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LETTER TO THE EDITOR

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Clinical trials of inhaled beclomethasone and mometasone for COVID-19 should be conducted

To the Editor,

Several recent studies have reported that systemic corticosteroids are effective against coronavirus disease 2019 (COVID-19).[1] COVID-19 mainly affects the respiratory system, with minor damage to other organs. Injury to the alveolar epithelial cells, presumably caused by an exaggerated immune response, is the main cause of COVID-19-related fatal acute respiratory distress syndrome.[2] COVID-19 is suggested to elicit inflammatory cytokine secretion, not only from alveolar macrophages but also from alveolar epithelial type 2 cells.[3] Therefore, immunosuppression should be weighted toward the lungs, especially the alveolar epithelial cells.

Although systemic corticosteroids may suppress the systemic immune responses to SARS-CoV-2, the incidence of opportunistic infections and delayed viral elimination may outweigh the advantages. This could be the reason why Horby et al[1] reported no clinical significance of systemic corticosteroids in mild cases without respiratory support. To reduce inflammation in the lungs, such as in patients with asthma, therapeutic effects can be achieved with low doses of inhaled corticosteroids (ICS) (<0.4 mg/day), which are associated with minimal detectable systemic bioactivity.[4] Immunosuppression at high doses of ICS is weighted toward the lungs, but moderate systemic immunosuppression could also be expected because of its dual local and systemic bioactivity.[4] Delivering corticosteroids directly to the alveoli by inhalation could effectively reduce inflammation in the lungs with fewer systemic side effects.

Nebulized budesonide improved oxygenation and significantly reduced inflammatory markers (tumor necrosis factor-α, interleukin 1β [IL-1β], and IL-6) in patients with acute respiratory distress syndrome.[5] There are several reviews of inhaled corticosteroids for COVID-19, but there is no clear evidence on whether the premorbid use of ICS has adverse or beneficial outcomes in COVID-19 patients.[6,7]

ICS can reach different sites in the lungs, depending on their particle sizes.[8] As the alveoli are the main sites for lung inflammation in COVID-19, steroids with smaller particle sizes that can efficiently reach the alveoli could be more promising. Among ICS, beclomethasone and ciclesonide, administered through pressurized metered-dose inhalers (pMDIs) have the smallest particle sizes (<2 µm) and reach the alveoli more easily.[8] The particles in the nebulizer are also small enough to reach the alveoli, but there is a concern that the exhaled particles may contain the virus, and could, therefore, infect medical personnel.

Apart from their anti-inflammatory effects, some ICS have been found to have antiviral effects. ICS, namely ciclesonide and mometasone suppressed the replication of SARS-CoV-2 and MERS-CoV in vitro, whereas dexamethasone, cortisone, prednisolone, and fluticasone did not exert antiviral effects.[9] A recent case report showed favorable outcomes in three COVID-19 patients treated with inhaled ciclesonide.[10] Compared to ICS administered through pMDIs, it is more difficult for corticosteroids administered through dry powder inhalers (DPI) to reach the alveoli, owing to their larger particle sizes. Mometasone may be worth considering, as it has antiviral properties and smaller particle size than budesonide.[6] Moreover, a mutant strain of ciclesonide-resistant MERS-CoV did not show resistance to mometasone.[7]

As of 5 July 2020, several clinical trials worldwide utilizing ICS for COVID-19 have been registered on ClinicalTrials.gov: four trials (one recruiting, three not yet) for ciclesonide and four trials (three recruiting, one not yet) for budesonide (one including formoterol).

The antiviral effects of inhaled corticosteroids as well as their smaller particle sizes, which is related to their ability to efficiently reach the alveoli, should be noted. Previous studies have not reported the anti-SARS-COV-2 effects of beclomethasone in vitro. We propose that clinical trials that test the clinical effects of beclomethasone, which has a similar particle size to ciclesonide, as well as studies that confirm its antiviral effects, should be conducted. This is because, if either or both drugs are found to be effective, it may be possible to speculate whether these effects are due to their antiviral or their anti-inflammatory effects. If beclomethasone is found to be clinically effective but not antiviral, the effect of particle size can be estimated by comparing it to budesonide, which also has no antiviral effect. For the same reason and in anticipation of the unique antiviral effect that is different from ciclesonide, we propose that clinical trials of mometasone, which have a smaller but similar particle size to budesonide, should also be conducted. Mometasone is also available in the form of a nasal spray, and clinical trials could be conducted to determine the preventive effects of intranasal mometasone in treating early-stage COVID-19.

The DPI requires a certain respiratory rate for inhalation, as the powder is inhaled by the patient. In contrast, the pMDIs use pressurized gas to atomize the drug and eject it into the air, making it suitable for use by compromised patients with a low respiratory rate. In addition, spacers help in enhancing the delivery of inhaled medication for respiratory patients.

In conclusion, inhaled corticosteroids could be promising therapeutic candidates for COVID-19, and should be prioritized for clinical trials in both mildly symptomatic outpatients and severely ill inpatients.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Both DM and GK contributed to the conception and design of the work, the acquisition, analysis, and interpretation of data as well as the drafting and revision of the manuscript. DM and GK approved the current version of the manuscript and agreed to be accountable for all aspects of the work.

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