUA patients through statistical analyses of clinical characteristics, drugs use, exacerbations and symptoms' control. For this purpose, only observational data on the clinical cohort have been retrospectively analyzed, as exhaustive functional and inflammatory values were available.

The aims are to: a) characterize Italian SUA patients comparing their features with those of other European and US severe asthmatic patients; b) assess factors associated with exacerbations' risk in the last 12 months.

Methods

493 SUA adult patients were consecutively enrolled when going to the clinical centers for the specialist visits between 2011 and 2014: 281 patients, from 24 Italian centres, under regular treatment with Omalizumab and 212 patients, from 3 centers, selected from the usual clinical routine.

All of them had a severe/uncontrolled asthma according to the World Health Organization Consultation on Severe Asthma (12).

The specialists filled in a questionnaire for each selected patient with information about disease severity, exacerbations, current pharmacological treatment, comorbidities, risk factors, health services use and clinical/functional data.

In selected patients, investigation of upper airway involvement and measurements of airway inflammation by non invasive methods were performed.

Data were inserted in RItA registry, implemented and hosted by the Information Technology Department of the Italian National Health Institute. The Registry is a secured web database that admits password protected anonymized data, after fully informed written consent.

The AGAVE study protocol, patient information sheet and consent form were approved by the Pisa University-Hospital Ethics Committee (Prot. n° 17658; March 10, 2011) and by the Ethics Committee of each involved site; a further approval for the statistical analyses of this manuscript was obtained by the Pisa University-Hospital Ethics Committee (Prot. n° 3690; December 17, 2015).

Statistical analyses

Continuous data were presented as mean±standard deviation or as median and interquartile range, for normally or non-normally distributed measures, respectively. One-way analysis of variance and Mann Whitney tests were used when appropriate for the comparison among different groups of patients, while categorical variables were evaluated by chi-square test.

Sensitivity analyses were performed after stratifying the sample by kind of patients: those selected from the usual clinical routine (enrolled by 3 clinical centres) and those selected because under regular treatment with Omalizumab (enrolled by 24 clinical centres), to assess potential differences in descriptive and clinical characteristics. Other sensitivity analyses were performed after stratifying the sample between allergic and non allergic patients, according to their doctor's definition. Results were reported in the supporting information section.

A multivariate logistic regression analysis, taking as dependent variable the presence of at least one exacerbation in the last year, and as independent variables anthropometric parameters (age, sex, body mass index - BMI) and clinical characteristics (allergic asthma, positive family history of asthma, age at asthma diagnosis, comorbidities, anti-IgE use, antiasthma therapy adherence), chosen on the basis on the results of the bivariate statistical analyses, was performed.

The eosinophilic inflammation was evaluated as following: a sputum eosinophil count ≥3% and/or peripheral blood eosinophil count ≥300 mm^3 and/or the fractional exhaled nitric oxide (FENO) ≥50 ppb (13). A cut-off ≥49.2% for the sputum neutrophil count, corresponding to the highest value of neutrophil count of Italian healthy subjects, was chosen (14).

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), rel. 16.0. A p-value ≤0.05 was considered statistically significant, a 0.05<p-value<0.10 was considered as borderline value.

Results

SUA patients description

General characteristics

493 patients were analyzed. The majority were females (60.6%) and the mean age was 53.8 yrs. Educational level was low with only 13% with an academic degree. 48.9% of subjects were employed, 21.9% retired (Table 1).

About 30% had late-onset asthma symptoms and adulthood diagnosis (starting after 40 yrs of age). The mean age for asthma symptoms onset was 30.2 yrs and for diagnosis 34.4 yrs. BMI was slightly higher (mean value 27.3 Kg/m^2) and 26.4% had a BMI indicating obesity. 33.2% were ex-smokers, 2.8% current smokers. The frequency of allergic asthma was 83.1% and positive family history of asthma was observed in 39.6%. 40.2% patients lived in a suburban area and 30.7% were exposed to fume/gas/dust at work (Table 1).

Lung function and inflammatory characteristics

The ratio between Forced Expiratory Volume in the first second (FEV_1) and Forced Vital Capacity (FVC) (FEV_1/FVC), the FEV_1 percentage predicted (FEV1% pred) and the FVC% pred showed a mean value of 70.0%, 75.1% and 91.3%, respectively (Table 2). About 60% of patients had a FEV_1/FVC <70% and a FEV_1% pred <80%.

Data showed eosinophilic inflammation patterns: 72.2% had a sputum eosinophil count ≥3%, 18.8% a FENO ≥50 ppb, 71.2% a peripheral blood eosinophil count ≥300 mm^3 (Table 2). Sputum was induced in 72 patients and the predominant phenotype was eosinophilic asthma (49.2%) (Table 2).

A median value of 323 kU/L of total serum IgE was found and 81.9% of patients had positive skin prick test (Table 2).

Pharmacological treatment

Median Inhaled Corticosteroids (ICS) dose (beclometasone dipropionate - BDP - equivalent dose) was 2000 µg (mean value 1528.6±784.1); 97.1% of SUA patients used ICS, 93.6% long-acting beta agonists (LABA) in association with ICS, 53.3% anti-leukotrienes (LTRAs), 64.1% anti-IgE, 16.0% OCS and 10.7% theophylline. Most patients were treated according to GINA step 5 (60.7%) and step 4 (26.3%). 4.1% of subjects received specific immunotherapy. According to the specialists opinion, 86% had a good adherence to antiasthma therapy and 93.5% had a correct use of inhalers (Table 3).

Comorbidities

Several comorbidities were observed: the most commonly reported were allergic rhinitis (62.4%), gastroesophageal reflux (42.1%), sinusitis (37.9%), nasal polyps and allergic conjunctivitis (30.2%) (Figures 1a-1b).

Asthma control

55.7% of patients had at least one exacerbation in the last 12 months; of them, 90.3% underwent OCS courses (mean frequency: 2.7 times in the last 12 months). 7.3% had at least one hospitalization during the previous year, 9.7% at least one emergency department (ED) visit (Table 3).

According to the 2010 WHO definition of severe/uncontrolled asthma (12), 1% of the patients were uncontrolled with difficult-to-treat severe asthma (*group 2)*, 84% were asthmatic for which control was not achieved despite the highest level of recommended treatment (*group 3a*), 15% were controlled only with the highest level of recommended treatment (*group 3b*) (Table 3).

Asthma was uncontrolled in 39.4% of patients according to 2015 GINA guidelines criteria (based on FEV_1 value, daily/nocturnal symptoms, daily activities limitations, rescue medications use) (11); the asthma control questionnaire (ACQ) and the asthma control test (ACT) scores confirmed a poor disease control with a mean value of 2.1 for ACQ and 19.4 for ACT (classifying patients with a score >1.5 for ACQ and <20 for ACT as uncontrolled (15,16)) (Table 3).

Sensitivity analysis

A comparison of general and clinical characteristics among patients enrolled by the 3 large centres following the usual clinical routine and those enrolled by the 24 small centres under regular treatment with Omalizumab was performed. The analyses showed some significant differences in the general characteristics: lower mean age (52.1 vs 56.0 yrs), higher level of education (16.1% vs 9.4% for university attendance), higher frequency of employed subjects (54.5% vs 41.2%), lower age at symptoms onset (27.8 vs 33.7 yrs) and asthma diagnosis (31.5 vs 38.5 yrs), lower positive family history of asthma (33.8% vs 46.8%), higher frequency of allergic asthma (100.0% vs 60.7%)

and higher frequency of non smokers (70.6% vs 55.0%) in patients treated with Omalizumab with respect to the patients treated according to the usual clinical practice (Table e1).

Only few differences were found in the clinical data: a higher mean level of FEV_1/FVC (72.7 vs 66.5), a lower mean value of FVC (88.6 vs 94.5), a lower median percentage of blood eosinophils (4.2% vs 5.3%) and a higher frequency of positive skin prick tests (98.1% vs 59.3%) in patients treated with Omalizumab (Table e2).

As regards the comparison among allergic and non allergic patients, few differences existed in the pharmacological treatments (Table e3); in particular a higher ICS equivalent dose (2000 vs 1600) in non allergic patients with respect to the allergic ones. A more frequently GINA uncontrolled asthma (63.4% vs 41.7%), a more frequent hospitalization in the last 12 months (14.6% vs 5.6%), a lower value of PEF (72.5% vs 81.7%), a higher median value of blood eosinophils (5.9% vs 3.9%) and a lower total serum IgE (161 vs 346) in non allergic patients with respect to the allergic ones were shown (Tables e3-e4).

Risk factors for exacerbations

Significant differences were found among patients with exacerbations and those without exacerbations. The former were older (55.4 vs 52.8 mean age), more frequently obese (31.1% vs 20.0%), had a later asthma symptoms' onset (32.0 vs 28.3 yrs) and asthma diagnosis (36.2 vs 32.9 yrs), they reported more frequently positive family history of asthma (44.1% vs 31.4%) and comorbidities, as well as, less frequently allergic asthma (72.5% vs 91.3%) (Table 4).

They showed a significantly lower pulmonary function (FEV_1% pred 73.2 vs 77.8), a borderline lower value of total serum IgE (276 vs 377) and a borderline higher value of blood eosinophils count (320 vs 260). Patients with exacerbations had a significantly higher inflammation pattern (26.3% vs 10.4% for FENO ≥50 ppb) (Table 4).

Patients with exacerbations were significantly more treated with GINA step 4b (22.4% vs 6.3%), with OCS (22.4% vs 5.3%), less treated with anti-IgE (45.1% vs 78.3%) and received a higher ICS median dose (2000 vs 1500 µg). Moreover, they had a significantly higher percentage of partial/poor antiasthma therapy adherence (16.3% vs 9.2%) (Table 4).

Patients with exacerbations showed a significantly higher frequency of uncontrolled asthma by GINA guidelines (50.9% vs 23.2%), a lower ACT score, a higher ACQ score and a larger use of health services (Table 4).

Multivariate analysis

Comorbidities were associated with a higher risk of exacerbations [odds ratio (OR) and 95% confidence interval (95% CI) 2.46, 1.11-5.41 for obesity; 2.87, 0.88-9.30, borderline, for psychic disorders; 1.86, 0.89-3.89, borderline, for nasal polyps). A partial/poor adherence to antiasthma therapy was associated with a borderline higher risk of exacerbations (OR, 95% CI 2.54, 0.97-6.67) and patients using anti-IgE were at significantly lower risk (OR, 95% CI 0.26, 0.12-0.53) (Figure 2).

Discussion

Main findings on SUA patients

The majority of SUA patients included in the RItA registry were females, with a late onset asthma, atopy and eosinophilic inflammation. Prevalent comorbidities were allergic rhinitis, gastroesophageal reflux and sinusitis. An important difference between the mean age of symptoms onset and the mean age of diagnosis was found (about 4 yrs). Moreover, patients with comorbidities and with a poor/partial antiasthma therapy adherence had a higher risk of exacerbations in the last 12 months, while the use of anti-IgE seemed to have a role in reducing exacerbations.

SUA patients description

Since the AGAVE project started in 2010, we had to take into account diagnostic criteria published until such year. In particular, in order to select patients to be inserted in the Registry, we considered the criteria reported in the decision-making steps proposed by the experts participating in the World Health Organization Consultation on Severe Asthma (12).

Our data were compared to those observed in the most important multicentre studies and in the available registries on severe asthma: SARP (Severe Asthma Research Program) (1); TENOR (The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens Study) (2); ENFUMOSA (European Network for Understanding Mechanisms of Severe Asthma) (3); UK multicentre registry on refractory asthma (4); BSAR (The Belgian Severe Asthma Registry) (5) (table 5).

General characteristics

Overall, the population included in the registries had similar characteristics in terms of gender (majority of women) and BMI (overweight); mean age ranged between 41 and 55 years (1-5).

We found a late onset asthma (starting at age >40 yrs) in 29.8% of patients, as in the Belgian registry (5). Our data showed a mean difference between the age of symptoms onset and the age of diagnosis of about 4 yrs. This diagnostic delay could be due to the communication difficulties between patients and physicians, indeed most patients do not report their bronchial symptoms to the general practitioner remaining undiagnosed. On the other hand, patients with respiratory problems and reduced lung function are not always recognized as such (17), maybe due to a lack of guidelines awareness or implementation (18).

The proportion of current smokers (2.8%) in Italian patients was lower than that observed in the other studies/registries; on the contrary, comparable results were found for past smoking history (about 30%) (2,4-5).

A high proportion of Italian patients had an allergic asthma (83.1%), showing a higher frequency of atopy with respect to the other studies (1,3-5). This may be due to the inclusion of a high percentage of patients under anti-IgE treatment. Moreover, an important percentage of positive family history of asthma was found, as in the UK registry (4).

Lung function and inflammatory characteristics

Overall, there was a moderate obstructive airway pattern, with values (mean FEV_1% pred 75.1%) similar to those of multicentre studies (2-3), but higher than those of the SARP study (1) and severe asthma registries (4-5). The mean value of FEV_1/FVC ratio was 70%, slightly higher than in the other studies/registries (1,4-5), but lower than in the ENFUMOSA study (3).

Italian patients had evidence of eosinophilic inflammation in line with the other registries (4-5).

Data from induced sputum samples, available only from Pisa clinical center, showed a higher proportion of eosinophilic asthma with respect to the other severe asthma studies/registries (3-5), but in line with other findings suggesting that eosinophilic asthma is more frequently encountered in severe asthma than in moderate one (19) and in late-onset asthma (20).

An elevated IgE level was found, higher than in the other studies/registries (1,3-5). Probably, this fact was due to the inclusion of a patients subset under regular treatment with anti-IgE.

Pharmacological treatment.

Italian patients received LTRAs (53.3%) more frequently than in UK registry (4) and less frequently than in the Belgian registry (5); theophylline (10.7%) and OCS (16.0%) were less common than in the other studies/registries (1,3-5). Differently, anti-IgE were more frequently used (1,4-5), due to the inclusion of a patients subset under regular treatment with anti-IgE.

SUA patients, as expected, were mainly treated according to GINA guidelines step 4 or 5 (26.3% and 60.7%, respectively) (11). About 10% of patients in the Italian Registry received a treatment not recommended by GINA guidelines for severe asthma (step 1, 2 or 3) due to the fact that patients using anti-IgE, after reaching high levels of asthma control, were likely prescribed to reduce either the uptake of OCS or the ICS dose. Indeed, a recent meta-analysis showed that anti-IgE treated patients more likely underwent to withdrawal of-corticosteroid therapy (21).

Italian patients showed high level of IgE, atopic status and an eosinophilic inflammation pattern both at systemic and airways level, confirming the importance of using biological treatments.

Comorbidities

Comorbidities observed among Italian patients were similar to those evidenced in other studies on similar populations (1,4-5), except for polyps and aspirin hypersensitivity that were more frequent in RItA registry.

Asthma control

About 40% of Italian patients had a poor asthma control according to GINA guidelines, confirmed by ACT and ACQ scores. These data were in line with the Belgian registry (5). Over 50% of patients reported at least one exacerbation in the previous 12 months.

7.3% of Italian patients had at least one hospitalization in the previous 12 months and 9.7% at least one ED visit. These data are in line with those reported in the TENOR study, related to the previous 3 months (2), but lower than those reported in the SARP study, related to the previous 12 months (1).

Risk and protective factors for exacerbations

Multivariate regression analysis results showed that obesity was associated with a significantly higher risk of exacerbations (OR 2.46), while psychic disorders (OR 2.87) and nasal polyps (OR 1.86) showed borderline values.

The relevant burden that obesity, upper airway disease and psychiatric disorders may cause on asthma symptoms, pulmonary function and response to treatment has been recently reported in another Italian study (22). Severe asthmatic patients with comorbidities had a higher frequency of poorly controlled asthma compared to those without (22).

Obesity is a risk factor for asthma and it is associated with disease severity, a poor response to corticosteroids and worse clinical control (i.e. more symptomatic days, use of rescue medication, direct/indirect costs) (23). Moreover, obesity, central adiposity and metabolic syndrome aspects have been implicated in the pathogenesis of the adult-onset asthma phenotype (24).

In Europe, a study on difficult-to-treat asthma showed that psychological disorders were significantly associated with frequent exacerbations (OR 10.8) (25). A more recent US study showed that mental disorders were significantly associated with the increased risk of asthma-specific hospitalizations and exacerbations, with the highest values in the age groups 18-45 yrs (incident rate 2.05 and 1.44, respectively) (26).

Asthma and nasal polyps frequently coexist and share similar features of inflammation and remodeling (27). Asthmatic subjects with chronic rhinosinusitis and nasal polyps had more frequently a poor control and increased airway obstruction compared with those without chronic rhinosinusitis and nasal polyps (28).

In the present study, notwithstanding the high rate of antiasthma therapy adherence, patients with a partial/poor adherence had a higher exacerbations risk (OR 2.54), in line with a recent review showing that a good adherence was associated with lower risk of severe asthma exacerbations (29). Indeed, adherence to antiasthma controller medications is one of the key drivers to improve persistent asthma management (30).

Italian patients in treatment with anti-IgE had a significantly lower risk of exacerbations (OR 0.26, i.e. 4 fold less than subjects not using IgE), after adjusting for comorbidity, allergic asthma and therapy adherence. These data are in line with those reported in a recent review showing the anti-IgE treatment positive effect (31). Moreover, an Italian study on severe asthmatic patients showed a significant reduction in exacerbations and health services use during Omalizumab treatment compared with the period before treatment (22). The anti-IgE effect on the reduction of exacerbation risk, independently of allergic status, is in line with recent data showing that anti-IgE may be beneficial for SUA patients in whom atopy status cannot be identified (32) and in patients with intrinsic asthma (33). Intrinsic asthma can display elevated concentrations of total serum IgE and of allergen-specific IgE antibodies in the airways, despite negative skin prick tests (34). On the other hand, anti-IgE could prevent asthma exacerbations by strengthening innate immunity, rather than by reducing allergy (33).

Strengths and Limitations

Our study was characterized by an elevated number of enrolled patients, coming from 27 centers well distributed over the country, thus they may be considered representative of all the Italian SUA patients.

A detailed and thorough questionnaire, based on the main items of the GINA guidelines, was used to obtain an exhaustive patients' characterization. It was reviewed and approved by an internal board comprised of pneumologists, allergists and epidemiologists.

A potential bias of this study was the enrollment of about 50% of the sample undergoing anti-IgE treatment, a higher percentage with respect to the clinical practice. These patients have different characteristics from those not using this treatment, indeed the Italian regulation defines the eligible patients for treatment with anti-IgE as follows: SUA patients undergoing LABA+ICS treatment, with a high level of total IgE and positivity to perennial allergens.

Nevertheless, our data showed consistency with those of the other registries and multicentre studies on severe asthma.

Conclusions

In summary, this is the first paper presenting demographic and clinical data from a wide Italian population sample of SUA patients. Further information will derive from the ongoing analyses of the 3-12 months follow-up.

Comparisons to multicentre studies and available registries on severe asthma showed data consistency across European and American populations (35). An international effort in the implementation and data analyses of registries on SUA patients could be an added value to better understand the clinical features and to better manage difficult-to-treat asthmatic patients, which represent a non negligible socio-economic burden for the health services. Asthma research collaboration was recently promoted and fostered by the European Respiratory Society (36).

Italian data showed the need of reducing the diagnostic delay, through an early detection of asthma and a subsequent early treatment, in order to improve the long-term prognosis of these patients, probably preventing the development of long-term modifications, such as remodeling, with a subsequent further impairment in pulmonary function (17).

It is to point out that a new Severe Asthma Network in Italy is under development: thus, our RItA data will provide a basis for future comparisons (37).

Moreover, the future availability in Italy of new biologic drugs with different specific targets requires an effort in phenotyping patients with severe asthma, in order to provide them a tailored treatment, as in the ongoing Refractory Asthma Stratification Programme (RASP-UK) aimed at developing a clinical model to assess and phenotype patients with severe asthma (38).

Authors contribution:

Conception and design and acquisition of data: SM, SB, MB, MS, ML, NM, FS, MB, LA, BB, PI, PR, CP, PP, GV; Analysis and interpretation of data: SM, SB, MP, MS, LLG, PP, GV; drafting the manuscript for important intellectual concept: SM, SB, MP, LLG, PP, GV; taking responsibility for the integrity of the work as a whole, from inception to published article: GV.

Conflicts of interest

Conflicts of interest for the authors: none. The statistical analyses and the content of the manuscript were not conditioned in any way from the unrestricted grant received by Roche S.p.A.

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Table 1. General characteristics of SUA patients

	N	
Female (%)	493	60.6
Age (mean±SD), yrs	483	53.8±13.4
Age range, yrs	483	19-86
Race (%):	216	
Caucasian		98.6
African		0.9
Hispanic		0.5
Educational level (%):	453	
Elementary		16.1
Medium high school		32.9
High school		38.0
University		13.0
Work position (%):	474	
Employed		48.9
Unemployed		6.8
Housewife		22.4
Retired person		21.9
Age at symptoms' onset (mean±SD), yrs	443	30.2±16.8
Age at symptoms' onset (%):	443	
<12 yrs		18.5
12-40 yrs		51.7
>40 yrs		29.8
Age at asthma diagnosis (mean±SD), yrs	452	34.4±16.8
Age at asthma diagnosis (%):	452	
<12 yrs		11.7
12-40 yrs		50.7
>40 yrs		37.6
BMI (mean±SD), Kg/m^2	481	27.3±5.0
BMI groups (%):	481	
Underweight/normal		35.4
Overweight		38.2
Obese		26.4
Smoking habits (%):	469	
Smokers		2.8
Ex-smokers		33.2
Non smokers		64.0
Pack-years* (mean±SD), n	92	21.6±23.9
Positive family history of asthma (%)	381	39.6
Allergic asthma (%)	472	83.1
Ever exposed to fume/gas/dust at work (%)	387	30.7
Area of residence (%):	214	
City centre		25.2
Suburb		40.2
Industrial area		1.9
Rural area		32.7

SD: standard deviation; BMI: body mass index

* analyzed only in smokers or ex-smokers

692 **Table 2. Lung function, inflammatory/allergic indices of SUA patients**

	N	Total
FEV_1% pred (mean±SD)	477	75.1±20.5
FVC% pred (mean±SD)	459	91.3±19.8
FEV_1/FVC % (mean±SD)	478	70.0±31.0
PEF% pred (mean±SD)	300	79.4±25.2
FENO (median, IQR), ppb	176	24.0(15.0-38.0)
FENO level (%): < 25 25-49 ≥ 50	176	 51.7 29.5 18.8
Blood eosinophils (median, IQR) (%)	253	4.4(2.1-7.4)
Blood eosinophils (median, IQR) (mm^3), n	208	300.0(170.0-495.0)
Blood eosinophils level ≥300 (mm^3) (%)	208	71.2
Sputum eosinophils (median, IQR) (%)	72	18.1(2.1-53.1)
Sputum neutrophils (median, IQR) (%)	65	38.3(16.8-69.8)
Sputum eosinophil level ≥3% (%)	72	72.2
Sputum neutrophil level ≥49.2% (%)	65	43.1
Sputum inflammatory phenotypes (%): Paucigranulocytic Eosinophilic (≥3%) Neutrophilic (≥49.2%) Mixed granulocitic	65	 7.7 49.2 23.1 20.0
Total serum IgE (median, IQR) (kU/l)	330	323.0(152.5-598.5)
Positivity to skin prick test	360	81.9%

693 FEV_1 % pred: percentage of predicted values of forced expiratory volume in the first second; SD:
694 standard deviation; FVC % pred: percentage of predicted values of forced vital capacity; PEF%
695 perc pred; percentage of predicted values of peak expiratory flow; FENO: fractional exhaled nitric
696 oxide; IQR: interquartile range; IgE: Immunoglobulin E
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705 **Table 3. Pharmacological treatment, control and health services use in SUA patients**

	N	Total
ICS (%)	488	97.1
ICS (µg) BDP equivalent dose (median, IQR)	398	2000 (800-2000)
LABA (%)	488	93.6
Ultra LABA (%)	488	0.8
LTRAs (%)	488	53.3
Theophylline (%)	488	10.7
Anti-IgE (%)	488	64.1
Oral corticosteroids (%)	488	16.0
GINA GL step (%)*: Step 1 Step 2 Step 3 Step 4a** Step 4b** Step 5 Not according to GL	414	 0.5 0.2 9.2 12.3 14.0 60.7 3.1
Specific immunotherapy (%)	196	4.1
Antiasthma therapy adherence (%): Good Partial Poor	478	 86.0 11.9 2.1
Correct use of inhalers (%): verified correct use verified uncorrected use not verified use	476	 93.5 2.1 4.4
ACT score (mean±SD), pts	398	19.4±4.6
ACQ score (mean±SD), pts	238	2.1±3.5
GINA control (%): Well controlled Partially controlled Uncontrolled	439	 8.0 52.6 39.4
WHO definition of severe/uncontrolled asthma (12): group 2 group 3a group 3b	488	 1.0 84.0 15.0
≥1 exacerbation last 12 months (%)	428	55.7
N° exacerbations last 12 months (mean±SD)	428	1.5±2.4
Patients with hospitalisations last 12 months (%)[#]	206	7.3
N° hospitalisations last 12 months (mean±SD)[##]	20	1.3±0.6
Patients with ED visits last 12 months (%)[#]	236	9.7
N° ED visits last 12 months (mean±SD)[##]	25	1.5±0.8
Patients with systemic corticosteroids use for exacerbation (%)[###]	237	90.3
N° times using oral steroids for exacerbation last 12 months (mean±SD)[####]	219	2.7±2.9

706 ICS: inhaled corticosteroids; BDP: beclometasone dipropionate; IQR: interquartile range; LABA: long-acting beta
707 agonists; LTRAs: leukotriene receptor antagonists; GINA GL: Global INitiative for Asthma guidelines; ACT: asthma
708 control test; SD: standard deviation; ACQ: asthma control questionnaire; ED: emergency department. * 74 subjects had
709 no information about ICS dose; thus, they were not classified according to GINA steps. ** step 4a: subjects using only
710 medium/high dose of combination LABA+ICS. ** step 4b: subjects using medium/high dose of combination LABA+ICS

plus a third controller. # analyzed only in subjects having lifetime hospitalization, ED visits .## analyzed only in subjects having hospitalization, ED visits in the last 12 months. ### analyzed only in subjects having exacerbations in the last 12 months #### analyzed only in subjects using oral steroids for exacerbations in the last 12 months

Table 4. Comparison between SUA patients according to the presence of exacerbations in the last 12 months

	≥1 exacerbation (N=238)	no exacerbation (N=189)	p-value
General characteristics			
Males (%)	38.2	43.4	0.282
Age (mean±SD), yrs	*55.4±13.5*	*52.8±13.4*	*0.053*
Smoking habits(%): Smokers Ex smokers No smokers	 1.8 35.5 62.7	 2.7 32.2 65.1	0.664
Educational level (%): Elementary Medium high school High school University	 20.0 32.0 36.4 11.6	 14.5 33.5 38.7 13.3	0.540
BMI groups (%): Underweight/normal Overweight Obese	 **31.0** **37.9** **31.1**	 **38.4** **41.6** **20.0**	**0.033**
Positive family history of asthma (%)	**44.1**	**31.4**	**0.019**
Allergic asthma (%)	**72.5**	**91.3**	**0.000**
Age at asthma symptoms' onset (mean±SD), yrs	**32.0±17.1**	**28.3±16.3**	**0.030**
Age at asthma diagnosis (mean±SD), yrs	**36.2±17.2**	**32.9±16.0**	**0.050**
Comorbidities			
Rhinitis (%): Allergic Non allergic	 **58.9** **11.0**	 **71.3** **2.1**	**0.001**
Sinusitis (%)	**43.3**	**33.3**	**0.039**
Nasal polyps (%)	**36.5**	**23.5**	**0.004**
Aspirin intolerance (%)	**26.2**	**17.7**	**0.040**
GERD (%)	*46.8*	*38.0*	*0.070*
Psychic disorders (%)	**11.0**	**5.5**	**0.049**
Clinical data			
Total serum IgE (kU/l) (median, IQR)	*276.0 (123.4-566.0) (n=137)*	*377.0 (167.0-623.0) (n=143)*	*0.053*
FEV_1% pred (%) (mean±SD)	**73.2±21.4**	**77.8±18.3**	**0.020**
Blood eosinophils (mm^3) (median, IQR), n	*320.0 (165.0-600.0) (n=89)*	*260.0 (170.0-415.0) (n=92)*	*0.081*

FENO (median, IQR), ppb	26.5 (16.0-53.1) (n=80)	21.5 (13.6-34.0) (n=77)	0.100
FENO level (%): < 25 25-49 ≥ 50	 **46.3** **27.5** **26.3**	 **59.7** **29.9** **10.4**	**0.034**
Treatment			
GINA step (%): Steps 1, 2 or 3 Step 4a* Step 4b* Step 5 Not according to GL	 **6.7** **16.2** **22.4** **54.8** **0.0**	 **16.3** **10.6** **6.3** **65.0** **1.9**	**0.000**
ICS (µg) BDP equivalent dose (median, IQR)	**2000 (1000-2000)**	**1500 (800-2000)**	**0.018**
Anti-IgE (%)	**45.1**	**78.3**	**0.000**
Oral steroids (%)	**22.4**	**5.3**	**0.000**
Anti-leukotrienes (%)	51.9	56.6	0.332
Theophylline (%)	10.5	11.1	0.853
Antiasthma therapy adherence (%): Good Partial/poor	 **83.7** **16.3**	 **90.8** **9.2**	**0.034**
Control			
GINA control (%): Well controlled Partially controlled Uncontrolled	 **5.9** **43.2** **50.9**	 **12.8** **64.0** **23.2**	**0.000**
ACT score (mean±SD), pts	**18.3±4.6**	**20.6±4.3**	**0.000**
ACQ score (mean±SD), pts	**2.8±4.7**	**1.5±1.8**	**0.014**
Patients with hospitalization last 12 months (%)	**18.6**	**2.2**	**0.000**
Patients with ED visits last 12 months (%)	**11.3**	**3.0**	**0.049**

SD: standard deviation; BMI: body mass index; GERD: gastroesophageal reflux disease; FEV_1 % pred: percentage of predicted values of forced expiratory volume in the first second; FENO: fractional exhaled nitric oxide; GINA: Global INitiative for Asthma guidelines; ICS: inhaled corticosteroids; BDP: beclometasone dipropionate; IQR: interquartile range; IgE: Immunoglobulins E; ACT: asthma control test; ACQ: asthma control questionnaire; ED: emergency department.

* step 4a: subjects using only medium/high dose of combination LABA+ICS

* step 4b: subjects using medium/high dose of combination LABA+ICS plus a third controller

in italic: borderline values; in bold: statistically significant values.

726 **Table 5. Comparison between severe asthma registries/studies**

	European registries/studies				US studies	
	UK (4)	**BSAR (5)**	**RItA**	**ENFUMOSA (3)**	**SARP (1)**	**TENOR (2)**
N	382	350	493	163	204	3489
Age (mean±SD)	---	55±0.8	54±13	42±12	41±13	49±15
Female (%)	63	57	61	80	64	71
BMI	28(median)	26(median)	27(mean)	27(mean)	---	30(mean)
Smoking status (%) Never Ex Current Ukn	 61 30 6 3	 57 31 12	 64 33 3	---	---	 64 32 4
Atopic status (%)	57	70	83	58	71	94
Positive family history of asthma (%)	51	---	40	---	---	---
Age at onset asthma (%): <12 12-40 >40	 ---	 32 36 31	 19 51 30	---	---	---
FEV_1% (mean±SD)	66±24	68±1.2	75±21	72±23	62±22	74±23
FVC% (mean±SD)	82±20	89±1.1	91±20	94±21	77±20	
FEV_1/FVC% (mean±SD)	63±15	63±0.7	70±31	80±17	65±13	
FENO (median, IQR)	35 (16-65) (n=133)	26 (4-250) (n=271)	24 (15-38) (n=176)	---	40±38 (mean±SD) (n=135)	---
Sputum eosinophil count (median, IQR) (%)	3 (0-11) (n=123)	7 (0-92) (n=86)	18 (2-53) (n=65)	11 (mean) (n=99)	---	---
Sputum neutrophil count (median, IQR) (%)	---	51 (0-99) (n=86)	38 (17-70) (n=65)	37 (mean) (n=99)	---	---
IgE (median, IQR)	130 (54-292) (n=349)	207 (2-10000) (n=295)	323 (153-599) (n=330)	---	---	---
Blood eosinophil count (median, IQR) (%)	---	3 (0-50) (n=272)	4 (2-7) (n=208)	4±5 (mean±SD)	---	---
Blood eosinophil count (median, IQR)	300 (250-11000) (n=360)	240 (0-3144) (n=272)	300 (170-495) (n=208)	---	---	---

(mm^3)						
ICS, BDP eq dose (median, IQR)	2000 (1000-2000)	2000 (0-6000)	2000 (800-2000) (1528±784, mean±SD)	1676±667 (mean±SD)	---	---
LTRAs (%)	38	65	53	---	51	---
Anti-IgE (%)	0.8	27	64	---	12	---
Theophylline (%)	38	22	11	46	18	---
Oral corticosteroids (%)	42	24	16	33	32	---
Nasal polyps (%)	13	19	30	---		---
Rhinosinusitis (%)	37	49	38	---	54	---
Gatroesophageal reflux (%)	41	36	42	---	41	---
Psychic disorders (%)	---	19	9	---	---	---
Bronchiectasis (%)	---	16	14	---	---	---
Churg Strauss syndrome(%)	---	3	3	---	---	---
Occupational asthma (%)	5	4	5	---	---	---
Aspirin-sensitive (%)	10	8	22	---	---	---
ACT (mean±SD), pts	---	13.0±0.4	19.4±4.6	---	---	---
ACQ (mean±SD), pts	---	2.6±1.3	2.1±3.5	---	---	---
Oral steroids courses during last 12 months (median, IQR)	4 (2-6)	2 (0-7)	2 (1-3)	---	---	---
Number of hospitalisations during last 12 months (median, IQR)	0 (0-2)	0.9 (0-7) (n=113)	1 (1-2)	---	---	---
Hospitalization during last 12 months (%)	---	---	7	---	28	5
ED visits during last 12 months (%)	---	---	10	---	40	15

SD: standard deviation; BMI: body mass index; IQR: interquartile range; FEV_1% pred: percentage of predicted values of forced expiratory volume in the first second; FVC% pred: percentage of predicted values of forced vital capacity; FENO: fractional exhaled nitric oxide; IgE:

730 Immunoglobulin E; ICS: inhaled corticosteroids; BDP: beclometasonedipropionate; LTRAs:
731 leukotriene receptor antagonists; ACT: asthma control test; ACQ: asthma control questionnaire;
732 ED: emergency department.
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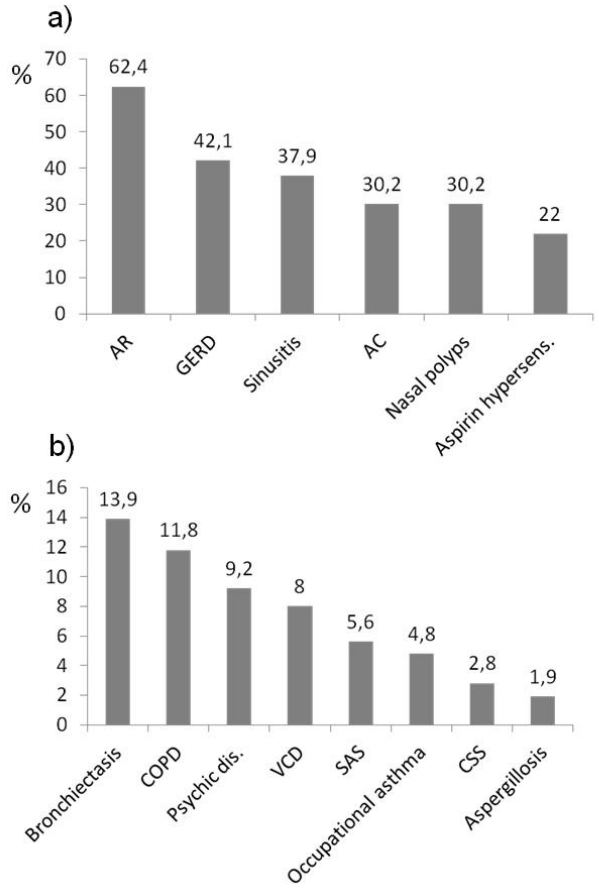
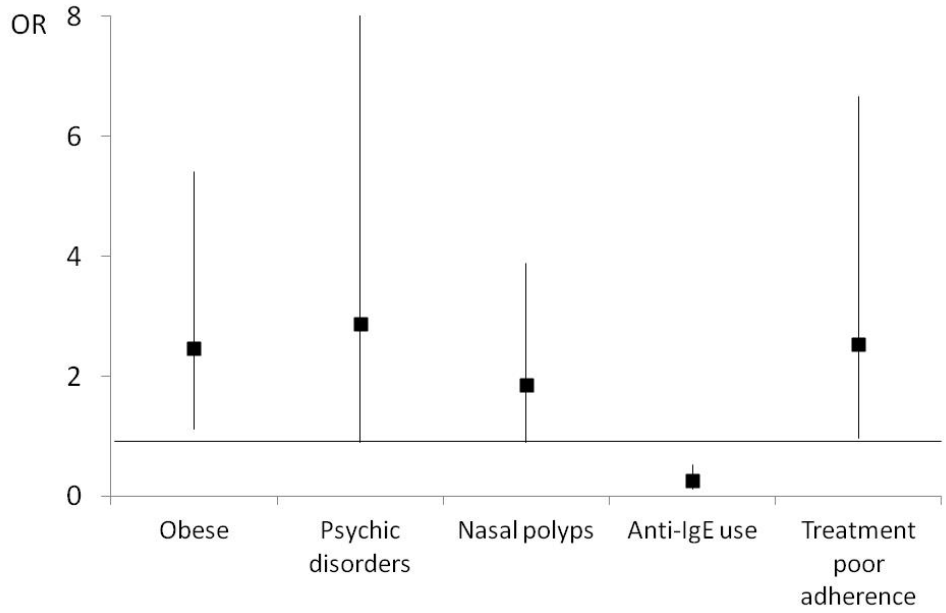
Figure 1. Comorbidities in SUA patients



a) More frequent comorbidities b) Less frequent comorbidities

AR: Allergic rhinitis; GERD: Gastroesophageal reflux disease; AC: Allergic conjunctivitis; COPD: Chronic Obstructive Pulmonary Disease; VCD: Vocal cord dysfunction; SAS: sleep apnea syndrome; CSS: Churg Strauss syndrome.

Figure 2. Significant/borderline risk factors for exacerbations in the last 12 months: OR and 95% CI



Adjusted for age, sex, allergic asthma, positive family history of asthma, age at asthma diagnosis, gastroesophageal reflux, rhinitis, sinusitis, aspirin hypersensitivity.