

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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

## Inhaled budesonide for early treatment of COVID-19

## **Authors' reply**

We share the enthusiasm of Rafael San-Juan and colleagues, Markus Zeitlinger and Marco Idzko, and Jae Chol Choi and Won-Young Kim in the search for an effective treatment in early COVID-19, and in the findings of the STOIC study.<sup>1</sup>

Zeitlinger and Idzko and Choi and Kim commented on the weakness of an open-label design and that the absence of an effect of the intervention on oxygen saturations negate the value of the trial findings. However, in a recently published openlabel phase 3 trial investigating the use of azithromycin in treating early COVID-19,2 open-label azithromycin compared with usual care did not lead to quicker symptom resolution or reduction in medical assessments, nor was a placebo effect found when compared with the other study groups despite widespread media support for azithromycin in COVID-19. Furthermore, the preprint report of the interim analysis of budesonide in early COVID-19 in the PRINCIPLE trial has replicated our phase 2 findings regarding guicker symptom resolution and potentially reduced urgent care visits and deaths.3 Choi and Kim discussed the interesting issue of interferons in atopy and their effect on susceptibility to SARS-CoV-2 infection. Although interesting, at present further mechanistic insight is awaited.

However, we find that our esteemed colleagues restricted their concern to the patients with most severe COVID-19, primarily the participant who had respiratory failure associated with SARS-CoV-2 infection. Although we agree that respiratory failure is important and indeed would be considered in the STOIC primary and secondary endpoints, we respectfully

disagree on what constitutes an important clinical deterioration event in the COVID-19 syndrome. At the time of the STOIC trial, as we reported in our Article,1 all people in the UK with COVID-19 symptoms seeking additional medical care were advised to contact a government telephone line for all urgent COVID-19 queries. This government-led change was instituted after the trial was registered. This telephone line was operated and managed by medical practitioners, and triaged individuals who needed additional assessment either directing them to a COVID-19 urgent care hub or an emergency department. The STOIC participants who attended the urgent COVID-19 hubs clearly had sufficient symptoms to pass the telephone triage, be seen in an urgent clinical setting, and necessitate further investigations in a hospital. Furthermore, as noted in our Article, approximately 20% of participants had oxygen saturations at or below 94% at any one point during the study, which did not all result in a primary endpoint but would have been of concern to many respiratory physicians.

Contrary to our respected colleagues, we believe the urgent events in STOIC, whether seen by a senior clinician in primary care or in the emergency department, are important for the patient and the health-care system, and the time and cost associated with presumed so-called mild COVID-19 should not be discounted.4 Although events like diabetic ketoacidosis, acute renal failure, and cough-related rib fractures are not primary ventilatory failure, we disagree that they do not constitute COVID-19 events. As our knowledge increases, COVID-19 is widely accepted to cause systemic illness, ranging from anosmia to fever to gastrointestinal symptoms. Renal failure of varying severities has been reported in COVID-19.5 Dismissing a life-threatening event such as diabetic ketoacidosis or acute kidney injury occurring after anorexia and gastrointestinal syndrome, which are typical after early or mild COVID-19, would be imprudent.

Finally, we hope that our colleagues agree, that early interventions that lead to improvement of symptoms are important to patients. Patients with COVID-19 who deteriorate are seeking medical care encompassing a much wider syndrome<sup>3</sup> and as clinicians we cannot assume that an illness that occurs in the community is thus all mild

SR reports grants and non-financial support from the National Institute for Health Research Biomedical Research Centre, during the conduct of the study; and non-financial support from AstraZeneca, personal fees from Australian Government Research Training Program, outside of the submitted work. MB reports grants from AstraZeneca, personal fees from AstraZeneca, Chiesi, GlaxoSmithKline, and scientific adviser to Albus Health and ProAxsis outside of the submitted work.

## Sanjay Ramakrishnan, \*Mona Bafadhel mona.bafadhel@ndm.ox.ac.uk

Nuffield Department of Clinical Medicine, University of Oxford, Oxford OX3 7FZ, UK (SR, MB); National Institute for Health Research (NIHR), Oxford Biomedical Research Centre, Oxford, UK (SR, MB); School of Medical and Health Sciences, Edith Cowan University, Perth, WA, Australia (SR)

- 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 Butler CC, Dorward J, Yu L-M, et al. Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, openlabel, adaptive platform trial. Lancet 2021; 397: 1063-74.
- Yu L-M, Bafadhel M, Dorward J, et al. Inhaled budesonide for COVID-19 in people at higher risk of adverse outcomes in the community: interim analyses from the PRINCIPLE trial. medRxiv 2021; published online April 12. https://doi.org/10.1101/2021.04.10.21254672 (preprint).
- Jin H, Wang H, Li X, et al. Economic burden of COVID-19, China, January-March, 2020: a costof-illness study. Bull World Health Organ 2021; 99: 112-24.
- 5 Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. Lancet Respir Med 2020; 8: 738–42.





If you would like to respond to an article published in The Lancet Respiratory Medicine, please submit your correspondence online at: http://ees.elsevier.com/ thelancetrm

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