



Chronic rhinosinusitis with nasal polyps impact in severe asthma patients: Evidences from the Severe Asthma Network Italy (SANI) registry

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ARTICLE INFO

Keywords:

Severe asthma
Nasal polyps
Oral corticosteroids
Comorbidities

ABSTRACT

Background: The clinical and laboratory features of patients enrolled in the Severe Asthma Network in Italy (SANI) registry, a web-based observatory collecting demographic, clinical, functional and inflammatory data of patients with severe asthma were evaluated, with a special emphasis to chronic rhinosinusitis with nasal polyposis (CRSwNP).

Methods: For each eligible patients the following information has been collected: demographic data, clinical features, asthma control in the previous month according to the GINA (Global Initiative for Asthma) Guidelines and standardized questionnaires, concomitant regular and on demand treatments and inflammatory markers.

Results: 695 patients with severe asthma enrolled in 66 SANI centers were analyzed. The prevalence of chronic rhinosinusitis with nasal polyposis was 40.6%. Atopic dermatitis and bronchiectasis was significantly more frequent in patients with CRSwNP than in subjects without nasal polyposis; similarly, FeNO values are significantly higher in subject with CRSwNP than in patients without nasal polyposis. Finally, patients with CRSwNP had a significantly higher number of asthma exacerbations per year, more days on oral corticosteroids and were more likely to be OCS long term users.

Conclusion: OCS sparing is needed in patients with severe asthma, mainly in subjects with CRSwNP, adopting adequate strategies such as a better adherence to the treatment with inhaled therapy according to the GINA recommendations, the use of biologic agents and a multidisciplinary approach of the patient.

1. Introduction

Chronic rhinosinusitis with nasal polyposis (CRSwNP), a subgroup of chronic rhinosinusitis [1–3] of growing importance, is characterized by an impaired health-related quality-of-life (HRQoL), a remarkable symptom burden, a frequent recurrence/relapse [4], and a troublesome and difficult-to-treat olfactory impairment [5–8]. Recently, the new approach Treatable Traits concept, firstly used in defining respiratory diseases, understanding and treating patients with chronic obstructive pulmonary disease (COPD) and/or asthma, has been also introduced in

the CRSwNP context [9]. In this perspective, the more data are collected in this topic the more insights will be available; to this purpose the registries are instrumental in providing structured data.

In previous observations, CRSwNP has been highlighted as a frequent feature of patients with severe asthma (SA). This was also detected in a cross-sectional analysis of data derived from the of Severe Asthma Network in Italy (SANI) registry [10] focusing on the first available baseline epidemiological, clinical, inflammatory, functional and treatment characteristics of a large Italian population of SA [11]: about 42% of severe asthmatics were reported to be affected also to CRSwNP.

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In other studies, the incidence of CRSwNP in SA patients was related to a poor asthma control, a high use of OCS and a defective QoL. Interestingly, CRSwNP was detected in over 60% of late-onset asthma patients [12]; besides, in this study late-onset asthma and CRSwNP patients received more than three OCS courses per year.

These characteristics are defining a particular clinical phenotype of patients with clear features of severity. All these observations are prompting to a careful evaluation of comorbidities, namely CRSwNP, in all SA patients, as recently reported also in the GINA 2019 recommendations [13]. The presence of CRSwNP can be a factor influencing the clinical outcome(s) of some biologic drugs in SA treatment, as reported in the reslizumab trial by Castro et al. [14].

There is still debate on defining CRSwNP as a mere severe asthma comorbidity or one of the clinical manifestations of a specific phenotype characterized also by late-onset, non atopic (intrinsic) and strongly eosinophilic asthma [12,15,16].

In the current report, the clinical and laboratory features of SA patients recruited by the SANI Centers by April 2019 were evaluated, with a special emphasis to CRSwNP comorbidity.

2. Methods

2.1. 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 [17]. Each reference center (Allergy and/or Respiratory Disease Units) was accredited based upon criteria such as enough trained personnel dedicated to asthma (specialists and nurses), population of treated asthmatic patients per year, availability of lung function equipment and other clinical procedures, 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 Italy. The study 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, 48 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 RedCap (Research Electronic Data Capture). 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.

2.2. Study population

Patients aged >12 years with a diagnosis of SA according to the ERS/ATS criteria [17] were eligible for inclusion into the study. 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 comorbidities, lung function, exacerbations, unscheduled visits), asthma control in the previous month according to the GINA (Global Initiative for Asthma) Guidelines [13] 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).

2.3. Ethical issues

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

2.4. 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 < 0.05 was considered statistically significant.

3. Results

The prevalence of CRSwNP in the 695 analyzed SA patients (mean age: 54.9 ± 16.6 years; 60.6% females; 2.5% smokers; 75.9% atopics; mean BMI: 26.6 ± 16.7; 42% with late-onset asthma defined using 40 years as cut-off) was 40.6%. Patients with CRSwNP didn't differ in terms of mean age, gender distribution, mean age of asthma onset, atopy and mean BMI from those without CRSwNP (Table 1).

Biomarkers, comorbidities and OCS use were analyzed. As far as comorbidities are concerned (Table 1), atopic dermatitis was significantly more frequent in patients with CRSwNP than in subjects without nasal polyposis, and a similar significant difference was detected for bronchiectasis. On the contrary, no difference was detected with regard to GERD in the two patients' groups. Fe_{NO} values are significantly higher in subject with SA and CRSwNP than in patients without nasal polyposis (Table 1). Serum IgE levels were higher than normal in both group of patients, but slightly higher, not statistically significant trend in those without CRSwNP (533,3 ± 1141,1 vs 379,4 ± 394,7, p = 0.058). The circulating eosinophils count was >300 in both groups without any demonstrated statistical difference (CRSwNP: 513,6 ± 607,2 cells/mcl vs non-CRSwNP: 471,9 ± 618,2 cells/mcl; p = 0.466).

As reported in Table 1, patients with CRSwNP had a significantly higher number of asthma exacerbations per year (mean annual exacerbation number requiring OCS treatment: 3,69 vs 2,46, p = 0.014). The analysis of the OCS use in the different populations (Fig. 1) showed that the number of OCS long-term users (defined as subjects on maintenance therapy with OCS or receiving ≥ 3 courses of OCS during the last 12 months) is significantly higher (p < 0.001) in CRSwNP SA patients. Finally SA patients with CRSwNP were consuming OCS on double as much days/year (79 vs 161; p > 0.02) than patients without nasal polyposis.

4. Discussion

According to the new GINA recommendations 2019 [13], the current procedures to diagnose SA should now include both nasal endoscopy and computed tomography (CT) of nasal and paranasal sinuses. This is nowadays mandatory in the light of the several reports stating the high prevalence of CRSwNP associated with severe asthma (particularly non allergic, late-onset, eosinophilic phenotype asthma for which CRSwNP is a relevant clinical manifestation), where Type 2 inflammation coming from the mechanism(s) involved in the immune response in asthma and

Table 1
Demographic and clinical characteristics of SANI population.

	All the patients (n = 695)	Patients with CRSwNP (n = 282)	Patients without CRSwNP (n = 413)	p values
Mean age, years	54.9 ± 16.6	54.9 ± 12.9	55.13 ± 13.7	0.836
Female, %	60.6	61.3	60.0	0.731
Mean age of asthma onset, years	33.7 ± 16.6	34.5 ± 15.9	33.0 ± 17.2	0.290
Atopy, %	75.9	72.6%	79.8	0.184
BMI (mean, Kg/m ²)	26.6 ± 16.7	27.1 ± 22.8	25.9 ± 4.8	0.390
Annual exacerbation rate, mean	3.03 ± 5.55	3.69 ± 7.43	2.46 ± 3.00	0.014
FEV ₁ % predicted, mean	73.6 ± 20.4	74.4 ± 19.3	73.0 ± 21.4	0.440
Prevalence of atopic dermatitis, %	5.9	8.6	3.4	0.019
Prevalence of bronchiectasis, %	15.5	20.9	11.9	0.001
Prevalence of GERD, %	26.9	27.5	24.6	0.572
FE _{NO} (mean, ppb)	44.3 ± 48.9	54.4 ± 53.8	34.6 ± 28.3	<0.0001
Blood eosinophils (mean, cells/mcl)	492.3 ± 612.5	513.6 ± 607.2	471.9 ± 618.2	0.466
Serum IgE (mean, kU/l)	459.2 ± 850.1	379.4 ± 394.7	533.3 ± 1114.1	0.058

CRSwNP, chronic rhinosinusitis with nasal polyposis; BMI, body mass index; FE_{NO}: Fractional Exhaled Nitric Oxide; GERD: GastroEsophageal Reflux Disease.

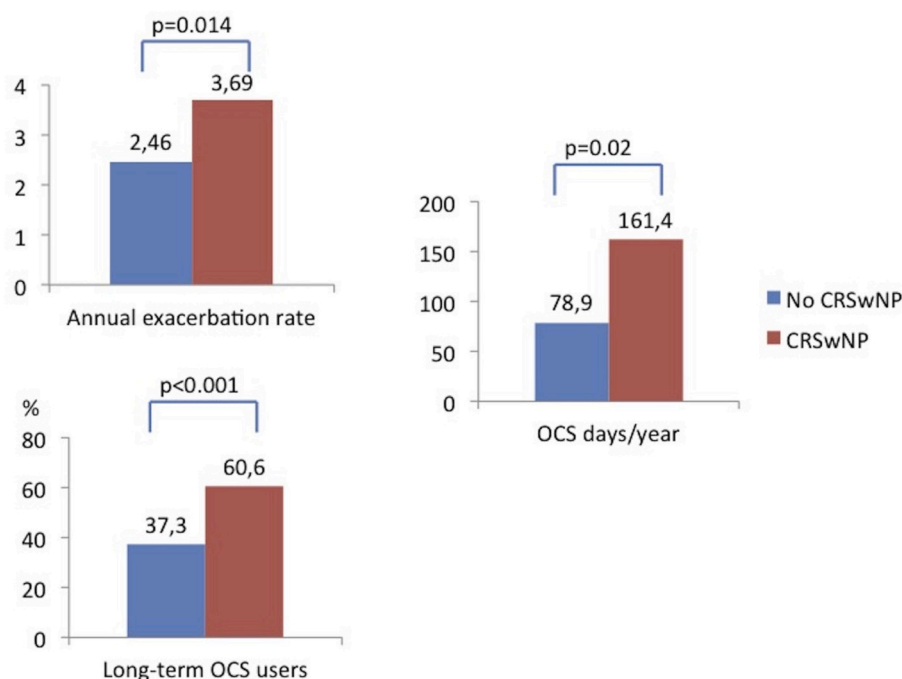


Fig. 1. Annual exacerbation rate and oral corticosteroids use in severe asthmatic patients with or without chronic rhinosinusitis with nasal polyps (CRSwNP).

other diseases is often present. Type 2 inflammation is related to the production of the so called “T2 cytokines”, namely IL 4, IL 5 and IL 13; this common pathway can be also considered as an expression of different clinical manifestations, so the word “commonality” is nowadays used to indicate Clinical Pathological Realities where a Type 2 driven mechanism(s) is involved [18]. In the same perspective, looking at the herein presented data and considering the more represented comorbidities, namely bronchiectasis and atopic dermatitis, a structured patient management should be programmed: in the first case, the risk of an episode of a bacterial infection has to be considered, possibly acting as triggers of asthma exacerbations. In the second one, a commonality can be envisaged and possibly treatment(s) effective on different disorders can be applied [18].

The presence of nasal polyposis in SA patients treated with biologic agents can impact the response to the biologics themselves, or it's at least identifying a subset of better responders to biologics among the SA patients [9].

In the SANI cohort of SA patients with CRSwNP (about 40% of the entire cohort), high Fe_{NO} levels have been detected whereas total IgE, although high in both groups, are lower than in patients without nasal polyposis; this does not suggest a relevant role of allergy in patients with

nasal polyposis. Eosinophils are not providing distinction, since their values are higher than 400 in both groups without any statistical difference; considering the higher and more frequent use of systemic corticosteroids in patients with severe asthma with associated CRSwNP, it is even probable that patients with this specific phenotype have higher baseline eosinophils in concordance with the described phenotype of severe intrinsic eosinophilic asthma. These data would suggest a higher eosinophilic inflammation of the lower airways, whereas the allergic mechanism(s) does not seem to play a relevant role in this phenotype of patients; taking together, these results suggest the hypothesis that polyposis is part of a specific clinical phenotype associated with intrinsic late-onset asthma [12,15,16]. Our data should prompt to use a cytological approach also to the study of nasal polyposis, where we know different treatable traits, so different mechanisms have been described [9]. In fact, the eosinophilic inflammation might address to more endotype (target) driven treatment. Noteworthy, the prevalence of CRSwNP in our cohort was about 40% of all severe asthmatics; this proportion is probably even underestimated as specific investigations to diagnose/rule out CRSwNP were not mandatory but only strongly suggested for all severe asthmatics enrolled into the SANI registry.

The last GINA pocket guide 2019, although still indicating low dose

OCS as added option in Step 5 patients not controlled with pharmacological treatment at the prescribed dosages (i.e. high ICS dose plus LABA plus LAMA) reported for the first time a warning about the side effects induced by the OCS treatment. In clinical practice, OCS is suspected to be very widely used in SA treatment, even more than the reported data by SA registries.

In the SANI report [11], the reported rate of SA patients on OCS treatment was >64% with a daily dose > 10 mg/day, meaning a very impacting percentage and a high dose of oral steroid. In fact, the study by Voorham et al. [19], evaluating different OCS dosages and the related potential to induce side effects, suggests to maintain the dosage below 5 mg/day in order to reduce, as much as possible, the risk of side effects. Analogously, Volmer et al. [20] reported the consequences of long-term use of OCS-induced side effects related to the dosages of the steroid itself. Systemic corticosteroid-induced morbidity in severe asthma patients have a relevant impact on health care costs, as reported by several authors [21,22] including a recently published pharmaco-economic evaluation endorsed by SANI [23].

It seems therefore advisable to reduce or to suspend, whenever possible, the use of OCS in SA patients using all possible alternative strategies [24] from the promotion of an effective adherence to inhalation therapy to the use of biologic agents that demonstrated a significant OCS sparing effect [25]. A recent study [12] showed that early-onset asthma patients have less CRSwNP than late-onset asthma patients, where the number of courses of OCS were higher than in early-onset asthma patients. In the current report, SA patients with CRSwNP have been found to be long-term OCS users (40% more than in patients without nasal polyposis) and they spent on OCS significantly more time (+100% versus patients without nasal polyposis). It is noteworthy that these are important clinical features of the subset of patients analyzed in the current study.

The data collected are strongly supporting the absolute need to properly investigate the nasal polyposis in asthma patients also in the pulmonology setting, since the presence of nasal polyposis can identify a risk population of asthma patients: SA patients are treated, by GINA definition, with high-dose ICS, but many are also on OCS and, due to the presence of nasal polyposis, they are also on nasal steroids: this group is certainly in overuse of steroids. Alternative therapeutic strategies, such as biologic agents acting on both diseases, can be considered a first-choice therapy in severe patients, considering their capability to reduce or to stop steroids use.

5. Conclusion

The results of this analysis confirm that OCS are frequently used in severe asthmatics as already reported in our previous observation from SANI registry [11]; the use of OCS is even more frequent, with almost the double of days of treatment per year, in patients with CRSwNP associated to severe asthma, with probable relevant impact on OCS-related adverse events and their associated health-care costs [23]. Considering the high burden of CRSwNP on severe asthma, as also showed in the present study, a multidisciplinary approach for severe asthma diagnosis and management, with a strict collaboration between allergists, respiratory physicians and ENT specialists is becoming an important tool in order to improve the treatment of the patients. Moreover, one of the main goal in managing patients with severe asthma associated with CRSwNP should be to reduce the use of OCS, applying and implementing the most effective strategies to achieve this aim: the implementation of adherence to the inhaled therapy for SA, accordingly to the GINA recommendations 2019 [13]; the use of biologic agents that showed OCS sparing effects [26–29]. In addition, preliminary evidences exist [30,31] about the effect of those same biologic agents on the outcomes of patients with CRSwNP. The phase III study by Bachert et al. [32] clearly reported a highly significant effect of dupilumab, an anti-IL 4 alpha receptor monoclonal antibody, on CRSwNP, including an OCS sparing effect. The use of these biological agents in patients with SA and

CRSwNP, being effective on both disorders, would be of great value both for the patient viewpoint and for the sustainability of these costly treatments.

Support statement

SANI is supported by Unrestricted Grants from AstraZeneca, Glaxo Smith Kline, Novartis & Sanofi Genzyme.

Take-home message

Severe asthmatics with chronic rhinosinusitis with nasal polyps are exposed to a significantly higher amount of oral corticosteroids compared to those without nasal polyposis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRedit authorship contribution statement

Giorgio Walter Canonica: Conceptualization, Supervision, Writing - original draft, Writing - review & editing. **Luca Malvezzi:** Conceptualization, Writing - original draft, Writing - review & editing. **Francesco Blasi:** Conceptualization, Writing - original draft, Writing - review & editing. **Pierluigi Paggiaro:** Conceptualization, Writing - original draft, Writing - review & editing. **Marco Mantero:** Writing - original draft, Writing - review & editing. **Gianenrico Senna:** Writing - original draft, Writing - review & editing. **Enrico Heffler:** Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing.

Acknowledgments

Concetta Sirena, Daniela Morrone & Silvia Rabotti for their unvaluable job in setting SANI and in collecting data.
Piero Zucchi for revising the manuscript.

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