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.

The use of inhaled corticosteroids in early-stage COVID-19

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For more on the **PRINCIPLE trial** see https://www.principletrial.org/

For more on the **RECOVERY trial** see https://www.recoverytrial.net/

The desperation of clinicians when faced with COVID-19 and the dearth of therapeutic options for its treatment have led clinical practice to reach for last-resort approaches, supported by tenuous data or hypotheses. The need for data-based clinical practice is clear from the initial wide use of hydroxychloroquine, shown subsequently to be harmful,[1,2] and the initial avoidance of oral corticosteroids, shown subsequently to be beneficial.[3] Now practice is changing toward the usual measured approach of gathering data and using restraint, trying above all to do no harm in this viral illness.

Platforms for remarkable well designed pragmatic pandemic research, such as PRINCIPLE and the earlier RECOVERY study platform, have emerged to inform practice. The focus of the PRINCIPLE adaptive trial platform on management of COVID-19 in the primary care setting is vital—less than 10% of patients are managed in hospital.

Early in the pandemic, epidemiological data showing that patients with chronic obstructive pulmonary disease (COPD) and asthma had a lower incidence of COVID-19 infection led to speculation that inhaled corticosteroids could have some benefit. A small open-label trial suggested possible benefit in patients not admitted to hospital.[4] Although there is a plausible mechanism for why inhaled corticosteroids could be beneficial, there are two reasons to be cautious: in the RECOVERY trial, although oral steroids offered benefit in seriously ill patients, they offered no benefit and possibly harm in those with less serious illness.[3] And for those with COPD and asthma who do get infected, population studies suggest that use of inhaled corticosteroids is associated with worse outcomes.[5,6] These inconsistent results leave primary care practitioners, heavily involved in care of high-risk patients with early-stage COVID-19 in the community, with little certainty of the potential benefits and harms of inhaled corticosteroids.

A new analysis of the PRINCIPLE trial by Ly-Mee Yu and colleagues[7] reported in *The Lancet* provides data from the largest trial of the use of inhaled corticosteroids in early-stage COVID-19. The primary outcome population included 833 participants who received inhaled budesonide plus usual care and 1126 who received usual care alone. The mean age was 64·2 years (SD 7·6), 1805 (92%) of 1959 participants were White, 1015 (52%) were women, and 1581 (81%) had comorbidities. The initial trial primary outcome was hospital admission or death, but this was changed before analysis because of lower than expected UK hospital admission rates (although the rate of hospital admissions or death in the trial was higher than the 5% estimated for the sample size calculation). Time to first self-reported recovery was added as a coprimary outcome. The results showed that using inhaled corticosteroids early in COVID-19 in patients aged 65 years and older and those aged 50 years and older with comorbidities shortened the time to first self-reported recovery by an estimated median of 2·94 days (95% Bayesian credible interval [BCI] 1·19–5·11), with an estimated time of 11·8 days (95% BCI 10·0–14·1) in the budesonide group versus 14·7 days (12·3–18·0) in the usual care group. The hospital admission or death outcome did not achieve the prespecified superiority threshold in the primary analysis population (72 [9%] of 787 in the budesonide group *vs* 116 (11%) of 1069 in the usual care group; model estimate 6·8% [95% BCI 4·1–10·2] *vs* 8·8% [5·5–12·7], odds ratio 0·75 [95% BCI 0·55–1·03]). The possibility of bias in the self-reported recovery outcome cannot be ruled out—placebos were not used and given that the primary and other secondary outcomes use self-report questions that are largely not based on instruments previously tested for reliability or validity, the well described placebo effect of inhalers could have inflated the effect size.

There remain puzzling questions about the dose–response and mechanisms of effect of inhaled corticosteroids in reducing time to self-reported recovery: in the patient group with less severe illness, the RECOVERY trial showed that use of systemic steroids appeared to result in worse outcomes than placebo, yet the dose of inhaled corticosteroids in the PRINCIPLE study is high enough to have systemic absorption. The data presented on differences in the effect of inhaled corticosteroids on individual symptoms are interesting: notably, the difference between groups was greater for gastrointestinal symptoms and myalgia than for respiratory symptoms as might have been anticipated. Also notable were the findings that the between-group

difference in global self-rating of how well patients felt had largely disappeared by day 28 and the time to alleviation of all symptoms was not different between groups, yet the difference in the WHO-5 Well-Being Index, a subjective psychological wellbeing scale, was still present at 28 days. Longer-term follow-up clarifying the effects on the trajectory of illness, especially on persistent morbidity after COVID-19, would be useful.

On the basis of the PRINCIPLE trial data, it seems reasonable to consider inhaled corticosteroid use in early COVID-19 in patients similar to the trial population group (people with ongoing symptoms from COVID-19 aged ≥65 years or ≥50 years with specific comorbidities) who are interested in using them (80% of participants in the inhaled budesonide group in PRINCIPLE used the inhaled corticosteroids for at least a week). Various subgroup analyses in PRINCIPLE do not provide any pointers to which particular patient or illness characteristics in the included population might be more likely to predict benefit. These trial data do not support use in younger populations who are at lower risk of complications (<65 years with no comorbidities or anyone <50 years). Because vaccination was uncommon in trial participants, an important question is whether and what effect would be seen in the fully vaccinated population who have a different illness severity and trajectory.

We see through two recent pragmatic COVID-19 treatment trial platforms an important shift in approach: trials funded by governments and not industry, answering the crucial questions driven by immediate clinician need and not product marketing, and providing data in the spaces of clinical equipoise—this importance should not be underestimated or lost.

We declare no competing interests.

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Optimising SARS-CoV-2 vaccination schedules

The objective of any vaccination strategy is to achieve long-term protection against infection and also to reduce the mortality and morbidity associated with the eventual development of disease. This dual perspective usually requires repeated immunisations. Several factors affect the immunological outcome of repeated immunisations, such as the antigen selected, the time between doses, and the type of vector.[1] Once the initial vaccination schedules have been approved, trials must be designed to optimise immunological outcomes by adjusting these parameters and others.

In *The Lancet*, Xinxue Liu and colleagues[2] present results for four of the eight intervention groups of the Com-COV clinical trial, showing that the immunological response of double-dose ChAdOx1 nCoV-19 (AstraZeneca; hereafter referred to as ChAd) is statistically lower than any other schedule including BNT162b2 (Pfizer–BioNTech, hereafter referred to as BNT) and ChAd at 28 days post boost dose, with a 28-day prime–boost interval. In addition, their findings support previous published data from an academic study done by the Instituto de Salud Carlos III, of which I was an investigator and author,[3] suggesting


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