Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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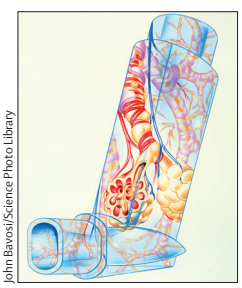
Inhaled corticosteroids in virus pandemics: a treatment for COVID-19?



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Active discussions are ongoing concerning the efficacy of systemic corticosteroids in COVID-19, with evidence to support[1] and advising against[2] their use. Illustratively, a Review[3] of past studies of corticosteroid efficacy on viral pneumonia of other causes—published early on in COVID-19 pandemic—concluded, in line with WHO guidelines[4] (which refer only to systemic corticosteroids) that no extant clinical data point to a benefit derived from corticosteroids for treatment of respiratory syncytial virus, influenza, severe acute respiratory syndrome coronavirus (SARS-CoV), or Middle East Respiratory syndrome coronavirus (MERS-CoV) respiratory infections and therefore that corticosteroids should not be used as a treatment in the COVID-19 pandemic. We agree that, at the time, no evidence existed to support that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection would benefit from systemic corticosteroids; and consequently treatment with corticosteroids was more likely to be associated with harm.[2] However, in the Review by Russell and colleagues,[3] whether the corticosteroids were inhaled or systemic was not distinguished. More recently, systemic corticosteroids, in the form of dexamethasone, have been shown to reduce mortality in patients with severe COVID-19.[5]

By contrast with clinical trial results, epidemiological data has suggested that corticosteroids might be associated with worse clinical outcomes. An epidemiological study from the OpenSAFELY group suggests that the use of inhaled corticosteroids (ICS) in patients with asthma and chronic obstructive pulmonary disease (COPD) is associated with worse clinical COVID-19 outcomes.[6] These findings might suggest that ICS use is not of benefit in patients with COVID-19, but this conclusion cannot be drawn from these data. First, as the OpenSAFELY authors observe, patients who were given ICS had more comorbidities than did those not given inhaled corticosteroids, a recognised risk factor for adverse COVID-19 outcomes; and second, most of the patients with asthma and COPD in this cohort did not develop or die from COVID-19. Therefore, we argue that the null hypothesis of no benefit from ICS in COVID-19 has yet to be fully explored.

ICS could be a therapeutic intervention for COVID-19 for several reasons. First, ICS use in patients at risk of acute respiratory distress syndrome (ARDS) has been shown to improve physiology and reduce levels of inflammatory markers.[7] A 50% reduction in ARDS was seen in at-risk patients who were using ICS before admission to hospital, even after controlling for age, sex, and chronic respiratory diseases.[8] Moreover, ICS use also appears to improve pulmonary physiology.[9]

Second, in-vitro data suggest a role for ICS in the inhibition of coronavirus replication (including SARS-CoV-2) in infected epithelial cells.[10] Investigation of gene expression of ACE2 and TMPRSS2 in the sputum of patients with asthma has shown reduced expression of these receptors in the presence of ICS[11] and attenuation of ACE2 receptors in human and murine in-vitro and in-vivo models.[12] These findings are highly relevant because SARS-CoV-2 pathology involves TMPRSS2 for spike-protein priming and direct action on the ACE2 receptor, which is highly expressed on epithelial cells in oral mucosa and type 2 alveolar cells. Since evidence exists of accelerated hyperinflammation at the onset of SARS-CoV-2 infection, this hyperinflammation is potentially modifiable by anti-inflammatory treatment. These data suggest a plausible mechanism for efficacy of ICS against COVID-19. We would propose that ICS could have a dual role: first, reducing the inflammatory ARDS-like response affecting a minority of patients with COVID-19; and second, directly inhibiting viral replication (appendix p 1).

Unlike other viral respiratory endemics (eg, influenza), we now know that comorbid chronic respiratory conditions are probably not a major risk factor in patients

See Online for appendix

with COVID-19. The absence of an increased incidence of asthma and COPD has been noted in several countries that have described the clinical characteristics of patients with COVID-19.[13] Globally, China has the highest burden of COPD, yet in a pooled analysis of 45 000 patients with COVID-19, fewer than 2% had a respiratory illness.[13] In early reports from Wuhan Province, China, only 1·1% of people with COVID-19 were noted to have COPD, while asthma was not even reported in this report.[14] These observations for ICS—while certainly not forming a complete picture—should not be ignored, especially since one would expect patients with pre-existing, serious lung conditions to be over-represented, not under-represented, among those with COVID-19 disease.

Whether use of ICS protects against COVID-19 is still unknown, but to dismiss this hypothesis as nonsense is premature. ICS as a therapeutic intervention still need to studied and clinical trials assessing their efficacy in COVID-19 are ongoing in various clinical settings, the results of which are eagerly awaited (NCT04416399 [UK]; NCT04355637 [Spain]; NCT04193878 [USA]; NCT04331470 [Iran]; NCT04377711 [USA]; NCT04330586 [South Korea]).

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COVID-19, asthma, and return to school

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Social distancing and lockdown measures have included the suspension of children and young people's education for several weeks to months. Although the precise educational and societal effects of closing schools are unknown, they are likely to be substantial and will almost certainly have exacerbated inequalities. In countries in which society is reconfiguring to a new normal, the priority must be preparing for reopening schools because of the potential lifelong impact on children and young people. However, with this return to school rapidly approaching, there should be particular considerations regarding children and young people with asthma.

There is an annual seasonal autumnal spike in asthma attacks in children and young people (the so-called September epidemic) due to colder weather, common viral infections, aeroallergen exposure, and reduced asthma medication compliance.[1] It is unclear where various countries will be with respect to ongoing community spread of COVID-19 in the autumn, but we anticipate constraints in ongoing health-care resource allocation in many parts of the world; for example, prioritisation of respiratory care in people with moderate to severe asthma, including limitation of exposure to aerosol generating