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EDITORIAL

Severe asthma at COVID-19 time: what is new on biologic therapies

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Severe asthma is a subset of difficult-to-treat asthma; it is characterized by uncontrolled respiratory symptoms despite both adherence to maximal optimized therapy and treatment of comorbidities and risk factors, or worsening of symptoms when maximal therapy is decreased.[1-9] The prevalence of severe asthma stands around 3.7%, calculated on the basis of step 4 or 5 ongoing treatment (according to the stepwise therapeutic approach provided by Global Initiative for Asthma [GINA], recommendations), symptom control and adherence evaluations. About 3-10% of patients with asthma are estimated to present severe asthma.[10]

Clinicians defined several phenotypes based on clinical presentation, onset age, disease severity, presence of allergic sensitization and eosinophilia. The diagnosis of severe asthma is based on the review of some clinical comorbidities (such as gastroesophageal reflux, chronic obstructive pulmonary disease, anxiety and depression, chronic rhinosinusitis, obstructive sleep apnea syndrome, bronchiectasis, cardiac failure, obesity, inducible laryngeal obstruction, and kyphosis) and risk factors (such as: tobacco smoking; environmental exposure to air pollutants, allergens, noxious chemicals, and molds; beta-blockers or non-steroid anti-inflammatory drugs therapies) that could hide a difficult-to-treat-asthma, in order to assess clinical phenotypes.[10] This approach is driven by precision medicine, a new medical model which tailors the management on individual genetic, genomic, environmental, psychosocial characteristics, but also personal preferences.[11]

Many studies identified and validated different phenotypes of severe asthma based not only on onset age and eventual comorbidities, but also on underlying immunological mechanisms, identifying the so called "endophenotypes" that are more closely related to the biological processes of the disease.[12] Notably, both type 2 and non-type 2 inflammation play important role in underlying immune responses of severe asthma pathophysiology. In particular, type 2 inflammation is characterized by the presence of eosinophilia in airways, associated with increased T helper type 2 (Th2) cytokines release from Th2 cells.[13] On the contrary, non-type 2 neutrophilic underlying mechanisms are less characterized, involving a dysregulated release of pro-resolving lipid mediators and a reduced number of natural killer cells.[14]

The activation of Th2 and group 2 innate lym-

phoid cells, may be triggered by both allergens, leading to interleukin (IL)-4, IL-5 and IL-13 release, and other external stimuli (virus, bacteria, irritants), through the production of IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) by epithelial cells; both the pathways induce type 2 inflammation, characterized by eosinophilia or increased fraction of exhaled NO (FeNO). In severe asthma, type 2 inflammation may present a relatively refractory response to high dose of inhaled corticosteroids (ICS), but responding to oral corticosteroids (OCS), nevertheless exposing the patient to serious adverse effects.[10]

Recent progresses in severe asthma treatment focused on target therapy, with the introduction of biological therapies as add-on treatment to step 5 of GINA recommendations. These biological drugs target specific cytokines involved in the pathophysiology of severe asthma, opening the way to precision medicine.[11]

Different biological agents have been recently approved for the treatment of type 2 severe asthma. Omalizumab is a recombinant humanized monoclonal anti-IgE antibody for allergic asthma; it binds to circulating IgE, preventing it from binding with both high- and low-affinity receptors on effector cells (mast cells and basophils), and leading to a reduction in the release of allergic mediators. Nowadays, there are several scientific evidences about omalizumab clinical effects, including a statistical reduction of asthma exacerbations, reduction of OCS dosage, and significant improvement of the quality of life (QoL).[10] Mepolizumab and reslizumab are both humanized recombinant monoclonal anti-IL-5 antibodies that bind to circulating IL-5, whereas benralizumab is a recombinant monoclonal anti-IL-5 receptor (R) alpha subunit antibody, leading to apoptosis of eosinophils; anti-IL-5 and anti-IL-5R reduce about 50% of severe exacerbations, improve QoL, lung function and symptoms control. Even OCS dose is reduced by 50% in patients in treatment with benralizumab and mepolizumab, when compared with placebo.[10] Finally, dupilumab is a recombinant human monoclonal anti-IL-4R alpha antibody, blocking IL-4 and IL-13 signaling;[15] in severe asthma patients with at least one exacerbation in the previous year, it demonstrated to lead to the halving of severe exacerbations frequency, with improvement of the QoL, symptoms control and lung function and a 50% reduction of the OCS doses *versus* placebo.[10]

Very recently, Akenroye *et al.* suggested a role of these biologic agents in viral exacerbated disease. It is likely that these biologics would reduce the risk of severe asthma exacerbations COVID-19 mediated, at least by reducing baseline airway inflammation, and possibly through specific antiviral properties. Omalizumab, cross-linking IgE, would lead to lower type 1 interferon (INF) production; mepolizumab, reslizumab and benralizumab, act by increasing the ratio of IFN-γ-to-IL-5 mRNA, which is associated with lower viral shedding and faster disease clearance. Finally, IL-4 is crucial for antibody switching to IgE, and IL-13 is a Th2 cytokine involved in airway hyper responsiveness and remodeling; both of them are involved in susceptibility and in clearance of viral infections affecting lower airways.[16]

Severe Acute Respiratory Syndrome Coronavirus -2 (SARS-CoV-2) was recently identified first in Wuhan (China), and defined as responsible of clinical manifestations named coronavirus disease 2019 (COVID-19).[17-20] Current guidance from the World Health Organization (WHO) highlights asthmatics as a high-risk group for severe illness from SARS-CoV-2. So far this suspect has not been confirmed by the most recently published studies: in fact, while Asiatic reports identified a low prevalence of asthma in patients affected by SARS-CoV-2,[21] in the USA the estimated prevalence was near to 20% in patients with laboratory-confirmed diagnosis of COVID-19.[22] In Italy, preliminary data seem to be in line with the Asian studies results: the frequency of asthmatic patients in COVID departments is estimated to be around 2-3% *versus* 6% in the general population (unpublished data). Allergic asthmatic subjects seem to be less likely infected by the SARS-CoV-2 and this could be due to different factors. The first hypothesis might be related to the anti-inflammatory effect exerted by the inhaled corticosteroids and their negative effect on the cytokine storm elicited by the virus. Furthermore, compliance to antiasthmatic treatment could be increased, due to fear that the viral infection could impair the clinical course.

At the time of writing this paper no studies specifically investigating the prognosis of severe asthmatic patients neither patients treated with biologic agents were published. Only very recently, an article about the post-mortem lung findings from a 37-year-old man with asthma was published: the patient met the clinical criteria for severe acute respiratory distress syndrome and died of COVID-19 infection. The lungs presented mucus plugging and other histologic changes due to asthma remodeling, as well as diffuse alveolar damage and fibrinous pneumonia. The presence of diffuse alveolar damage was similar to descriptions of autopsy lung findings from patients with severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus.[23]

A GINA working group has recently published a document with the answers to frequently asked questions on asthma management. Regarding biological treatments, experts suggest that they should be maintained with the aim of limiting the need for OCS.[24] Even the British Thoracic Society (BTS) statement suggests that biologics should not be stopped since there are no evidences of immunity suppression.[25] The published National Health Institute for Health and Care Excellence (NICE) rapid guidelines underline the indication to continue the ongoing biologic treatment; moreover, they confirm the possibility of starting a monoclonal antibody during COVID-19 outbreak but only after assessing risks and benefits ratio.[26]

About their administration, BTS recommends that biologics would be better administered via homecare or similar schemes; patients should be advised to continue to attend their biologic treatment scheduled administrations until they are transitioned to home care or they receive the treatment intravenously.[25] NICE rapid guidelines suggest to train the patient to a self-administration or to a supervised administration in a community clinic or at home; moreover, a remote monitoring would be advisable.[26] Finally, a recently published consensus-based expert panel of allergy/immunology specialists from USA and Canada provides some practical indications to clinicians for severe asthma management. In particular, they confirm the continuation of the ongoing treatment, preferably at home with the initiation of a self-administration after a maximum of 2 in-hospital visits. In Europe, omalizumab is now approved for home-administration after the first administration in clinic; for the other biologics, the switch to prefilled syringes encourages the at home self-administration, but only after an adequate training to recognize early signs and symptoms of serious adverse reactions.[27]

In conclusion, further studies are needed to define interactions between SARS-CoV-2 and asthma; up to now, the risk of severe COVID-19 may not be dramatically increased in asthmatic patients but the incidence may be variable worldwide due to the different methodology of published studies, since the latter are still inconclusive ad inhomogeneous. The recommendable target however is to maintain asthma under control and limit the occurrence of asthma symptoms and severe exacerbations with the minimum effective dosage of steroids and the ongoing biological treatments.

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