Dexamethasone and remdesivir: finding method in the COVID-19 madness

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A pandemic produces record advances—and painful missteps. The infectious-disease community is now leading multinational randomised clinical trials whose magnitude and logistical challenges resemble those of cardiovascular medicine. They achieve enviable statistical power and speed but must sacrifice complexity and nuance to do so. Data entry must be minimal and outcomes easily measurable, precluding virological and other laboratory-based assessments. Before peer review, their potentially blunted messages are broadcast to non-experts by press releases and preprint websites run by a confusing mix of commercial and non-profit organisations. The principles of evidence-based medicine are being increasingly set aside in favour of strong opinions and politically loaded statements.

We are grateful for large-scale randomised controlled trials and the accessibility of their findings. But specific expertise is often needed to help parse results: rigorous critical appraisals should accompany journalistic and lay-public summaries, as patients and other stakeholders might lack the time and background to examine new evidence in detail. More explanatory research assessing key microbiological outcomes is needed. And although new or repurposed therapies might draw the attention of an anxious, pandemic-weary public, we must adhere to fact: access to oxygen and well-staffed supportive care reduces mortality more than any medicinal product.

The RECOVERY trial is a timely case study.[1] Its preliminary results show a significant proportional reduction in day-28 mortality with dexamethasone—up to one-third in ventilated patients. Yet those results should be accompanied by a careful look at the trial's choice of outcome timepoint, its particular population, and post-hoc and subgroup analyses done after multiple testing procedures. For many COVID-19 patients, mortality occurs after day 28. In line with British hospital demographics, the intensive-care unit (ICU) population consisted of relatively younger patients (mean age 59 years) with little baseline cardiopulmonary illness. These patients are not highly representative of other countries' ICU patients, who are more likely to be elderly and more comorbid. In addition, dexamethasone was putatively harmful for patients with early, non-severe disease, in whom viral replication was likely to be ongoing and the cytokine storm not yet at peak. The news of a substantial reduction in mortality is so welcome that we might forget that cause-specific mortality was not reported, nor were data on adverse events and co-infections or super-infections observed in other viral pneumonias treated with glucocorticoids.[2] Effects on viral kinetics also need clarification. Yet the British RECOVERY data, which led to early termination of similar studies[3] and which will drive the results of present and future meta-analyses,[4] have already been considered representative enough for recommendations to be issued on glucocorticoid use in patients of any age or comorbid status with severe or critical disease.[5]

Meanwhile, remdesivir is positioned as a large-spectrum, direct-acting antiviral. Information on its effects on SARS-CoV-2 shedding is thus crucial to confirm the in-vivo activity of a drug now priced at over US$2000 per course[5] given the difficulties in showing a major mortality benefit. Yet data on shedding duration have been reported neither by the large Adaptive COVID-19 Treatment Trial[6] nor the multinational phase 3 RCT;[7] of note, a smaller trial from China saw no difference in viral shedding in patients randomly assigned to remdesivir or placebo.[8] Although remdesivir was shown to have an effect in shortening time to hospital discharge in patients with severe pneumonia,[6] data are conflicting in patients without hypoxaemia.[7] Despite years of market availability of neuraminidase inhibitors, the same controversy still exists regarding the antiviral effect of these drugs in patients with severe disease,[9] mainly because lower respiratory tract virology data are scarce.

In the early months of this pandemic, our eagerness to help and to meet societal expectations led us to adopt interventions based on weak, preclinical evidence. But we have now identified the factor most strongly protective against COVID-19 mortality: high socioeconomic status.[10] Rapid access to oxygen and a bed in well-staffed facilities is the first step to reduce mortality. In both high-income and low-income and middle-income countries, allocation of resources should prioritise this access.

There is an urgency to finding a COVID-19 therapy for patients with severe disease, and dexamethasone is a central piece of that puzzle. Nonetheless, although large randomised controlled trials allow for rapid and statistically powerful results, their preprint releases should be interpreted with caution, and smaller, more granular trials with more thorough data collection and more nuanced outcomes should not be abandoned nor prematurely terminated. Searches for magic bullets should continue; we lack drugs specifically designed to target SARS-CoV-2. Combination therapies with antiviral and anti-inflammatory agents will bring new challenges. The results of these searches will thus require careful, committed scrutiny, and our patients deserve sober analyses.

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1 Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with COVID-19—preliminary report. *N Engl J Med* 2020; published online July 17. https://doi.org/10.1056/NEJMoa2021436.
2 Alshabani K, Haq A, Miyakawa R, Palla M, Soubani AO. Invasive pulmonary aspergillosis in patients with influenza infection: report of two cases and systematic review of the literature. *Expert Rev Respir Med* 2015; **9:** 89–96.
3 Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *JAMA* 2020; **324:** 1307.
4 Siemieniuk RA, Bartoszko JJ, Ge L, et al. Drug treatments for COVID-19: living systematic review and network meta-analysis. *BMJ* 2020; **370:** m2980.
5 Lamontagne F, Agoritsas T, Macdonald H, et al. A living WHO guideline on drugs for COVID-19. *BMJ* 2020; **370:** m3379.
6 Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19—final report. *N Engl J Med* 2020; published online Oct 17. https://doi/10.1056/NEJMoa2007764.
7 Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of remdesivir *vs* standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. *JAMA* 2020; **324:** 1048–57.
8 Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020; **395:** 1569–78.
9 Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. *Lancet* 2015; **385:** 1729–37.
10 Wadhera RK, Wadhera P, Gaba P, et al. Variation in COVID-19 hospitalizations and deaths across New York City boroughs. *JAMA* 2020; **323:** 2192–95.