EDITORIAL

A Large, Simple Trial Leading to Complex Questions

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The rapid spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the lack of known effective treatments for coronavirus disease 2019 (Covid-19) have caused an unprecedented situation for patients and clinicians — regimens with uncertain value are being used worldwide while being evaluated in clinical studies. The writing committee for the World Health Organization (WHO) trial Solidarity[1] now reports in the *Journal* interim results regarding four pharmacologic treatments that have generated substantial interest: regimens based on remdesivir, hydroxychloroquine, lopinavir, and interferon beta-1a. At 405 hospitals in 30 countries representing all six WHO regions, 11,330 adults were randomly assigned to receive either one of these regimens — as available — or to receive hospital-specific standard care. The report provides rate ratios for death over a 28-day period for each regimen as compared with standard care: remdesivir, 0.95 (95% confidence interval [CI], 0.81 to 1.11); hydroxychloroquine, 1.19 (95% CI, 0.89 to 1.59); lopinavir, 1.00 (95% CI, 0.79 to 1.25); and interferon beta-1a, 1.16 (95% CI, 0.96 to 1.39).

Launching and executing this ongoing trial is a remarkable achievement. Patients underwent randomization at hospitals in high-income countries such as Canada, France, and Switzerland and in low- and middle-income countries such as Peru, the Philippines, and South Africa. The rapid, widespread enrollment is a testament to the commitment of the WHO and its partners and was enabled by a design that allowed, for each patient, the rapid collection, recording, and transmission of a small amount of high-information data. In 6 months, the trial team accumulated information on the collective experience of more than 11,000 hospitalized patients in settings with varied and evolving standards of care, capacity to administer treatment, and treatment options.

What do the estimated treatment effects represent? Context is essential when interpreting the results of any randomized trial. No intervention acts on two persons in an identical fashion: patients present with different risk factors, are treated in different health care settings, and begin treatment at different stages of illness. In particular, the effectiveness of an antiviral agent can depend on whether a patient presents early (during viral pathogenesis) or later (when immunopathologic conditions or other complications may be more important). Even when a protocol provides a detailed description of an intervention and its control, an estimated treatment effect is an average over these sources of heterogeneity. The Solidarity trial averages over another source of heterogeneity not normally encountered in a more conventional design — variation within and between countries in the standard of care and in the burden of disease in patients who arrive at hospitals.

The Solidarity trial nonetheless adds important new information. The data show no evidence of a meaningful benefit on in-hospital mortality for hydroxychloroquine, lopinavir, or interferon beta-1a when averaged across a wide range of settings, either overall or in important subgroups (Figs. S6 through S9 in the Supplementary Appendix of the article, available at NEJM.org). Viewed collectively with previous studies, the Solidarity trial sends the clear message that these drugs as currently used should no longer be considered viable treatment options for Covid-19.

The case for the continued use of remdesivir

is more nuanced. In this large trial, no substantial mortality benefit was noted with remdesivir across a variety of health care settings. The 95% confidence interval for the rate ratio for death (0.81 to 1.11) implies that a 20% reduction in mortality is inconsistent with these data. However, other data suggest that the drug may still have an important role. The Adaptive Covid-19 Treatment Trial[2] showed that remdesivir led to a shorter median time from randomization to recovery (10 days, vs. 15 days with placebo) and may have reduced the time to hospital discharge (12 days vs. 17 days) but did not show a mortality benefit. Spinner et al.[3] found that a 5-day course of remdesivir improved clinical status 11 days after the initiation of treatment but that a 10-day course did not. Wang et al.[4] found a possible benefit with remdesivir regarding time to recovery, but only in the subgroup of patients who had received a diagnosis less than 10 days before the start of treatment. Even without a reduction in in-hospital mortality, reducing the time to recovery and hospital discharge among patients who survive is important, both for patients and for stressed health care systems, and was the basis for the recent approval of remdesivir by the Food and Drug Administration.[5]

Large, simple randomized trials such as Solidarity focus on easily measured definitive outcomes that can be collected quickly and accurately. In 7 months from the beginning of enrollment to publication, the Solidarity trial answered the critically important question of possible mortality benefits of four highly touted regimens. It has informed the research agenda for the treatment of Covid-19. For three of the four drugs that were studied (hydroxychloroquine, lopinavir, and interferon beta-1a), there is no evidence of benefit. The benefit with the fourth (remdesivir) may be its ability to change the course of hospitalization in some patients, but the results of the Solidarity trial tell us not to expect substantially reduced mortality. The next set of questions regarding remdesivir can be answered only in placebo-controlled trials with complex data. Should remdesivir be reserved for the treatment of patients with selected risk factors? What is a more effective timing for the use of remdesivir, and should it be used in combination with other agents? How is the course of hospitalization affected by the type and level of care delivered in particular settings? Detailed examination of these questions within the Solidarity trial would have undermined the very simplicity that made it possible. How to answer these more complicated and nuanced questions quickly remains a challenge for the scientific community. It will not be simple to achieve clarity on when and how — or even whether — to use remdesivir.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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This editorial was published on December 2, 2020, at NEJM.org.

1. WHO Solidarity Trial Consortium. Repurposed antiviral drugs for Covid-19 — interim WHO Solidarity trial results. N Engl J Med. DOI: 10.1056/NEJMoa2023184.
2. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 — final report. N Engl J Med 2020;383:1813-26.
3. 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.
4. 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.
5. Rubin D, Chan-Tack K, Farley J, Sherwat A. FDA approval of remdesivir — a step in the right direction. N Engl J Med. DOI: 10.1056/NEJMp2032369.

DOI: 10.1056/NEJMe2034294