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Severe asthma in adolescents and adults: a national, multicenter registry in real life

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Summary
The number of patients with uncontrolled asthma is growing especially in young people. Although current therapies improve the disease management, the heterogeneity of clinical outcomes results in patients whose asthma is refractory to standard therapies. To understand not responsive phenotypes, we instituted a web-registry aimed to collect real life data of adolescent and adult patients.
One-hundred and five Italian medical Centers are part of the network. Participants above 14 years and affected by severe asthma will be included in the study. Demographic and clinical data will be collected for 5 years on a dedicated electronic database.
For the first time in Italy, our study will provide information on epidemiological, clinical and therapeutic aspects related to the natural course of the disease, filling the gap between adolescents and adults.

Introduction

Asthma is a chronic heterogeneous respiratory obstructive airways disease characterized by different clinical phenotypes resulting from complex interaction between environmental and genetic factors (1). Although asthma remains one of the most prevalent diseases worldwide, with constantly growing numbers especially in pediatric age, it is often underdiagnosed and not properly treated. The results are a late diagnosis, low treatment efficacy (2), a reduced life expectancy accompanied by frequent hospitalizations and, consequently, high costs for the Health Care System (3-5).
For these reasons, in the past two decades the Global Initiative for Asthma (GINA) (6) developed a network of individuals, organizations, and public health officials to deliver the best care

to patients with asthma. However, due to asthma's multiple phenotypes, individuals can vary their response to the standard therapy, developing severe respiratory obstructive crises with a greater risk of *near fatal asthma* and mortality (7). To address the needing of the best approach to the management of that subgroup of patients, the American Thoracic Society and the European Respiratory Society (ATS/ERS) published recommendations and guidelines on the evaluation and treatment of severe asthma (SA) in children and adults (8). According to ATS/ERS, patients with SA require treatment with high doses of inhaled corticosteroids (ICS) plus a second controller as a long-acting β2-agonist, leukotriene modifier or theophylline and/or continuous or near continuous systemic corticosteroids (CS) (6,9-11).
In case of unsatisfactory control of asthma, the availability of biologic therapies enables addressing the patients to the most appropriate treatment and reducing therapeutics dropouts.
These treatments offer an improvement in the management of the disease, but the heterogeneity of clinical outcomes and phenotypes suggests that many subjects could be difficult to treat and drugs could be not efficacious, especially in children (12-14).
To face up this problem, the Society of Pediatric Respiratory Diseases (SIMRI) developed, for the first time in Italy, a registry for the collection of pediatric cases of SA with the aim to identify risks factors, clinical phenotypes and develop a *customized therapy* (15). Nevertheless, the SIMRI-registry results have two limitations: i) adolescents are not admitted to pediatric medical units and for this reason they are not recorded in the registry; ii) it is impossible to evaluate how the disease progresses and evolves from adolescence to adulthood. In turn, the Italian registry on severe/uncontrolled asthma has recently provided first results concerning adult patients exclusively (16).
In this context, the creation of a single registry to join pediatric and adult cases of SA is fundamental. The partnership of the Italian Association of Hospital Allergists and Immunologists (AAIITO) Italian Association of Hospital Pulmonologists (AIPO) proposed the institution of the Italian Registry on Severe Asthma (IRSA), aimed to collect data of *real life* in adolescents and adult patients. The IRSA will give the opportunity to follow the natural course of the disease, improving knowledge on the evolution of asthma phenotypes not responsive to the standard therapy, contributing to a more appropriate management of the patient and a more targeted design of future clinical studies.

Materials and methods

Study design

The IRSA is an ongoing observational, non-interventional, transversal and/or retrospective multicenter study of 5-years duration, involving 4.800 patients and 105 Italian Centers and local hospitals specialized in pulmonary and allergic diseases, planned thanks to the co-operations of AIPO Centro Studi (**figure 1**). The primary study outcome is to collect data of adolescents and adults affected by SA, in a "*real life*" setting, in order to: i) identify risks factors, ii) analyze multiple clinical phenotypes, and iii) understand the epidemiological, clinical and therapeutic aspects related to the pathology. To complete our results, a secondary outcome is carried out to determine etiological and clinical features of subjects with *near fatal* episodes of asthma.
Patients affected by SA are enrolled by the Unit of Allergy and Pulmonology of participating centers, at first admission (or retrospective) and followed-up every 12 months for the entire duration of the study (**figure 2**).
At the first visit, patients are asked to accept written informed consent, except for young people where parents or legal representatives have the responsibility to approve the participation to the study. The Investigator has to withdraw the patient from the study if the participant revokes his/her consent to participate to the Registry.
After acceptance, demographic and clinical data are collected by the physician on a web-based Electronic Case Report Form (eCRF).
Patients enrolled for the study assume their own medical treatment according to the characteristics of their disease, as prescribed by the physician. All changes to the therapy are recorded

Figure 1 *- Geographic distribution of participating Italian Centers. The map shows how the 105 Centers partecipating to the Registry are geographically distributed. Cities with three or more participating Centers are reported as a big circle.*

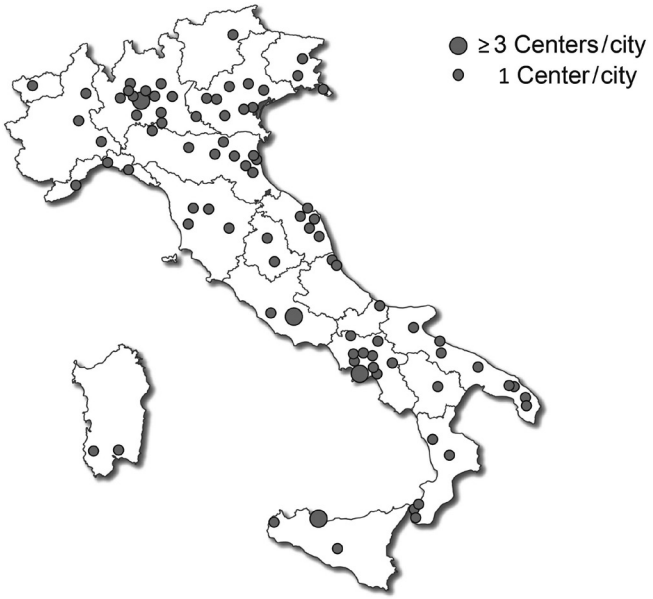
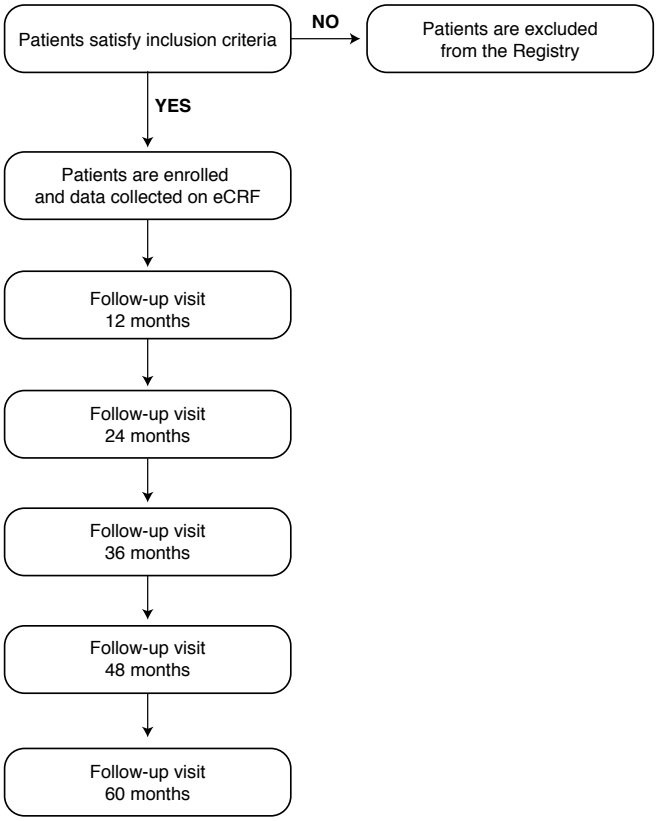


***Figure 2** - Flowchart. Schematic representation of the IRSA protocol.*



at the follow-up visit.
Subjects are followed until the end of the study.

Study population

Eligible patients are male or female ≥ 14 years of age, with a diagnosis of SA according to the GINA guidelines (http://ginasthma.org) on regular treatment with: i) high doses of inhaled corticosteroid (ICS) and long-acting β2-agonists (LABAs); or ii) med/high doses of ICS/LABA + leukotriene receptor antagonist (LTRA); or iii) med/high doses of ICS/LABA + theophylline; or iv) Oral steroids for at least 150 days/year + inhalation therapy. Patients with a clinical history of chronic obstructive pulmonary disease (COPD) or other respiratory diseases are excluded from the study.
All patients provided written informed consent prior to enrollment, and personal data used to identify patients were replaced with a study ID number prior to further data processing. The study was approved by the Ethics Committee Milan Area 3 of the Coordinating Center. However, for multi-center studies, multiple submissions to local institutional ethics committees are required, and satellite clinical sites can start enrollment only after having received the favorable opinion of the Ethical Committee. This is a no-profit study according to the Italian Law, D.M. 17.12.2004.

Data collection

Data of patients eligible for the study are collected on the eCRF and registered in the electronic database developed by CINECA (Bologna, Italy, www.cineca.it), a no-profit Consortium made up of 70 Italian universities, 8 Italian Research Institutions and the Italian Ministry of Education, operating in the management and development of web-based services. For each participating subject, the eCRF required the following information:

1. Demographic data (i.e. sex, high, weight, body mass-index);
2. History of smoking;
3. History of asthma and allergies;
4. Level of asthma control assessed by Asthma Control Test (ACT) or Asthma Control questionnaire (ACQ);
5. Number of exacerbations and hospitalizations in the 12 months preceding the visit;
6. Direct and indirect health costs;
7. Presence of co-morbidities (i.e. nasal polyposis, hypertension, diabetes, gastro-oesophageal reflux, obesity);
8. Laboratory data and functional tests (i.e. total IgE, leucocytes, neutrophils, lymphocytes, eosinophils, Forced Expiratory Volume in one second [FEV1], FEV1/Forced Vital Capacity [FEV1/FVC], FeNO);
9. Asthma therapy, including biologics;
10. Follow-up after 12 months from the first visit (ACT or ACQ score, exacerbations, laboratory data and functional tests, evaluation of effectiveness of medical treatment).

All the eCRFs are stored on-line in the central database for data processing, and analysis will be performed on aggregated data. The access to the eCRF is regulated by personal user credentials (user-id and password) linked to the Investigator responsible for data collection. Participating Centers are allowed to consult only their enrolled patients, and the access to information (registration/consultation of data) is encrypted by the Internet HTTPS protocol. Data are collected according to the European Regulation (EU) 2016/679 (General Data Protection Regulation - GDPR) and can be processed only with the informed consent of patient.

Ethical aspects and respect for confidentiality

The present study is carried out according to the Helsinki Declaration and National and International law on Observational Studies, in order to ensure the maximum protection for the subjects involved in the study. The proposed protocol is performed

according the Good Clinical Practice (GCP - ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996). The promoter of the study is committed to the protection of sensitive, clinical and personal data of the subjects involved in the study, as established by the Italian Legislative Decree n. 196/2003 (Data Protection Code) and by the latest GDPR 2016/679 (applicable in all the Member States of the European Union since 25 May 2018). Investigators are responsible for obtaining patient's informed consent after adequate information about the aims, methods, expected benefits and foreseeable risks of the study. Experimenters or agents should also inform participants that their participation or interruption will not cause modifications to the normal clinical practice.

Statistical analysis

This is an observational and descriptive study. The sample size was estimated assuming that the Severe Asthma disease has a prevalence of the 5% in the overall Italian patients affected by asthma. Based on the inclusion criteria, we estimate to enroll 4,800 patients affected by SA. In this context, we assume to be able to accurately estimate the prevalence of a specific characteristic (i.e. smoking). For example, supposing that the 30% of patients are smokers, the sample size of 4,800 subjects will produce a 95% confidence interval with an estimated error of 2.6%. Sample size was calculated using the PASS v.11 software (NCSS, LLC. Kaysville, Utah, USA).

Results will be represented as mean, median, standard deviations (SD), quartiles, and outliers, respectively for normally and non-normally distributed values. Data will be graphically presented as histograms, box-plots and whisker-plots. Tables of frequency distributions (numbers and percentages) will be prepared for categorical variables or with mean ± SD for continuous variables.

Comparisons of specific subgroups of data will be done with the Chi-square test or the exact Fisher test (for categorical variables), or with the two tailed t-test or the non-parametric test "Rank-sum" of Wilcoxon (for continuous variables). Differences among comparisons groups will be determined by the analysis of variance (ANOVA) for repeated measurements or, in the case of non-homogenous distribution, by the non-parametric Kruskal-Wallis test. Statistical analysis will be performed using the Statistical Analysis Software v 9.4 (SAS) (SAS Institute Cary, NC, USA).

Conclusions

Severe asthma is a heterogeneous disease in adults as well as in adolescents, with different clinical and inflammatory phenotypes. SA treatment is particularly challenging due to the high morbidity and disease-related costs. Biologic therapies represent a significant opportunity for customized treatment to patients who do not respond to traditional asthma therapy, but a more accurate selection of patients with SA is needed. Despite this, the routinely use of reliable and non-invasive biomarkers in patients whose asthma is refractory to standard therapy is still missing. For all these reasons, there is an urgent need to characterize patients affected by severe uncontrolled asthma in *real life*. Several registries collecting cases of SA have been recently created in different countries, each of them with their strengths and weaknesses.

For the first time in Italy, the IRSA project will give the opportunity to understand the epidemiological, clinical and therapeutic aspects related to the pathology, filling the gap between adolescents and adults, identifying risks factors, analyzing multiple clinical phenotypes, and monitoring treatments safety and efficacy.

We believe that collecting data across a large range of ages will provide new information, useful to improve asthma health care and the management of affected patients, according to the best clinical practice.

Conflict of interest

The authors declare that they have no conflict of interest.

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References

1. Wenzel S. Severe asthma: from characteristics to phenotypes to endotypes. Clin Exp Allergy 2012; 42:650-8.
2. Chung KF. Unmet needs in adult asthma. Clin Exp Allergy 2000; 30Suppl1:66-9.
3. Serra-Batlles J, Plaza V, Morejón E, Comella A, Brugués J. Costs of asthma according to the degree of severity. Eur Respir J 1998; 12:1322-6.
4. Antonicelli L, Bucca C, Neri M, De Benedetto F, Sabbatani P, Bonifazi F, et al. Asthma severity and medical resource utilisation. Eur Respir J 2004; 23:723-9.
5. Nunes C, Pereira AM, Morais Almeida M. Asthma costs and social impact. Asthma Res Pract 2017; 3:1-11.
6. Global Initiative for Asthma. Global strategy for asthma management and prevention 1995.
7. D'Amato G, Vitale C, Lanza M, Sanduzzi A, Molino A, Mormile M, et al. Near fatal asthma: treatment and prevention. Eur Ann Allergy Clin Immunol 2016; 48:116-22.

8. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014; 43:343-73.
9. Ducharme FM, Lasserson TJ, Cates CJ. Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. Cochrane Database Syst Rev 2006:CD003137.
10. Cox G, Thomson NC, Rubin AS, Niven RM, Corris PA, Siersted HC, et al. Asthma control during the year after bronchial thermoplasty. N Engl J Med 2007; 356:1327-37.
11. Ni Chroinin M, Lasserson TJ, Greenstone I, Ducharme FM. Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children. Cochrane Database Syst Rev 2009:CD007949.5-8.
12. Bush A, Saglani S. Management of severe asthma in children. Lancet 2010; 376:814-25.
13. Lang A, Mowinckel P, Sachs-Olsen C, Riiser A, Lunde J, Carlsen KH, et al. Asthma severity in childhood, untangling clinical phenotypes. Pediatr Allergy Immunol 2010; 21:945-53.
14. Humbert M, Busse W, Hanania NA. Controversies and opportunities in severe asthma. Curr Opin Pulm Med 2018; 24:83-93.
15. Montella S, Baraldi E, Cazzato S, Aralla R, Berardi M;, Brunetti LM, et al. Severe asthma features in children: a case-control online survey. Ital J Pediatr 2016; 42:1-9.
16. Maio S, Baldacci S, Bresciani M, Simoni M, Latorre M, Murgia N, et al. AGAVE group. RItA: The Italian severe/uncontrolled asthma registry. Allergy 2018; 73:683-95.