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## COMMENT

## Biologics and anti-Sars Cov2 vaccination in severe asthma riding the big wave: Unity is strength!

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In the spring of 2020, at the beginning of Covid-19 pandemic, there was a consistent medical concern raised about patients suffering from severe chronic respiratory diseases. For asthma patients, the GINA guidelines, as well as all international scientific societies, promptly provided statements strongly recommending inhalation therapy maintenance, as well as monoclonal antibodies treatment.<sup>1-3</sup> Indeed, at that time optimal asthma control and prevention of exacerbations represented a priority to reduce the risk of infection associated with admission to ER or hospitalization. In this regards we developed a telemedicine-based approach to monitor patients at home remotely, thus reducing access to hospital and consequently the risk of infection over the prolonged lockdown.<sup>4,5</sup> At the same time, we encouraged severe asthmatic patients to self-administer biologics after an appropriate face-to-face consultation or even by remote training.<sup>4</sup> Alternatively, home care projects were launched for the delivery and administration of biological drugs by healthcare personnel.<sup>6</sup>

In the pre-vaccination era, severe asthma patients treated with biologics targeting type 2 inflammation were not generally considered at increased risk for COVID-19, when compared with age- and geography-matched non-asthmatic population.<sup>7,8</sup> In the Severe Asthma Network in Italy (SANI), 26 cases of infections out of 1504 patients (1.73%)

were reported and related mortality was 7.7%, lower than that observed in the general Italian population (14.5%).<sup>9</sup> Accordingly, the Dutch Severe Asthma Registry RAPSODI recorded an incidence of Sars-Cov-2 infection equal to 1.4% among severe asthma patients on biologics.<sup>10</sup> However, in this population the incidence of COVID-19 related hospitalization and intubation were higher, and death was 5 times higher than that observed in a comparable sample of Dutch population for age and sex.

At that time, from our experience among the 145 severe asthma patients (79/66 F/M; mean age 59±3 ys) treated with monoclonal antibodies, 12 (8%) contracted Sars-Cov-2 infection and one was admitted to ICU for respiratory failure and severe pneumonia. The remaining patients received home therapy with oral cortisone and antibiotic (azithromycin), with an average recovery time of 18±3 days.

The anti-Sars-Cov-2 vaccine became available at the beginning of 2021. Subsequently, an International Consensus produced by multidisciplinary group of international experts recommended vaccination for asthmatic subjects. However, an allergy evaluation was mandatory for patients with a history of severe allergic reaction to vaccine/excipient.<sup>11</sup>

At our clinic, in April 2021 we timely offered to administer the anti-Sars-Cov-2 vaccination to severe asthmatics. No serious adverse events were recorded. Less than 20% of patients reported side effects, most of which classified as very common side effects.<sup>12</sup> In terms of patient reported outcomes, a significant improvement of both ACT and AQLQ was observed between the first and the second dose administration, ruling out the risk of asthma exacerbations related to the COVID-19 vaccine. During 2021 we also administered

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the third dose of Sars- Cov-2 vaccine to severe asthma patients, without observing any side effects.

In the spring 2022, on the Omicron pandemic wave, 177 severe asthma patients (99/78 F/M; mean age 56±4 ys) were on biologic treatment at our clinic: 33% were on Benralizumab 31%, on Mepolizumab, 26% on Omalizumab and 10% on Dupilumab. Among them 93 (52%) were infected by Sars-CoV-2 and one had re-infection. Nobody required hospitalization and in all cases the disease was treated at home. Most of the subjects (82%) presented a paucisymptomatic or asymptomatic infection, whereas in the remaining ones the administration of oral corticosteroids was prescribed. Anti-Sars-Cov-2 monoclonal antibody therapy was also used in 3 subject. The average recovery time was 11±2 days.

After two years of Covid-19 pandemic, the reported data provide us a glimmer of light and lead to some considerations.

According to the evidence from literature, allergic asthmatic subjects seem to be less likely to be infected by SarS-CoV-2. This could be for several reasons.<sup>13</sup> First, the anti-inflammatory action of inhaled corticosteroids (ICS) and their possible “turn off” effect on “cytokine storm” elicited by the virus. Second a down regulation of ACE2 and TMPRSS2 receptors, which can be related to the allergic inflammation per se or the action of ICS.<sup>14</sup>

On clinical ground, biologics targeting type-2 inflammation seem to decrease the risk of COVID-19 related asthma exacerbations by reducing airway inflammation and possibly through specific antiviral properties. In fact, Omalizumab, crosslinking IgE, leads to lower IFN production. Mepolizumab, Reslizumab and Benralizumab, increase the ratio of IFN  $\gamma$  /IL-5 mRNA, which is associated with lower viral shedding and faster disease clearance.<sup>15</sup>

Based on the negligible number of patients reporting side effects after vaccination and the lack of asthma exacerbations consequent to vaccine,<sup>12</sup> a prolonged COVID-19 vaccination campaign worldwide in patients with severe asthma is advisable.

In summary, the combination of biological treatment and anti-Sars-Cov-2 vaccination kept patients with severe asthma controlled even in the presence of the highly contagious Omicron wave causing only a disease of mild-medium severity.

These results and the above considerations undoubtedly need to be confirmed by a large number of cases and require further research. To this end, national registries of severe asthma patients and the use of international platforms become essential in order to come to more definitive conclusions.

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Conceptualization: G.G., V.A.; Data curation: G.G., M. B., C. B. F.; Formal analysis: G.G., V.A.; Funding acquisition, Writing-Original draft: G.G., V.A.; Writing-Review & Editing: G. G., V.A. All authors agree to be accountable for all aspects of the work.

## Declaration of Competing Interest

No potential conflict of interest was reported by all the authors.

## Statement

The studies involving human participants were reviewed and approved by local Ethics Committee of Hospital University of Padua, Italy. The patients/participants provided their written informed consent to participate in this study.

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## Data availability statement

The data is available for reproduction of results on request from the corresponding author.

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