Effect of Dexamethasone in Hospitalized Patients with COVID-19: Preliminary Report

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This preprint article presents the preliminary results of the Dexamethasone versus usual care arm of the RECOVERY trial, a randomized, controlled, open-label platform trial evaluating multiple interventions in patients hospitalized with COVID-19. (recoverytrial.net)

QUESTION The PICO of the study is as follows.

P – people hospitalized with SARS-CoV-2 (age limitation of >18 years recently removed)
I – Dexamethasone (oral or IV), 6mg/day + usual care for 10 days (or until discharge or death)
C – usual care
O – all cause mortality within 28 days (primary outcome). Secondary outcomes include time to discharge from hospital and among people not receiving invasive mechanical ventilation at randomization, receipt of invasive mechanical ventilation or death.

METHODS Hospitalised patients with clinical suspected or laboratory confirmed SARS-CoV-2 infection were randomised in a ratio of 2:1 to either usual standard of care or usual care plus dexamethasone. Participants and clinicians were not blinded to the allocated treatment. Information on adherence, receipt of other study treatments, duration of admission and vital status were collected at discharge, death or 28 days after randomisation (whichever occurred earlier). Cox regression was used to estimate the mortality rate ratio for the primary outcome of 28-day mortality. Pre-specific analysis of the primary outcome was performed in subgroups defined by age, sex, level of respiratory support, days since symptom onset and 28-day mortality risk.

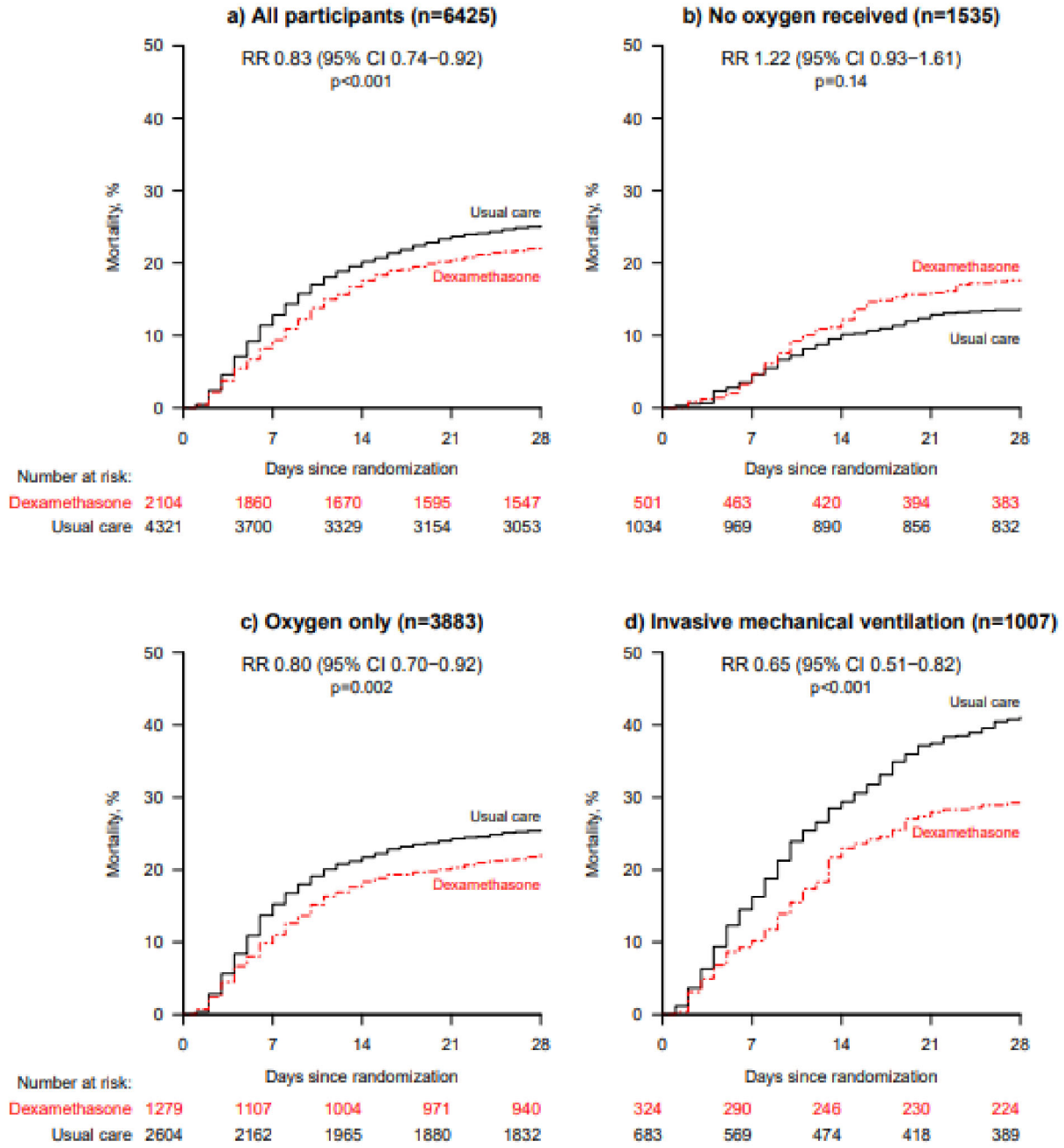
RESULTS 21.6% (454/2104) of participants receiving dexamethasone and 24.6% (1065/4321) of participants allocated to usual care died with 28 days (age-adjusted rate ratio 0.83 95% CI 0.74-0.92). Mortality rate reductions varied depending on level of respiratory support received at randomisation – dexamethasone reduced deaths in patients receiving invasive mechanical ventilation (RR 0.65 95%CI 0.52-0.82) and those receiving oxygen without invasive ventilation (RR 0.80 95%CI 0.70-0.92) but did not reduce deaths among those receiving no respiratory support at randomisation (RR 1.22 95%CI 0.93-1.61) (Figure).

DISCUSSION The following key points were discussed.

- Randomization was considered to be adequate, attrition was not of concern and though participants and clinicians were not blinded to allocation, the primary outcome was objective, which mitigates the potential for bias to some extent. Results were adjusted for imbalance in age between the study groups (mean age of those allocated dexamethasone was 1.1 years higher than those allocated usual care).
- The RECOVERY trial is a factorial design whereby participants after randomization to usual care or one of 4 treatments, may be further randomized (under prespecified conditions) to no additional treatment or an immunomodulatory treatment. It is unclear from the study report, how many of the participants may have been further randomized at the time of writing.
- Given what is currently known about the course of SARS-CoV-2, it would be useful to examine the longer-term consequences for those in the trial. Post-trial linkage studies would be useful for this purpose.
- Post protocol calculation of study sample size was considered appropriate given the circumstances in which the trial was conducted. Platform trials, such as this operate within a single 'master' trial protocol and will be of vital importance for future epidemics. Providing scenarios with data that may be used for calculation of sample size (such as presented in this article) could be included in the master protocol.
- Responses to the trial related to interim analysis (which appeared to be conducted fortnightly) and potential for type 1 error from multiple testing were discussed. Reporting of timing and methods of interim analysis conducted, criteria related to stopping, results, and any adjustments for multiple testing would be useful.
- It was noted that rate of the use of dexamethasone in the usual care group was 7%. It would be useful to know the 'typical' rate of steroid use in a population such as this and then to consider whether the decision to use a steroid in participants in the usual care group, may be affected by participation in the trial (a potential ethical issue given evidence for the effectiveness of steroids for severe pneumonia from well conducted systematic reviews)
- Analysis of mortality by level of respiratory support at randomization shows a qualitative interaction with dexamethasone being potentially harmful when respiratory support is not required, but beneficial when oxygen or invasive ventilation is required. The possibility of a therapeutic interaction – dexamethasone works only in the presence of high levels of inspired oxygen was suggested. This could be tested in a 2x2 factorial design trial where participants (who clinicians determine do not require oxygen) are randomized to oxygen or not and dexamethasone or not.
- An overall high rate of mortality in this trial was noted (approximately 15% among those participants who did not receive oxygen at randomization).

OVERALL SUMMARY This trial provides vital information about a promising treatment for critically ill SARS-CoV-2 patients, and demonstrates that pragmatic, rigorous research can be rapidly designed and conducted in the context of the pandemic. More detail in the reporting of methods and results, and responses to pre-print comments in the peer-reviewed publication, will add value to the article overall.

Figure 1: 28−day mortality in all patients (panel a) and separately according to level of respiratory support received at randomization (panels b−d)



RR=age−adjusted rate ratio. CI=confidence interval. The 'oxygen only' group includes non−invasive ventilation. Note: in the RECOVERY trial press release of 16 June 2020, effects in subgroups of level of respiratory support received were shown with 99% CIs, not 95% CIs as inadvertently stated. The age−adjusted rate ratio and 99% confidence intervals remain unchanged in this analysis: no oxygen required, RR 1.22 (99% CI 0.86−1.75); oxygen only, RR 0.80 (99% CI 0.67−0.96); invasive mechanical ventilation, RR 0.65 (99% CI 0.48−0.88).