The polyhedric reality of the interaction between COVID-19, asthma and inhaled corticosteroids

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The impact of ICS on the prognosis for #COVID19 in #asthma patients requires a thorough evaluation of a range of factors that interact in this process, in order to draw solid conclusions, since at the present time the debate continues https://bit.ly/3xLNBrc

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In December 2019, a pneumonia outbreak of unknown origin was identified in Wuhan, China. It was given the label coronavirus disease 2019 (COVID-19) and the virus causing it was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1, 2]. On 11 March 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic [3]. By 5 April 2022, there had been 490 853 129 confirmed cases of COVID-19, including 6 155 344 deaths, reported to the WHO [4]. As of 4 April 2022, a total of 11 183 087 530 vaccine doses had been administered but, despite this, there is still a relevant case incidence rate throughout the world [4]. In the last few months of the pandemic, factors associated with a higher incidence rate or worse prognosis of COVID-19 have been identified, such as older age, obesity, high blood pressure and diabetes mellitus [5–8].

In the case of asthma, the relationship is less clear, since some authors have reported that it may be a risk factor for the incidence rate or severity of COVID-19 [9], whereas others have not observed any prognostic value of asthma for the disease [10, 11]. Nevertheless, the results of other studies seem to support the theory that asthma is a protective factor for it [12].

The relationship between asthma severity and COVID-19 prognosis is also unclear. Most studies conducted in the initial phases of the pandemic suggested that the level of severity did not influence it [11, 13]. However, more recent studies have shown a worse prognosis for patients with moderate or severe asthma than in those with a mild form of it [14].

These divergences appear to back up the hypothesis that there are factors other than asthma itself, or the combined effect of several of them could be the reason why there are varying prognoses of COVID-19 for patients with asthma. In this process, it has been suggested that the asthma phenotype produces different responses to a SARS-CoV-2 infection. There are studies which find a better prognosis or lower risk of disease for patients with the T2 *versus* the non-T2 phenotype, in patients with early-onset *versus* late-onset asthma, and in allergic *versus* non-allergic patients [15–17].

Regarding the relationship between asthma and COVID-19, one of the factors to consider is the maintenance treatment of the former, especially with inhaled corticosteroids (ICS), which are the key drugs

for maintenance therapy [18]. The benefit of this medication for asthma is clear, but Aristotle's aphorism "A friend to all is a friend to none" could also be true, in that it might not be beneficial for patients with certain comorbidities. In fact, some studies seem to support a higher incidence of pneumonia in patients with asthma who are treated with ICS [19].

Pathophysiological mechanisms have been identified that show the impact of ICS on the prognosis of these patients. The SARS-CoV-2 infection of respiratory epithelial cells is dependent on angiotensin-converting enzyme 2 (ACE-2) and transmembrane serine protease 2 (TMPRSS2) proteins for the attachment and priming of the S protein, respectively [20]. In addition, ICS use is associated with a dose-dependent reduction in the expression of ACE-2 and TMPRSS2 [20], antiviral type I interferon production is impaired in patients treated with high doses of ICS [21] and ciclesonide *in vitro* blocks viral replication of SARS-CoV-2 [22].

The information currently available does not allow definitive conclusions to be drawn about the impact of ICS on the prognosis of asthma patients with COVID-19. In a recent article in *ERJ Open Research*, Adir *et al*. [23] analysed the association between ICS treatment and COVID-19 prognosis, evaluating SARS-CoV-2 infection based on a positive PCR, moderate–severe COVID-19 incidence, and mortality, but did not observe any meaningful relationship between ICS treatment and the assessed outcomes. The studies available, which analyse the association of this treatment with the prognosis of asthma patients with COVID-19, offer conflicting results. When it comes to ICS treatment, some authors report a worse evolution [24, 25], others a better one [26, 27], and in the remainder, coinciding with the results of Adir *et al*. [23], no relevant impact has been shown [9, 12].

The divergence in the results could be due to the interaction of other factors that may function as confounders. Indeed, patients with more severe asthma are treated with higher doses of ICS, so the negative impact on prognosis might be more because of baseline asthma severity than a drug effect. In a number of the publications available, there is no information on the baseline severity of asthma, which is likely to explain the discrepancies observed in the results to a certain extent [9, 23].

Another aspect to consider is the variability in asthma management among populations. Even in treatments that require a certain amount of personalisation, such as monoclonal antibodies, significant differences in terms of how they are prescribed have been identified among health areas in close proximity to each other that have similar health systems [28].

Likewise, another factor that could justify the differing results is the prevalence of asthma, which is not the same among areas that are relatively near each other [29].

It is also known that not all ICS are the same, owing to there being significant differences in protection against airway hyperresponsiveness and systemic activity, implying that by considering ICS as a whole, the wide range of impacts described from one study to another may be the outcome [30].

When John Churton Collins told us that "In prosperity our friends know us; in adversity we know our friends", he was advising us to consider external factors in order to evaluate our friendships. In the same way, the impact of ICS on the prognosis for COVID-19 in patients with asthma requires a thorough evaluation of a range of factors that interact in this process, in order to draw solid conclusions, since at the present time the debate continues.

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