



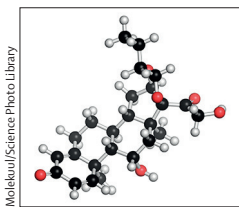
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Early treatment with inhaled budesonide to prevent clinical deterioration in patients with COVID-19



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In most individuals, infection with SARS-CoV-2 is either asymptomatic or produces mild illness (COVID-19) that resolves spontaneously; yet, a small proportion of patients with COVID-19 develop severe disease, require hospitalisation (often in a critical-care setting), and die.¹ A dysregulated type I interferon response to SARS-CoV-2 with overproduction of proinflammatory cytokines seems to be a key pathogenic mechanism underlying progression to severe COVID-19 and death.¹ Thus, controlling this excessive inflammatory response might potentially prevent disease progression.

Inhaled corticosteroids have been used for more than 30 years in the treatment of several inflammatory respiratory conditions, such as asthma and chronic obstructive pulmonary disease (COPD), to control dysregulated airway inflammation, with a good efficacy and safety track record.^{2,3} In the context of the current pandemic, it was noted that patients with asthma and COPD appear to be under-represented among COVID-19-infected individuals seeking emergency care, and it was hypothesised that the chronic use of inhaled corticosteroids might have controlled the excessive inflammatory response induced by SARS-CoV-2 in these individuals.⁴ Yet, a later observational study did not support this possibility.⁵

In *The Lancet Respiratory Medicine*, Sanjay Ramakrishnan and colleagues⁶ explored this hypothesis in a prospective, randomised, open-label, phase 2 trial that compared treatment with 1600 µg (two puffs of 400 µg to be taken twice per

day) of inhaled budesonide, a widely used inhaled corticosteroid, versus usual care in 146 adults within 7 days of the onset of mild COVID-19 symptoms.⁶ The primary outcome of the trial was urgent care visit, emergency department assessment, or hospitalisation.⁶ Results showed that, in the per-protocol analysis, this primary outcome occurred in ten (14%) participants in the usual care group and one (1%) participant in the budesonide group (difference in proportions 0.131, 95% CI 0.043–0.218; $p=0.004$), indicating a relative risk reduction of 91% for budesonide; importantly, the number needed to treat with budesonide to reduce COVID-19 deterioration was eight patients.⁶ Secondary outcome results showed that clinical recovery was also significantly reduced in the budesonide group.⁶ Based on these observations, the authors concluded that early administration of inhaled budesonide in patients infected with SARS-CoV-2 reduced the likelihood of needing urgent medical care and enhanced clinical recovery.⁶

Ramakrishnan and colleagues’ study is important because it is the first to show that an easily accessible therapeutic intervention is effective to prevent COVID-19 clinical deterioration. However, the study has a potentially important limitation that needs careful consideration: it was terminated early due to “the impact of the national pandemic control measures and national prioritisation rules for clinical research trials in the UK”⁶ and, as a result, the number of randomised patients ($n=146$) was much lower than that estimated originally ($n=398$).⁶ Although

logistic conditions limiting recruitment into the study are understandable, under these circumstances it is not possible to exclude a potential type I error, so p values might not be valid.⁷ To address this potential limitation, an independent statistical assessment used bootstrap simulations of a virtual trial with the same study design, primary endpoint and duration, and concluded that the estimated power was more than 99% to reject the null hypothesis.⁶ However, this *in silico* exercise is only hypothesis generating,⁸ supporting, but not confirming, the working hypothesis.

In any case, and acknowledging this important limitation, the study's results are encouraging. Inhaled budesonide is a low cost, safe (time censored), effective (number needed to treat of eight), simple, and widely available therapeutic option, which can be of great help around the world, particularly in low-income and middle-income countries,⁹ and can effectively complement the global vaccination strategy. Several potential mechanisms might underlie these clinical observations. First, inhaled corticosteroids (including budesonide) have been used successfully for decades to downregulate the excessive inflammation that characterises several chronic airway diseases such as asthma and COPD,^{2,3} so it is plausible that inhaled budesonide might have contributed to control the inflammatory response in early COVID-19,⁴ as systemic dexamethasone seems to do in patients with severe COVID-19.¹⁰ Second, in patients with asthma and COPD, inhaled corticosteroids reduce the pulmonary expression of the SARS-CoV-2 viral entry receptor, angiotensin-converting enzyme 2.^{11,12} Finally, some inhaled corticosteroids (including budesonide) reduce or block SARS-CoV-2 replication *in vitro*.^{13,14}

Future research will have to explore if the observations in the study by Ramakrishnan and colleagues⁶ are exclusive to budesonide, or represent a class effect of inhaled corticosteroids. In this context, it is worth mentioning that there are other ongoing randomised clinical trials using other inhaled corticosteroids or exploring the effects of budesonide in more severe (hospitalised) COVID-19 patients. Likewise, the observation that clinical recovery was accelerated in patients treated with budesonide⁶ might suggest that it can prevent or reduce COVID-19 sequelae,¹⁵ but this also requires specific research.

A final lesson from this study is the importance of doing well designed randomised clinical trials during a pandemic situation. Under these tragic circumstances, compassionate care is understandable but unable to produce the scientific evidence needed to guide best patient care.

AA and RF are the leading investigators of a multicentre, randomised clinical trial supported by AstraZeneca, which is currently exploring the effects of inhaled budesonide in hospitalised patients with COVID-19 pneumonia (NCT04355637).

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