Azithromycin, RECOVERY, and the power of large, simple trials

Published Online
February 2, 2021
https://doi.org/10.1016/S0140-6736(21)00307-X
See Online/Articles
https://doi.org/10.1016/S0140-6736(21)00149-5

One of the many challenges for clinical trials during a pandemic such as COVID-19 is the need to provide reliable and clear answers rapidly. High-quality, adequately powered, simple randomised clinical trials have been crucial in advancing knowledge of potential treatments for COVID-19.[1] Principles underpinning such trials include the use of the uncertainty principle to determine eligibility, which allows for rapid enrolment of participants and streamlined data collection, making these studies easy to implement in routine practice.[2] Platform and adaptive trial designs further improve the large, simple trial concept, allowing investigation of multiple experimental therapies throughout the trial with sufficient statistical power for clinically relevant outcomes.[3]

RECOVERY represents a large, simple, randomised platform trial. Results for other potential treatments for COVID-19—ie, dexamethasone, hydroxychloroquine, and lopinavir–ritonavir—have been published previously.[4–6] In *The Lancet*,[7] the RECOVERY Collaborative Group report the results of a trial of azithromycin in patients admitted to hospital with COVID-19. Azithromycin is a widely available, inexpensive drug, and has an excellent safety profile for other conditions; thus, if shown to be effective and safe, it could represent a treatment option for patients with COVID-19. The trial enrolled 7763 participants, of whom 2582 patients were randomly allocated to receive azithromycin (500 mg once per day by mouth or intravenously for 10 days or until discharge) and 5181 patients were randomly allocated to receive usual care alone. The trial took place at 176 hospitals in the UK. Outcomes were ascertained through a 1-page electronic case report form and linkage to national health data systems. The mean age of study participants was 65·3 years (SD 15·7), approximately a third (2944 [38%] of 7763) were women, and the median time since symptom onset was 8 days (IQR 5–11). The investigators found no benefit of azithromycin for the primary outcome of 28-day mortality when added to the standard care regimen (rate ratio 0·97, 95% CI 0·87–1·07; p=0·50). There was also no difference between groups in duration of hospital stay. In addition, among those not on invasive mechanical ventilation at baseline (94% of the included participants), no difference was seen in the proportion meeting the endpoint of invasive mechanical ventilation or death. Results were similar across all prespecified subgroups.

The strengths of the RECOVERY trial were the use of concealed randomisation, the intention-to-treat analysis, and the large sample size. Limitations that merit consideration are the open-label design and the fact that 17% of patients in the usual care group were given azithromycin or another macrolide antibiotic.

The results of this investigation into azithromycin as part of the RECOVERY trial confirm and extend those of the COALITION II trial,[8] which showed that the addition of azithromycin to standard of care treatment did not improve the clinical outcomes of patients admitted to hospital with severe COVID-19. Given that the addition of azithromycin to existing standard of care regimens did not improve outcomes in the RECOVERY and COALITION II trials, routine use of azithromycin in patients admitted to hospital with COVID-19 should be avoided, to allow better allocation of health-care resources.

Collaborative research efforts such as RECOVERY, COALITION COVID-19 Brazil,[8–10] and SOLIDARITY[11] are evidence that pragmatic, randomised clinical trials can be promptly initiated in different countries and settings during a pandemic, as we have seen with COVID-19. Ongoing randomised clinical trials from these collaborative research efforts and from other groups are testing other potential therapies for COVID-19 such as anticoagulants, newer antivirals, anti-inflammatories, and immunomodulatory agents. Results from these

Reuters/Toby Melville

studies will help to inform treatment decisions in clinical practice. The experience and the knowledge gained from successfully launching these studies in a matter of weeks has important implications for research not only in COVID-19 but also for future pandemics and for common diseases.[12] Finally, innovations such as big data technologies and linkage with electronic health records, mobile applications, and wearable devices can further transform pragmatic randomised clinical trials, making them larger, more efficient, and easier to implement.

I am a member of the COALITION COVID-19 Brazil executive committee. I report grants from Pfizer and EMS Pharma related to COVID-19 research and grants not related to COVID-19 research from AstraZeneca, Servier, Amgen, Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, and Novartis.

Otavio Berwanger
otavio.berwanger@einstein.br

Academic Research Organization, Hospital Israelita Albert Einstein, 05652–900 Sao Paulo, Brazil

1 Califf RM, Curtis LH, Harrington RA, Hernandez AF, Peterson ED. Generating evidence for therapeutic effects: the need for well-conducted randomized trials. *J Clin Invest* 2021; **131:** e146391.
2 Yusuf S, Collins R, Peto R. Why do we need some large, simple randomized trials? *Stat Med* 1984; **3:** 409–22.
3 Bauchner H, Fontanarosa PB. Randomized clinical trials and COVID-19: managing expectations. *JAMA* 2020; **323:** 2262–63.
4 RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19—preliminary report. *N Engl J Med* 2020; published online July 17. https://www.nejm.org/doi/full/10.1056/NEJMoa2021436.
5 Horby P, Mafham M, Linsell L, et al. Effect of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med* 2020; **383:** 2030–40.
6 Horby PW, Mafham M, Bell JL, et al. Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2020; **396:** 1345–52.
7 RECOVERY Collaborative Group. Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021; published online Feb 2. https://doi.org/10.1016/S0140-6736(21)00149-5.
8 Furtado RHM, Berwanger O, Fonseca HA, et al. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. *Lancet* 2020; **396:** 959–67.
9 Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. *N Engl J Med* 2020; **383:** 2041–52.
10 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:** 1307–16.
11 WHO SOLIDARITY Trial Consortium. Repurposed antiviral drugs for COVID-19—interim WHO Solidarity Trial results. *N Engl J Med* 2020; published online Dec 2. https://doi.org/10.1056/NEJMoa2023184.
12 Kalil AC. Treating COVID-19-off-label drug use, compassionate use, and randomized clinical trials during pandemics. *JAMA* 2020; **323:** 1897–98.