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.

Higher-dose dexamethasone for patients with COVID-19 and hypoxaemia?

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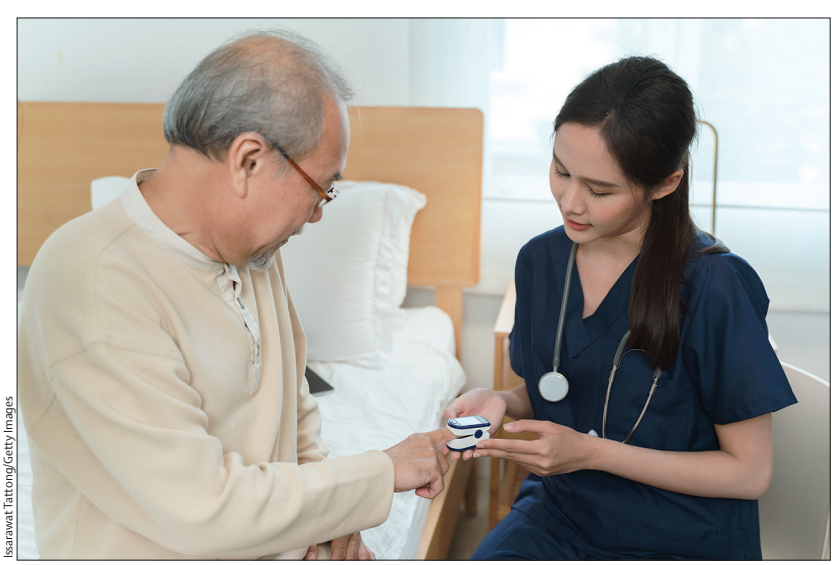
Early in the COVID-19 pandemic, the RECOVERY trial showed that anti-inflammatory therapy with 6 mg daily dexamethasone improved survival in patients requiring oxygen supplementation.[1] Additional anti-inflammatory therapy with either interleukin-6 (IL-6) inhibitors or the Janus kinase inhibitor baricitinib was later shown to provide further benefit to such patients.[2,3] However, because IL-6 inhibitors and Janus kinase inhibitors might be less appropriate for some patients (eg, those who are pregnant or who have liver or kidney impairment) and are likely to be unavailable in some health-care systems because of high cost, finding alternatives to these drugs is important. A simple alternative would be to increase the dose of dexamethasone. In the international, blinded COVID STEROID 2 trial, which evaluated 12 mg versus 6 mg doses of dexamethasone in patients with COVID-19 and severe hypoxaemia, Munch and colleagues[4] and Granholm and colleagues[5] found that mortality at 28, 90, and 180 days was five percentage points lower in patients assigned to 12 mg dexamethasone than in those assigned to 6 mg dexamethasone.[4,5] Although these results were not significant, a preplanned Bayesian analysis indicated a 95% probability of benefit on mortality with the higher dose.[6]

In this issue of *The Lancet*, the RECOVERY Collaborative Group[7] reports the results of a multicentre, multicountry, randomised, open-label platform trial evaluating a higher dose of dexamethasone (20 mg once daily for 5 days followed by 10 mg once daily for 5 days) compared with usual care (6 mg dexamethasone once daily for 10 days) in 1272 patients with COVID-19 receiving no oxygen (n=8) or simple oxygen supplementation (n=1264). 769 (60%) participants were male and 503 (40%) were female, with a mean age of 61·1 (SD 17·5) years; 688 (54%) were Asian, 454 (36%) were White, 14 (1%) were Black, and 116 (9%) were of other or unknown ethnicity. These patients were a subgroup of the RECOVERY trial population, which also included patients who were ventilated and on extracorporeal membrane oxygenation (ECMO). Enrolment into this subgroup was closed early following one of the repeated interim analyses and consequent recommendation from the data monitoring committee. The enrolment of the subgroup of patients who are ventilated or on ECMO continues. Death at 28 days (the primary outcome) occurred in 123 (19%) of 659 participants allocated to higher-dose dexamethasone and in 75 (12%) of 613 patients allocated to usual care (rate ratio 1·59, 95% CI 1·20–2·10). The occurrence of non-COVID-19 pneumonia and hyperglycaemia was also higher in the higher-dose group.[7]



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Strengths of this study include the pragmatic design; the use of mortality as the primary outcome; and the enrolment of patients in different health-care systems (including those of the UK, Nepal, Indonesia, Viet Nam, South Africa, and Ghana), which affords generalisability. Because adaptive stopping of recruitment into intervention groups and subgroups continues to be used in the RECOVERY trial, the repeated interim analyses are an important asset. The decision to stop recruitment was made by the data monitoring committee; however, the criteria for such a decision are not clear. This lack of transparency is a limitation and somewhat reduces the confidence in the observed effect size, although not in its direction. The scarcity of data regarding the flow rate of oxygen is also challenging. Almost all patients were recorded as receiving simple oxygen at enrolment; however, in the absence of further details, such flow rates can range from 1 L/min to 20 L/min. Of the

patients who died by day 28, more than three-quarters of those in both groups seem to have died without receiving invasive mechanical ventilation. The use or not of mechanical ventilation was a post-randomisation intervention and was possibly influenced by treatment limitations for patients with multiple comorbidities, resource constraints, and clinician decisions. The effect of this intervention on the final distribution of mortality between the two groups remains unclear, particularly in an unblinded trial. 28-day mortality in the group that received standard-dose dexamethasone was 12%, which seems to be high for a cohort of patients who were not critically ill, of whom more than half were vaccinated, and—based on the period of enrolment—many of whom were probably infected with the omicron (B.1.1.529) rather than the delta (B.1.617.2) variant. Other recent trials of interventions reported lower mortality in hospitalised, non-critically ill patients with COVID-19 from similar geographical settings.[8,9]

How do we reconcile the subgroup results of the RECOVERY trial with the results of other trials of corticosteroids in the treatment of COVID-19? The COVID STEROID 2 trial enrolled 1000 patients with COVID-19 receiving at least 10 L/min of oxygen (54% of patients), continuous positive airway pressure or non-invasive ventilation (25% of patients), or invasive ventilation (21% of patients). The 28-day mortality in the higher-dose group was 27·1% compared with 32·6% in the standard-dose group (adjusted risk ratio 0·86, 99% CI 0·68–1·08); the CIs of the mortality estimates therefore do not overlap between the two trials. Like RECOVERY, the COVID STEROID 2 trial also enrolled many patients in Asia (38% in India), but patients allocated to the higher dose received less dexamethasone (12 mg daily for up to 10 days) than those in the higher-dose group in the RECOVERY trial. Overall, the patients enrolled in the COVID STEROID 2 trial seemed to be more critically ill, but the two trial populations did appear to overlap in severity (eg, 25% of the population in the COVID STEROID 2 trial would probably have been eligible for the RECOVERY trial subgroup on the basis of oxygen flow rates at baseline [<20 L/min], but there were no data on flow rates at baseline in the RECOVERY subgroup). Other trials have found benefit from higher doses of dexamethasone versus placebo in mechanically ventilated patients with COVID-19, and dexamethasone versus standard care in mechanically ventilated patients with non-COVID-19 acute respiratory distress syndrome.[10,11]

With changing SARS-CoV-2 strains and increased use of vaccination, and therefore potentially fewer patients becoming critically ill from COVID-19, predicting the future use of anti-inflammatory strategies in these patients is difficult. Patients with COVID-19 receiving low-flow oxygen are likely to be harmed by high doses of dexamethasone, whereas those receiving higher-flow oxygen or mechanical ventilation could benefit from a high dose versus a standard dose of dexamethasone. The oxygen flow rates associated with harm and benefit cannot be defined precisely at present, but are probably greater than 10 L/min, which was the inclusion criterion in the COVID STEROID 2 trial. We will be better informed when the results of the subgroup of patients on ventilation or ECMO in the RECOVERY trial become available and when all trials of higher-dose versus standard-dose dexamethasone in patients with COVID-19 and hypoxaemia have undergone meta-analysis.[12]

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Efficacy of maternal vitamin B12 supplementation for improving infant outcomes in settings with high deficiency

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Maternal vitamin B12 supplementation to improve early neurodevelopment in infants has been proposed for some time now because vitamin B12 is a neurotropic vitamin, and infant neurodevelopment and growth are important dimensions for attained human capital and a healthy and successful adult life. In *The Lancet*, Ram K Chandyo and colleagues[1] report a community-based, double-blind, randomised controlled trial in a Nepalese region, which is endemic for biochemical vitamin B12 deficiency. Chandyo and colleagues[1] evaluated the effect of daily maternal vitamin B12 supplementation (50 µg per day) from early pregnancy until 6 months post partum on infant growth and neurodevelopment. The authors deserve compliments for their large and rigorous efficacy trial, which included 800 pregnant women, with 400 (50%) women randomly assigned to receive vitamin B12 supplementation and 400 (50%) women randomly assigned to the placebo group (mean age was 27·7 years [SD 4·0]). At baseline, 569 (71%) of the women had plasma vitamin B12 concentrations indicating low or marginal status (<221 pmol/L). The primary outcomes were length-for-age Z-scores (LAZ) at age 12 months, and the cognitive composite score of the Bayley Scales of Infant and Toddler Development, 3rd edition (Bayley-III) at age 6 months and 12 months. In this trial, there was no improvement in infant growth or neurodevelopment associated with vitamin B12 supplementation. The mean LAZ score at age 12 months was –0·57 (SD 1·03) in the vitamin B12 group and –0·55 (1·03) in the placebo group with a mean difference of –0·02 (95% CI –0·16 to 0·13). The mean cognitive composite scores (ie, at age 6 and 12 months) were 97·7 (SD 10·5) in the vitamin B12 group and 97·1 (10·2) in the placebo group, with a mean difference of 0·5 (–0·6 to 1·7). There was also no significant difference in infant haemoglobin concentrations despite a substantial biomarker response and improved vitamin B12 status among mothers and infants.

The existing evidence for maternal vitamin B12 supplementation and infant neurodevelopment in south Asia has been confusing. A smaller, but similar, vitamin B12 supplementation (50 µg per day) study in south India from early pregnancy until 6 weeks post partum, documented slightly higher expressive language scores only at age 30 months, but not at age 9 months or 72 months,[2–4] suggesting that measurements of these domains at young ages can be evanescent and tenuous. Furthermore, there was no benefit of vitamin B12 supplementation for the more robust electrophysiological measures (event-related potentials) at age 72 months.[4] In another smaller trial from rural western India, a lower dose of vitamin B12 supplementation (2 µg per day) from preconception until birth resulted in improved maternal and cord blood vitamin B12 status.[5] In this trial, cognition and language domains at age 24–42 months were better in infants of mothers who received just vitamin B12 supplements, but not in infants of mothers who received the same dose of vitamin B12 and other micronutrients (eg, vitamin A, vitamin D, vitamin E, vitamin C, vitamin B1, vitamin B2, vitamin B3, vitamin B6, zinc, copper, selenium, and iodine).[5] These confusing findings could be related to the small numbers of mothers and infants studied, but also