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 budesonide for early treatment of COVID-19

We read with interest the Article by Sanjay Ramakrishnan and colleagues[1] in *The Lancet Respiratory Medicine* on the efficacy of inhaled budesonide in the treatment of early COVID-19 illness in people in the community. The use of inhaled corticosteroids might be associated with poor outcomes among people being treated for COVID-19 in hospital.[2] However, generally, users of inhaled corticosteroid have more comorbidities than non-users, which might have influenced the study's findings. The study by Ramakrishnan and colleagues is important because the selection bias introduced by a non-hospital setting is less than that introduced by a hospital setting, and a non-hospital setting allows researchers to assess independent drug action. Nevertheless, we would like to address several issues regarding primary outcomes, viral load, and asthma prevalence.

First, the primary endpoint of COVID-19-related urgent care visits is vague. In the per-protocol population, the primary outcome occurred in 11 participants, and only one participant was admitted to a respiratory high-dependency unit. The finding that there were no differences in baseline demographics and clinical characteristics between the participants with and without a primary outcome might cause one to question the severity of the primary-outcome events. Indeed, this was an open-label study. Inclusion in the usual care group might have had a substantial effect on a participant's behaviour and willingness to seek urgent care or visit an emergency department.

Second, no difference in the decrease in viral load was observed between the budesonide and usual care groups. This finding does not support the additive inhibitory effect of budesonide against SARS-CoV-2.[3] Additionally, considering the early phase of SARS-CoV-2 infection, the viral titres in this study were relatively low.[4] The best explanation for these results is that the participants had low disease severity and viral replication, and so were theoretically less likely to benefit from budesonide treatment than anticipated.

Third, the asthma prevalence was high (14–16%) in both groups. These proportions are surprising because participants were excluded from the study if they had recently used (within 7 days) inhaled or systemic corticosteroids. Antiviral and allergic responses reportedly are reciprocally regulated.[5] Thus, patients with atopic conditions might be less susceptible to COVID-19 or have an increased response to inhaled corticosteroids, which, if not adequately controlled, would introduce a significant bias.

Nevertheless, Ramakrishnan and colleagues should be credited for conducting the first randomised trial in which the therapeutic potential of inhaled corticosteroids in early COVID-19 illness was assessed. Further studies exploring the effects of inhaled corticosteroids in patients with severe COVID-19 using mechanistic evidence are needed.

We declare no competing interests.

*Jae Chol Choi, *Won-Young Kim*
wykim81@cau.ac.kr

Department of Internal Medicine, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Dongjak-gu, Seoul 06973, South Korea

1 Ramakrishnan S, Nicolau DV Jr, Langford B, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. *Lancet Respir Med* 2021; published online April 9. https://doi.org/10.1016/S2213-2600(21)00160-0.

2 Choi JC, Jung SY, Yoon UA, et al. Inhaled corticosteroids and COVID-19 risk and mortality: a nationwide cohort study. *J Clin Med* 2020; **9:** 3406.

3 Yamaya M, Nishimura H, Deng X, et al. Inhibitory effects of glycopyrronium, formoterol, and budesonide on coronavirus HCoV-229E replication and cytokine production by primary cultures of human nasal and tracheal epithelial cells. *Respir Investig* 2020; **58:** 155–68.

4 He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med* 2020; **26:** 672–75.

5 Gonzales-van Horn SR, Farrar JD. Interferon at the crossroads of allergy and viral infections. *J Leukoc Biol* 2015; **98:** 185–94.

Published **Online**
May 12, 2021
https://doi.org/10.1016/S2213-2600(21)00212-5