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Inhaled budesonide for mild COVID-19. Is there more to it than just airways?

To the Editor

As healthcare systems in many countries buckle under the immense pressure of rising COVID cases, a drug which can reduce emergency visits would be a huge boon. The results of the STOIC trial, therefore, are very uplifting [1]. Inhaled budesonide, a safe and simple intervention, seems to reduce hospital visits by almost 90% among mild COVID cases. None of the published, peer-reviewed trials have yet shown tangible benefits for this endpoint. In fact, seldom do therapeutic strategies show an effect size of this magnitude [2].

Therefore, it is only prudent to examine the data closely — is the effect of budesonide limited to reduction in emergency visits, or does it alter pathobiology of disease progression. Although the study excluded patients with recent use of inhaled or systemic glucocorticoids, there was a 15% prevalence of current or past asthma in both groups. Viral infections are known triggers of asthma, as acknowledged by the authors, which may present as worsening breathlessness leading to emergency visit. It is possible that it is only reversing the airway hyperreactivity in those already at risk, and not altering COVID pathophysiology. It would be interesting to know if the difference in outcomes is being disproportionately driven by this subset.

Patients in the treatment arm showed faster improvement in systemic symptoms, and lower antipyretic requirement. However, the biological plausibility of this effect is unclear. Systemic effects of 800 μg of inhaled budesonide are minimal, and it would be unusual to expect reduction in systemic inflammation. Unfortunately, the study did not collect data on inflammatory markers to explore this aspect. Moreover, the difference in respiratory symptom scores is not significant, while the difference in systemic symptom scores is. Also, the faster clinical recovery in the budesonide group plateaued after day-14, and the perceived difference in clinical recovery remained the same until day-28. Possibly there may be a bias in self-reporting due to the non-placebo-controlled nature of the study. Above all, the decision to terminate the trial early despite such a small number of events (3 in the treatment group *vs* 11 in the control group) raises strong concerns of chance association.

The situation of a COVID physician is no better than that of Coleridge's Mariner [3] — surrounded by a sea of over 100,000 studies, 100 clinical trials, and few dozen treatment options — yet only one or two drugs actually changing clinical outcomes [4]. In this situation, a 90% reduction in emergency visits is by itself an unparalleled feat. Such magnitude of effect is not seen with any other treatment, and the work of the authors is laudable. However, understanding exactly what drives this phenomenon is of utmost importance.

Conflict of interest

None declared.

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