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Dexamethasone in the management of covid -19

Preliminary trial results are mostly good news, but timing is everything

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On 16 June, investigators on the covid-19 RECOVERY trial revealed in a press release[1] that participants with severe covid-19 (2104) given 6 mg dexamethasone once daily had an 8-26% lower mortality than 4321 participants given standard care. Changes in the NHS covid-19 treatment protocol were soon announced based on these results. The results remain neither peer reviewed nor published, although a preprint is available.[2] In the face of an ongoing, geographically mobile, lethal pandemic in which few highly effective—let alone affordable—treatments are available, the RECOVERY press release appropriately generated a great deal of attention, including both enthusiasm and concern.

Until the RECOVERY release, the only evidence based treatment available was remdesivir—an RNA polymerase inhibitor that modestly shortens time to hospital discharge in patients with severe covid-19[3] but doesn't reduce respiratory tract viral load.[4 5] RECOVERY is the first large randomised trial to test immunosuppression as a therapeutic option. It is important to note that tempering a maturing immune response to the SARS-CoV-2 virus is different from having underlying immunosuppression at the time of infection.

Illness trajectory

Covid-19 is a biphasic illness with an innate immune response that transitions into a broadly effective adaptive immune response, except for in a minority of people who develop severe disease. The pathogenesis of SARS-CoV-2 differs fundamentally from that of its predecessors SARS-CoV-1 and MERS, for which poor outcomes correlate with viraemia and high viral loads in the lung at time of death.[6-8]

Guidance from the US Centers for Disease Prevention and Control (CDC)[9] recommends against corticosteroid therapy in coronavirus infections because steroids "prolonged viral replication" in patients with MER, although the difference in time to viral clearance wasn't statistically significant in the primary data.[6 10] Unlike the MERS coronavirus, SARS-CoV-2 is rarely found in blood during the symptomatic phase of covid-19, even in people with severe disease.[11] Furthermore, hypoxaemia may develop just as the viral load in the upper respiratory tract is falling rapidly or becoming undetectable.[12 13]

Patients admitted to hospital with covid-19 typically report symptom onset three to five days after exposure (fatigue, chills), progressing to fever and dry cough 48 hours later. Transition to severe disease with hypoxaemia occurs five to seven days into the symptomatic illness, about 8-14 days after original exposure. In the RECOVERY trial, dexamethasone was beneficial for participants treated seven or more days into the symptomatic phase, with the onset of hypoxaemia. Importantly, there was a non-significant trend (P=0.14) towards possible harm affecting participants without hypoxaemia and not on mechanical ventilation. RECOVERY findings therefore support use of dexamethasone only for patients with hypoxaemia, not those with milder disease. The data do not support use of dexamethasone or other corticosteroids in the outpatient setting.

Timing is everything

Corticosteroids such as dexamethasone have broad effects on innate and adaptive immunity. Adaptive immunity may be integral to covid-19 immunopathology, as the onset of acute respiratory distress syndrome correlates temporally with the appearance of a specific antibody against SARS-CoV-2.[14] In March 2020, a retrospective evaluation of the covid-19 clinical experience in China reported that, in the subset of patients who progressed to ARDS, objectively sicker patients who received methylprednisolone had lower mortality rates than patients not receiving methylprednisolone.[15] In RECOVERY, corticosteroid therapy increased 28 day survival in covid-19 patients developing acute respiratory distress syndrome. Despite concerns about the possibility of steroid associated complications, it would not be reasonable to delay use of a widely available treatment with a demonstrated mortality benefit.

Evidence gaps

Unresolved questions remain, however. RECOVERY investigators did not explore optimal type of corticosteroid nor timing, dose, or duration of giving this drug class. The dose of dexamethasone used was roughly half the functional corticosteroid dose used to prevent treatment induced acute respiratory distress syndrome in moderate or severe pneumocystis pneumonia. Even though dexamethasone worked, it is not clear whether corticosteroids are the best option for all patients in the second phase of the illness or whether treatment may be less beneficial for some subsets, such as people with diabetes. Ongoing trials of immune modulation with calcineurin inhibitors may shed light on these questions.

Adults requiring ventilation in RECOVERY were relatively young, with a mean age of 59 years. In a post hoc subset analysis, dexamethasone did not benefit the two older age groups, so the benefits and risks of dexamethasone for oldest adults remain unclear. Virological measures such as viral load were not reported and would be helpful in future studies as they may ultimately guide treatment decisions, including timing. Longer term follow-up of the

original cohort will be critical to identify harms associated with corticosteroid use.

The RECOVERY investigators and collaborators should be congratulated for organising and completing this trial during a pandemic. The UK's unified healthcare system lends itself to collaboration, and a study like this is difficult to pull off in fragmented academic medical environments such as those in the US and elsewhere. Perhaps less desirable, is the now common practice of communicating clinical trial data early through press releases. Clinicians and policy makers need access to detailed data and analyses before making or accepting therapeutic decisions or recommendations.

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