**Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report**

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## Article Summary

This randomized, controlled, open-labelled adaptive-platform trial involved 176 hospitals across the United Kingdom to establish whether steroids conferred a 28-day mortality benefit in Covid-19 patients. From March to June 2020, 11,303 patients hospitalised with proven Covid-19 or clinical suspicion were randomly assigned to one of four treatment groups. 2,930 were assigned to other treatment arms (hydroxychloroquine, lopinavir-ritonavir or azithromycin). 1,948 were excluded given a contraindication to dexamethasone. 6,425 underwent web-based non-stratified 2:1 randomization between dexamethasone and usual care. 2,104 were randomized to 6mg of dexamethasone for up to 10 days.

The primary outcome of all-cause 28-day mortality was significantly reduced in the treatment group with an age-adjusted risk ration of 0.83 *(22.9% vs 25.7%, 95% CI 0.75-0.93, P < 0.001).* Pre-specified subgroup analysis was based on respiratory support with considerable difference across groups. The risk ration on mechanical ventilation was 0.64 *(95% CI 0.51 to 0.81 29.3% vs. 41.4%)* and among those receiving oxygen was 0.82 (*23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94*). There was no difference in mortality among patients not requiring respiratory support at randomization (*17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55).* The authors concluded that dexamethasone confers a significant benefit in hospitalised patients requiring supplemental oxygen (*NNT=25*) or mechanical ventilation (*NNT=8*) with no benefit in patients not requiring oxygen.

## Critical Appraisal

Undertaking a robust trial during a pandemic is an admirable task with unique advantages and disadvantages[1]. This was a large, rapidly conducted trial with a simple, affordable intervention and a clinically meaningful binary outcome. The platform-adaptive design allowed novel treatments to be efficiently assessed[2-4]. The cohort was reflective of clinical practice with well-matched groups except age which was adjusted. The subgroup analysis based on oxygen-requirement is clinically relevant.

The trial has shortcomings. The open-label design is susceptible to systemic bias[2]. While mortality is a binary outcome, withdrawal of care in an ICU-setting can alter this objectivity as can a lack of standardised care or uniform indications for escalation of respiratory support[5-7]. Being a pragmatic trial, there is a scarcity of in-depth data, for instance viral load. Finally, while the recruitment and follow-up is impressive, 15% were not PCR-confirmed and follow-up was short thus long-term mortality is unknown.

## Reflection

Initial guidelines for COVID-19 treatment stated that glucocorticoids were contraindicated[8]. The DEXA-ARDS Trial demonstrated that dexamethasone decreased mortality in ARDS[9]. Wang et Al. attempted to demonstrate similar effects in COVID-19-ARDS however the study was underpowered[10,11]. RECOVERY builds on this providing good evidence for utilizing steroids as standard of care in patients hospitalised with acute hypoxic respiratory failure secondary to Covid-19 in order to reduce short-term mortality. Given our similarity to the cohort, the results are expected to be applicable to our population and given the inclusion of pregnant and breast-feeding women this extends to them. However, when modifying guidelines, we need to ensure the appropriate patients are chosen at the appropriate time as it is evident that patients without an oxygen requirement may be harmed. Looking forward, a randomised control trial with adequate blinding and variable dosing with granular data will allow for firmer certainty in these findings and add to our understanding of not only the benefit of steroids but the mechanism that underpins this. Nonetheless, this trial has undoubtedly altered clinical practice already.

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