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 and angiotensin-converting enzyme-2 in COPD

To the Editor:

Finney et al[1] elegantly showed in mice that inhaled corticosteroid (ICS) down-regulated the severe acute respiratory syndrome coronavirus-2 entry receptor angiotensin-converting enzyme 2 (ACE2) via suppression of type 1 interferon. It was also found that in 36 patients with chronic obstructive pulmonary disease (COPD), the use of ICS was associated with reduced expression of ACE2 compared with non-ICS users, whereas ACE2 expression is increased in cultured bronchial epithelial cells from patients with COPD and in turn suppressed by fluticasone propionate. They go on to postulate that this effect might therefore reduce susceptibility of patients with COPD to coronavirus disease 2019 (COVID-19).

The OpenSAFELY cohort showed that among 105,249 patients with COPD taking ICS combination therapy compared with 43,308 patients taking long-acting beta-agonist and long-acting muscarinic antagonist (LABA/LAMA) combination, the adjusted hazard ratio for mortality from COVID-19 was 1.39 (95% CI, 1.10-1.76).[2] The risk of death was more pronounced in those patients prescribed triple therapy with ICS/LABA/LAMA than those patients prescribed dual therapy with ICS/LABA, with hazard ratios (vs LABA/LAMA) of 1.43 (95% CI, 1.12-1.83) and 1.29 (95% CI, 0.96-1.74), respectively. Hence, reduced expression of ACE2 associated with ICS use does not appear to be associated with a commensurate reduction in COVID-19–related deaths per se. However, the risk of mortality not related to COVID-19 was also observed to be higher in patients with COPD taking ICS-containing therapy versus LABA/LAMA, with an adjusted hazard ratio of 1.23 (95% CI, 1.08-1.40). This in turn perhaps suggests that other factors such as local immunosuppression due to ICS in the presence of impaired mucociliary clearance and altered microbiome[3] may have contributed to increased deaths in patients with COPD, or possibly that patients taking ICS had more severe disease.

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Reply

To the Editor:

We thank Lipworth et al[1] for their correspondence regarding our article recently published in the *Journal of Allergy and Clinical Immunology*.[2] We agree that it is currently unclear whether inhaled corticosteroid (ICS) use in chronic obstructive pulmonary disease (COPD) imparts an overall protective or detrimental effect on susceptibility to coronavirus disease 2019 (COVID-19). Theoretically, any potentially beneficial effects of ICS related to COVID-19, such as angiotensin-converting enzyme 2 attenuation and/or suppression of inflammation, could be offset by detrimental effects. For example, we have previously reported that ICSs suppress type I interferon, leading to secondary bacterial infections and mucus hypersecretion during respiratory viral infections.[3] It should also be noted that, in animal models, angiotensin-converting enzyme 2 has a protective functional role against acute lung injury[4] and thus the suppressive effect of ICSs may have adverse consequences in the context of active infection.

Lipworth et al cite the increased risk of death in patients with COPD taking any ICS combination therapy versus those on dual bronchodilators without ICS identified in the OpenSAFELY cohort.[5] It is worth noting that the increased risk for patients with COPD prescribed ICS/long-acting beta-agonist did not reach significance (adjusted hazard ratio, 1.29; 95% CI, 0.96-1.74), suggesting that the increased risk ascribed to triple ICS/long-acting beta-agonist/long-acting muscarinic antagonist therapy (1.43; 95% CI, 1.12-1.83) may not be solely related to the ICS component but possibly due to increased disease severity. This is supported by a negative control analysis showing an increase in deaths not related to COVID-19 in patients with COPD prescribed ICS (1.23; 95% CI, 1.08-1.40).[5] Unmeasured disease severity is thus likely to be an important confounder in OpenSAFELY, a retrospective observational study with the power to reveal associations and generate hypotheses, but which cannot define causal relationships. For this, randomized controlled trials are needed and several are under way (NCT04416399 [UK]; NCT04355637 [Spain]; NCT04377711 [USA]; NCT04330586 [South Korea]). The results from these studies will be informative for disentangling whether the beneficial effects of these commonly prescribed inhalers outweigh any potential adverse effects.

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