COVID-19 in Severe Asthma Network in Italy (SANI) patients: clinical features, impact of comorbidities and treatments

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Abstract

BACKGROUND: COronaVIrus Disease 19 (COVID-19) pandemic is affecting almost the entire world since February 2020. Patients with chronic pulmonary diseases, such as asthma and chronic obstructive lung disease potentially and theoretically may be more vulnerable and therefore seriously ill if infected by SARS-CoV-2; however, according to the first epidemiological studies published so far, chronic pulmonary diseases are under-reported. No data is available, so far, about the incidence of COVID-19 in severe asthmatics and about which are the COVID-19 outcomes in this subgroup of patients. METHODS:: In this study, we investigated the incidence of COVID-19 cases in a large population of severe asthmatics in Italy, describing their clinical characteristics and clinical course of COVID-19 disease. RESULTS: Twenty-six (1.73%) out of 1504 severe asthmatics were identified as confirmed or highly suspect with COVID-19. Nine (34.6%) of infected patients experienced worsening of asthma during the COVID-19 symptomatic period. Severe asthmatics affected by COVID-19, compared to those who did not contracted the infection, had a significantly higher prevalence of non-insulin-dependent diabetes mellitus (NIDDM) (15.4% vs 3.8%, p=0.002); among COVID-19 patients the proportion of those treated anti-IL5 biologic agents was higher (71%) compared to the number of patients treated with anti-IgE (29%). CONCLUSIONS: In our large cohort of severe asthmatics, the incidence of COVID-19 was particularly low, with higher prevalence of NIDDM as comorbidity, suggesting that NIDDM might be a risk factor for COVID-19 in severe asthmatics.

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Short title: COVID-19 and severe asthma in real-life

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Conflict of interest statements:

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MAIN TEXT:

INTRODUCTION

Since the end of February 2020 Italy, first non- Asian Country, has reported an ever increasing number of COronaVIrus Disease 19 (COVID-19) patients, which has reached over 200,000 confirmed Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) infected subjects and resulted in more than 34000 deaths (data updated to June 19th, 2020[1]). The SARS-CoV-2 infection has spread all over the world becoming one of the biggest pandemics of the last centuries. COVID-19 clinical manifestations spectrum ranges from mild

to critical, including diffused interstitial pneumonia, respiratory failure, shock, or multiorgan dysfunction, leading to death in about one third of hospitalized patients [2] with a overall case-fatality rate in the general population of about 7% of infected subjects[3].

Patients with chronic pulmonary diseases, such as asthma and chronic obstructive lung disease (COPD), are potentially more severely affected by by SARS-CoV-2 infection [4]. Indeed, it is well established that respiratory viral infections are associated with severe adverse outcomes in patients with asthma, including increased risk of asthma exacerbation episodes [5]. In addition, it has been suggested that type 2 immunologic profile, which characterizes a large proportion of asthmatic patients, is associated with impaired antiviral immune response [6] and a greater expression in airway epithelial cells of molecules associate with SARS-CoV-2 infectivity [7]. Nonetheless, according to the epidemiological studies published so far, chronic pulmonary diseases are not amongst the most common clinical conditions in COVID-19 patients, ranging from 0.3 to 2.5% [8-10].

A proportion of asthmatics, accounting about 5-10% of entire asthma population, continue to experience symptoms and exacerbations despite treatment with high-dose inhaled corticosteroids (ICS) in combination with other controller drugs and/or chronic use of oral corticosteroids (OCS): these are considered severe asthma patients [11]. Given the deranged immunological responsiveness that characterizes severe asthma patients, one would expect increased vulnerability to SARS-CoV-2 infection. No data is available on the susceptibility of severe asthmatics to COVID-19 infection and on the clinical outcomes of the infection in these patients. Real-life, registry-based observatories are a unique opportunity to rapidly collect clinical information on the impact of COVID-19 on large populations of severe asthmatics.

The aim of the this study was to investigate the incidence of COVID-19 infection in the population of the Severe Asthma Network in Italy (SANI), one of the largest registry for severe asthma worldwide[12,13], and in an additional Center (Azienda Ospedaliero Univeristaria di Ferrara, Ferrara, Italy); we also aimed to describe their clinical characteristics and clinical course of COVID-19 disease.

METHODS:

PATIENTS:

SANI is a web-based observatory collecting demographic, clinical, functional, inflammatory biomarkers data of patients with severe asthma according to European Respiratory Society (ERS)/American Thoracic Society (ATS) classification [11] and aged > 12 years, recruited by accredited centers homogeneously spread out the national territory [12,13]. All centers, have been contacted and inquired to report confirmed (i.e. patients with positive test result for the virus SARS-CoV-2 from analysis of nasopharyngeal or oropharyngeal swab specimens) or highly suspect cases of COVID-19 (i.e. patients with symptoms, laboratory findings and lung imaging typical of COVID-19 but without access to nasopharyngeal or oropharyngeal swab specimens because of clinical contingencies/emergency) among their cohorts of severe asthma.

Demographic and clinical data of the entire population of severe asthmatics enrolled in the study and all reported cases of confirmed or suspect cases of COVID-19, have been obtained from the registry platform and collected from the additional Center (Azienda Ospedaliero Univeristaria di Ferrara, Ferrara, Italy). Additional data about COVID-19 symptoms, treatment and clinical course have been collected for all cases reported.

GENERAL INFORMATION ON COVID-19 IN ITALY:

Open access data about the number of confirmed cases of SARS-CoV-2 infected subjects in the Italian general population have been collected from the Civil Protection Department of the Italian Government website[1], and used to draw a thematic map representing the number of cases divided by administrative regions.

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 patient outcomes published by the Effective Health Care Program of the Agency for Healthcare Research and Quality

(https://effectivehealthcare.ahrq.gov/topics/registries-guide-3rd-edition/research/). The protocol was 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 according to 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).

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.

RESULTS:

Twenty-six (1.73%) out of 1504 severe asthmatics had confirmed (11 out of 26) or highly suspect COVID-19 (15 out 26); eighteen (69.2%) were females and mean age was 56.2 $\pm$ 10 years. The geographical distribution of COVID-19 cases is presented in Figure 1.

Nine (34.6%) infected patients experienced worsening of asthma during the COVID-19 symptomatic period; four of them needed a short course of oral corticosteroids for controlling asthma exacerbation symptoms.

The most frequent COVID-19 symptoms reported were fever (100% of patients), malaise (84.6%), cough (80.8%), dyspnea (80.8%), headache (42.3%) and loss of smell (42.3%). Four patients (15.3%) have been hospitalized, one of which in Intensive Care Unit (ICU); among hospitalized patients, two (7.7%) died for COVID-19 interstitial pneumonia. No deaths have been reported among the non-hospitalized patients.

Severe asthmatics affected by COVID-19, had a significantly higher prevalence of non-insulin-dependent diabetes mellitus (NIDDM) compared to non-infected severe asthma patients (15.4% vs 3.8%, p=0.002; odds ratio: 4.7). No difference in the prevalence of other comorbidities (including rhinitis, chronic rhinosinusitis with or without nasal polyps, bronchiectasis, obesity, gastroesophageal reflux, arterial hypertension, cardiovascular diseases) was found between infected and non-infected severe asthmatics included in the study.

Twenty-one out of 26 patients with COVID19 (confirmed or highly suspected) were on biological treatments. Among severe asthmatic patients treated with biological agents and experiencing COVID-19 (n=21), 15 (71%) were on anti-IL-5 inflammatory pathway (Mepolizumab n= 13; Benralizumab n=2 - counting for the 2.9% of all severe asthmatics treated with anti-IL5 in our study population) whilst 6 (29%) were on anti IgE (Omalizumab - 1.3% of all severe asthmatics treated with omalizumab in our study population).

Table I summarizes demographic and clinical characteristics of the 26 patients COVID-19.

DISCUSSION

In our large cohort of severe asthmatics, COVID-19 was infrequent. This finding does not support the concept of asthma as a particularly susceptible condition to SARS-COV2 infection [4]. This is in line with the first published large epidemiological data on COVID-19 patients, in which asthma is under-reported as comorbidity[8-10]. Two of the 26 severe asthmatics with COVID-19 died of SARS-CoV-2 infection; with a rate that is lower (7.7%) the COVID-19 mortality rate in the general population (14.5% in Italy[1]). All together these findings suggest that patients with severe asthma are not at high risk of the SARS-CoV-2 infection and of severe forms of COVID-19. There are potentially different reasons for this. Self-containment is the first, because of the awareness of virus infections acting as a trigger for exacerbations, and therefore they could have acted with greater caution, scrupulously respecting social distancing and lockdown, constantly applying the hygiene rules of prevention, and being more careful in regularly taking asthma medications. Indeed, recent publications report a significant increase in adherence to inhalation therapy during the COVID-19 pandemic among asthma patients [14].

Another possible explanation stands in the intrinsic features of type-2 inflammation, that characterizes a

great proportion of severe asthmatics. It has been recently reported that respiratory allergies and controlled allergen exposures are associated with significant reduction in angiotensin-converting enzyme 2 (ACE2) expression[15], the cellular receptor for SARS-CoV-2[16]. The opposite relationship occurs between Rhinovirus and allergies, where Intercellular Adhesion Molecule 1 (ICAM1), the adhesion molecule used by the virus to enter respiratory cells, is overexpressed in allergic airways [17,18]. Interestingly, ACE2 and Transmembrane Serine Protease 2 (TMPRSS2) (another protein mediating SARS-CoV-2 cell entry) have been found highly expressed in asthmatics with concomitant NIDDM [19], the only comorbidity that was more frequent reported in COVID-19 severe asthmatics compared to the remaining population of patients with severe asthma.

The third possible explanation refers to the possibility that ICS might prevent or mitigate the development of Coronaviruses infections: in-vitro studies have shown that ICS alone or combined with bronchodilators inhibit coronavirus replication and the related cytokine production [20]. By definition, patients with severe asthma are treated with high doses of ICS [11] and this may have had a protective effect for SARS-CoV-2 infection.

Noteworthy, among the patients of our case-series of severe asthmatics with COVID-19, the proportion of those treated anti-IL5 biologic agents was higher (71%) compared to the number of patients treated with anti-IgE (29%). Although the number of cases is too small to draw any conclusion, it is tempting to speculate that different biological treatments can have specific and different impact on antiviral immune response [21,22]. In addition we may speculate of the consequence of blood eosinophils reduction: eosinopenia has been reported in 52-90% of COVID-19 patients worldwide [23]and it has been suggested as a risk factor for more severe COVID-19, and increase in eosinophils has been associated with better response to anti-viral therapy [24].

In conclusion, we reported that in a large cohort of severe asthmatic patients only a small minority experienced symptoms consistent with COVID-19, and these patients had peculiar clinical features including high prevalence of NIDDM as comorbidity. Further real-life registry-based studies are needed to confirm our findings and to extend the evidence that severe asthmatics are at low risk of developing COVID-19.

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TABLES:

Table I – Demographic and clinical characteristics of severe asthmatics with COVID-19.

AD: atopic dermatitis; ALB: albuterol; AMC: amoxicillin/clavulanate; AR: allergic rhinitis; AZM: azithromycin; BENRA: benralizumab; BX: bronchiectasis; Cax: ceftriaxone; CIP: ciprofloxacin; CRSsNP: chronic rhinosinusits without nasal polyps; CRSwNP: chronic rhinosinusitis with nasal polyps; CVD: cardiovascular diseases; GERD: gastroesophageal reflux disease; HCQ: hydroxychloroquine; HTN: hypertension; IBP: ibuprofen; ICS/LABA: Inhaled corticosteroids/Long-acting beta2-agonists; LAMA: long-acting muscarinic agents; LMWH: low molecular weight heparins; LPV/r: lopinavir/ritonavir; LTRA: leukotriene receptor antagonists; LVX: levofloxacin; MDD: major depressive disorder; MEPO: mepolizumab; MV: mechanical ventilation; NIDDM: non-insulin-dependent diabetes mellitus; NIV: non invasive ventilation; OCS: oral corticosteroids; OMA: omalizumab; PCM: paracetamol; ;TMP-SMX: trimethoprim/sulfamethoxazole; TOZ: tocilizumab

ID	Region	Suspect or Confirmed COVID-19	Age	Sex	BMI	Atopy	Smoker	Comorbidities	COVID-19 Symptoms	Asthma exacerbation during COVID-19	Asthma therapy	C 1 T a
1	Emilia Romagna	Confirmed	48	F	34	Yes	No	GERD	Fever	No	ICS/LABA LTRA, OMA	A A
2	Emilia Romagna	Confirmed	67	M	33	Yes	No	NIDDM	Fever, Dyspnoea	No	ICS/LABA OCS	A C
3	Emilia Romagna	Confirmed	65	F	33	Yes	No	BX, CVD, Anxiety, Osteoporosis	Fever, Cough, Dyspnoea	No	ICS/LABA	A I C M

ID	Region	Suspect or Confirmed COVID-19	Age	Sex	BMI	Atopy	Smoker	Comorbidities	COVID-19 Symptoms	Asthma exacerbation during COVID-19	Asthma therapy	C 1 T a
4	Emilia Romagna	Suspect	32	M	33	Yes	No	AR	Fever, Cough, Malaise, Anosmia, Ageusia, Sore throat, Dyspnoea, Wheezing, Diarrhea, Headache, Arthralgia, Myalgia	No	ICS/LABA OMA	A F
5	Lombardia	Confirmed	45	F	20	Yes	Ex	CRSwNP, GERD,	Fever, Cough, Malaise, Anosmia, Ageusia	No	ICS/LABA LTRA, OCS, MEPO	A

ID	Region	Suspect or Confirmed COVID-19	Age	Sex	BMI	Atopy	Smoker	Comorbidities	COVID-19 Symptoms	Asthma exacerbation during COVID-19	Asthma therapy	C 1 T a
6	Lombardia	Confirmed	45	F	27	No	No	CRSwNP, GERD	Fever, Cough, Malaise, Anosmia, Ageusia, Dyspnoea, Chest tightness, Chest pain, Respiratory failure	No	ICS/LABA LTRA, BENRA	I C
7	Lombardia	Confirmed	65	F	28	No	No	GERD, CVD, NIDDM, Osteoporosis	Fever, Cough, Dyspnoea, Respiratory failure	No	ICS/LABA MEPO	I N
8	Lombardia	Suspect	58	F	21	Yes	No	GERD	Fever, Cough, Malaise, Rhinitis, Dyspnoea	Yes	ICS/LABA OMA	I

ID	Region	Suspect or Confirmed COVID-19	Age	Sex	BMI	Atopy	Smoker	Comorbidities	COVID-19 Symptoms	Asthma exacerbation during COVID-19	Asthma therapy	C 1 T a
9	Lombardia	Suspect	56	M	26	Yes	Former	AR, GERD, BX	Fever, Cough, Malaise, Rhinitis, Dyspnoea, Chest tightness, Wheezing, Arthralgia	Yes	ICS/LABA MEPO	A s i a
10	Lombardia	Confirmed	62	M	33	Yes	No	AR, CRSsNP, GERD, BX, HTN	Fever, Cough, Malaise, Anosmia, Dyspnoea, Chest tightness, Respiratory failure, Nausea	No	ICS/LABA LTRA, MEPO	A F A C T

ID	Region	Suspect or Confirmed COVID-19	Age	Sex	BMI	Atopy	Smoker	Comorbidities	COVID-19 Symptoms	Asthma exacerbation during COVID-19	Asthma therapy	C 1 T a
11	Lombardia	Confirmed	66	F	28	Yes	Yes	AR, CRSsNP, CVD, Glaucoma, Cataract, NIDDM	Fever, Cough, Malaise, Conjunctivitis, Dyspnoea, Chest tightness, Chest pain, Wheezing, Nausea, Headache	Yes	ICS/LABA LTRA, MEPO	A
12	Lombardia	Suspect	51	F	25	Yes	No	None	Fever, Malaise, Anosmia, Ageusia, Sore throat, Dyspnoea, Chest tightness, Headache	No	ICS/LABA	A

ID	Region	Suspect or Confirmed COVID-19	Age	Sex	BMI	Atopy	Smoker	Comorbidities	COVID-19 Symptoms	Asthma exacerbation during COVID-19	Asthma therapy	C 1 T a
13	Lombardia	Suspect	37	F	19	No	No	CRSwNP, AD	Fever, Cough, Malaise, Rhinitis, Anosmia, Ageusia, Sore throat, Dyspnoea, Wheezing, Headache	Yes	ICS/LABA LTRA, MEPO	A
14	Piemonte	Suspect	66	F	23	Yes	No	AR, CRSwNP, GERD	Fever, Cough, Malaise, Rhinitis, Anosmia, Sore throat, Dyspnoea, Wheezing, Diarrhea, Headache	Yes	ICS/LABA LTRA, OMA	A I

ID	Region	Suspect or Confirmed COVID-19	Age	Sex	BMI	Atopy	Smoker	Comorbidities	COVID-19 Symptoms	Asthma exacerbation during COVID-19	Asthma therapy	C 1 T a
15	Piemonte	Suspect	57	F	34	Yes	No	AR, GERD	Fever, Cough, Malaise, Dyspnoea, Chest tightness, Wheezing	Yes	ICS/LABA LTRA	A F
16	Piemonte	Suspect	66	F	26	No	No	CRSwNP, MDD, Osteoporosis	Fever, Cough, Malaise, Rhinitis, Dyspnoea, Headache	No	ICS/LABA LAMA, MEPO	A F
17	Piemonte	Suspect	59	F	21	Si	No	None	Fever, Cough, Malaise, Anosmia, Ageusia, Conjunctivitis, Dyspnoea, Chest tightness, Chest pain, Wheezing, Headache	Yes	ICS/LABA LAMA, BENRA	A C T S C

ID	Region	Suspect or Confirmed COVID-19	Age	Sex	BMI	Atopy	Smoker	Comorbidities	COVID-19 Symptoms	Asthma exacerbation during COVID-19	Asthma therapy	C 1 T a
18	Piemonte	Suspect	61	M	25	No	No	CRSwNP	Fever, Malaise, Ageusia, Dyspnoea, Diarrhea, Headache	No	ICS/LABA LAMA, MEPO	N
19	Piemonte	Suspect	55	F	23	Yes	No	None	Fever, Cough, Malaise, Ageusia, Diarrhea	Yes	ICS/LABA LAMA, OMA	N
20	Veneto	Confirmed	53	F	23	No	No	None	Fever, Cough, Malaise, Anosmia	No	ICS/LABA MEPO	N
21	Liguria	Suspect	50	M	28	Yes	Yes	AR, CRSwNP	Fever, Cough, Malaise, Rhinitis, Dyspnoea	No	ICS/LABA LTRA, MEPO	N
22	Liguria	Suspect	46	F	27	Yes	Yes	None	Fever, Cough, Malaise, Rhinitis, Sore throat, Dyspnoea, Diarrhea	No	ICS/LABA MEPO	N

ID	Region	Suspect or Confirmed COVID-19	Age	Sex	BMI	Atopy	Smoker	Comorbidities	COVID-19 Symptoms	Asthma exacerbation during COVID-19	Asthma therapy	C 1 T a
23	Liguria	Suspect	70	M	25	No	Ex	CRSwNP, Osteoporosis	Fever, Cough, Malaise, Dyspnoea, Chest tightness	No	ICS/LABA OMA	A
24	Liguria	Suspect	60	F	20	No	No	CRSwNP, BX	Fever, Cough, Malaise, Dyspnoea, Headache	No	ICS/LABA MEPO	A
25	Campania	Confirmed	70	F	39	Yes	Ex	AR, GERD, CVD, NIDDM	Fever, Cough, Malaise, Dyspnoea, Chest tightness, Wheezing, Respiratory failure, Headache	Yes	ICS/LABA LTRA, MEPO	A C C

ID	Region	Suspect or Confirmed COVID-19	Age	Sex	BMI	Atopy	Smoker	Comorbidities	COVID-19 Symptoms	Asthma exacerbation during COVID-19	Asthma therapy	C 1 T a
26	Marche	Confirmed	51	M	28	No	No	CRSwNP	Fever, Malaise, Rhinitis, Anosmia, Headache, Arthralgia, Myalgia	No	ICS/LABA MEPO	A I

FIGURE LEGENDS:

Figure 1 – Geographical distribution of severe asthmatics with COVID-19 (number of cases within the red circles) and subjects with positive nasopharyngeal swab positive for SARS-CoV-2 within the general population. The total number of patients with severe asthma for each single region is reported under the each region name