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.

Inhaled corticosteroids: not just for asthma, but for COVID-19?

Published Online
April 7, 2022
https://doi.org/10.1016/S2213-2600(22)00053-4

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A multipronged approach has been developed for the treatment of COVID-19 disease: antivirals and antibody therapy are effective during early infection when the SARS-CoV-2 load is high, whereas systemic steroids and cytokine blockade are best for the late inflammatory phase[1–3] (figure). In human challenge studies of respiratory syncytial virus infection, the pre-existing so-called immunological tone of the respiratory mucosa is crucial to the receptiveness of the mucosa to viral infection.[4] However, so far, in SARS-CoV-2 infection, there has been little focus on altering the condition of the respiratory mucosa. In this issue of *The Lancet Respiratory Medicine*, Jonathan R Baker and colleagues[5] provide an update on the outcomes of the STOIC study,[6] showing that there is a distinctive nasal inflammatory response during the initial phase of infection, which might be altered by early administration of inhaled budesonide. This is important, since corticosteroid inhalers are widely used for asthma and are cheap, safe, and readily available.

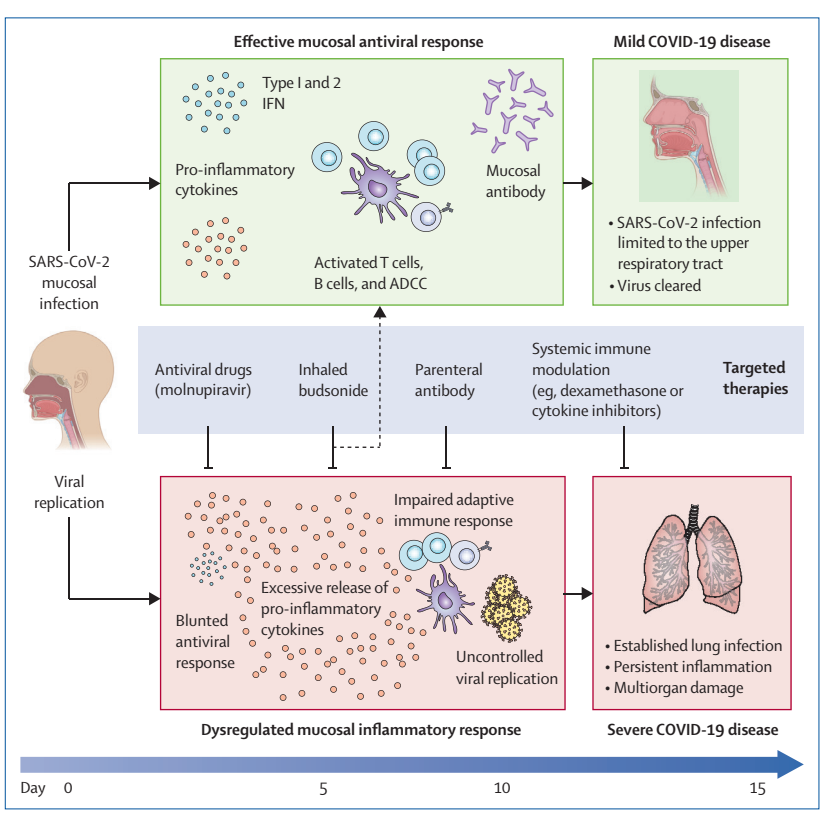

Figure: **Early mucosal events and disease outcome in COVID-19**
Different aspects of the dysregulated inflammatory response can be targeted through early intervention to prevent severe disease. Inhaled budesonide might redirect the mucosal inflammatory response towards an effective antiviral response (dashed arrow). ADCC=antibody-dependent cellular cytotoxicity. IFN=interferon.

In the influenza A H1N1 pandemic of 2009–10, asthma was a major risk factor for severe disease.[7] During the first wave of COVID-19, it was assumed that asthma would again be a predictor of poor outcomes, but the OpenSAFELY study[8] of 24 million patients with SARS-CoV-2 infection in the UK showed that asthma is only a weak risk factor and that patients with chronic obstructive pulmonary disease or asthma who use corticosteroid inhalers have worse outcomes after SARS-CoV-2 infection (perhaps because they tend to have debilitating previous lung disease). However, a multicentre UK study reported that patients aged 50 years or older with severe asthma who had used inhaled corticosteroids within 2 weeks of admission show improved survival.[9] Therefore, there is considerable uncertainty about the effect of inhaled corticosteroids in COVID-19 disease.

Baker and colleagues recruited 146 participants experiencing new symptoms of COVID-19; these patients were randomly assigned (1:1) to receive inhaled dry-powder budesonide or standard care.[6] After treatment with budesonide, there were changes in the inflammatory profile in both nasal and plasma samples, although the route of administration was to the lung. However, the changes in the concentration of inflammatory mediators such as interleukin (IL)-10 and IL-33 were small, albeit statistically significant ($p<0·05$). The authors speculate that inhaled budesonide, taken within 7 days of symptom onset, alters disease outcome by modulating inflammation in the nasal mucosa.[5]

The findings by Baker and colleagues also show a blunted antiviral response in 11 individuals with COVID-19 who clinically deteriorated. This finding suggests that some appropriate antiviral inflammation is required to prevent severe disease, which might explain why systemic dexamethasone has not been shown to benefit patients with mild COVID-19 disease, and in fact might cause harm.[2] Systemic steroids cause widespread immunosuppression, which might be helpful during the late inflammatory phase of severe COVID-19, but cause harm in the early phase of illness by dampening mucosal inflammation required to clear the virus. It is possible that inhaled steroids redirect rather than suppress mucosal inflammation, thus preventing severe disease (figure).

Although the STOIC study showed that inhaled budesonide treatment reduced the relative risk of clinical deterioration by 91%, this finding was not replicated in the PRINCIPLE trial.[6,10] In that prospective study, inhaled corticosteroids in older patients (aged ≥65 years or ≥50 years with comorbidities) shortened the time to self-reported recovery by 2·94 days, but did not reach significance in terms of preventing hospitalisation or death.[10] The cohort studied by Baker and colleagues are, by comparison, younger (mean age 45 years), but the reasons for the different conclusion are unclear. Of note, both studies included few participants with asthma (15% in the STOIC study[6] and 13% in the PRINCIPLE trial[10]), the typical users of inhaled corticosteroids.

An important question remains. How might delivery of budesonide to the lower respiratory tract affect the nasal mucosa and the outcome of COVID-19? Although Baker and colleagues[5] show that type 2 inflammatory mediators are reduced after budesonide treatment, the differences in individual mediators were not large nor were they present in both the plasma and nasal samples. Notably, Baker and colleagues[5] did not assess the lower respiratory tract where we might expect to see greatest changes. It is possible that the changes found by Baker and colleagues[5] in the nasal mucosa and plasma might represent only a small fraction of more distinct changes occurring in the lower respiratory tract, and that these changes in the lower respiratory tract affect the outcome of COVID-19. Assessment of the lower airway is not always possible in clinical studies of this type but would be useful to bring clarity to these findings.

The findings of Baker and colleagues[5] represent an important step towards improving our understanding of how local immune responses drive disease outcome in COVID-19, highlighting the need to consider treatments that target mucosal and systemic responses. Although the study provides evidence that inhaled budesonide might be beneficial in some cases of early COVID-19, further research is needed to understand exactly how this effect is mediated and which patients might benefit most.

PJMO reports grants from the EU Innovative Medicines Initiative (IMI) 2 Joint Undertaking during the submitted work; grants from UK Medical Research Council, EU-IMI, UK National Institute for Health Research, and UK Research and Innovation-Department for Business, Energy and Industrial Strategy; and personal fees from Pfizer, Nestle, Janssen, and Sequris, outside the submitted work. FL declares no competing interests.

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The pandemic and the great awakening in the management of acute hypoxaemic respiratory failure

Published **Online** March 16, 2022 https://doi.org/10.1016/S2213-2600(22)00051-0

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The ability to provide invasive mechanical ventilation (IMV) and high-quality, supportive intensive care was substantially limited during the peak of the pandemic because of the unprecedented demand for intensive care unit (ICU) resources. As a result, clinicians turned towards less invasive and innovative approaches to manage patients with acute hypoxaemic respiratory failure. Techniques such as awake prone positioning of non-intubated patients, a seemingly simple approach that was largely only tested in observational studies before