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Weekly Journal Scan

Re-purposed antiviral drugs without a purpose in COVID-19: a valuable lesson for clinicians

Comment on the interim results of the WHO Solidarity Trial, which were published in the *New England Journal of Medicine* (DOI: 10.1056/NEJMoa2023184)

Key Points

- The World Health Organization (WHO) Solidarity Trial is an adaptive, randomized, open-label trial designed to help determine whether any of four repurposed antiviral drugs (Remdesivir, Hydroxychloroquine, Lopinavir, and Interferon-β1a) could have an effect on in-hospital mortality of COVID-19 patients.
- In 405 hospitals in 30 countries, 11 266 adult patients (81% younger than 70 years, and 62% male) were randomized equally between whichever study drugs were locally available and open control (up to five options: four active and local standard-of-care). The intent-to-treat primary analyses were of in-hospital mortality in the four pairwise comparisons of each drug-treated group vs. its control (concurrently allocated the same management without that drug, despite availability). Secondary endpoints were initiation of ventilation and hospitalization duration.
- Overall, 1253 deaths were reported (at median Day 8, interquartile range 4–14). Kaplan–Meier 28-day mortality was 11.8% (39% if already ventilated at randomization, 9.5% otherwise). Log-rank death rate ratios (RRs) [with 95% confidence intervals (CIs) and numbers dead/randomized, each drug vs. its control] were stratified for age and ventilation at entry: Remdesivir, RR = 0.95 (0.81–1.11, $P = 0.50$; 301/2743 active vs. 303/2708 control); Hydroxychloroquine, RR = 1.19 (0.89-1.59, $P = 0.23$; 104/947 vs. 84/906); Lopinavir, RR = 1.00 (0.79–1.25, $P = 0.97$; 148/1399 vs. 146/1372); Interferon, RR = 1.16 (0.96–1.39, $P = 0.11$; 243/2050 vs. 216/2050).
- No study drug definitely reduced mortality (in unventilated patients or any other subgroup of entry characteristics), initiation of ventilation or hospitalization duration.

Comment

Following the advice of a WHO COVID-19 research forum and other expert groups, four re-purposed anti-viral drugs were identified that might have at least a moderate effect on mortality, based on the assumption that a reduced SARS-CoV-2 viral load might mitigate disease progression and improve outcome. In March 2020, WHO launched a large, simple, multi-country (including high-income countries such as Canada, France, and Switzerland as well as low- and middle-income countries such as Peru, the Philippines, and South Africa), open-label, randomized trial, the Solidarity trial, among hospitalized patients to evaluate the effects of Remdesivir, Hydroxychloroquine, Lopinavir, and Interferon-β1a on in-hospital mortality.[1] The trial involved the rapid collection, recording, and transmission of a small amount of highly informative data, and its design was adaptive: drugs could be dropped because of futility and promising ones added.[2] Hydroxychloroquine,[3,4] Lopinavir,[5] and Interferon were eventually dropped on the basis of the regulatory assessment of the evidence and/or WHO recommendation, before the publication of this interim analysis because of no apparent benefit on in-hospital mortality (or other clinically relevant outcomes), underlying the unprecedented rapidly shifting therapeutic landscape during the pandemic.

Each comparison between a study drug and its controls was evenly randomized and unbiased, as both groups were affected equally by any differences between countries or hospitals and by any time-related trends in patient characteristics or standard of care.[1] The largely negative results of the Solidarity trial should be considered in the context of the evidence on mortality from all properly randomized trials. There are four trials of Remdesivir vs. control (with Solidarity providing more than three-quarters of the available evidence). Combining data appropriately in a meta-analysis of the four trials, the Remdesivir vs. control death RR was 0.91 (95% CI 0.79–1.05).[1] The 95% CI is compatible with the prevention of a small fraction of all deaths (less than 20%), but it is also compatible with the prevention of no deaths. Even without an effect on 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,[6] and was the basis for the approval of Remdesivir by the Food and Drug

Administration.[7] In Solidarity, however, initiation of ventilation, and hospitalization duration were not definitely reduced by any trial drug, including Remdesivir, either overall or in any particular subgroup.[1]

What lessons can be learned from the Solidarity trial? First of all, even under dramatic circumstances such as during the first wave of COVID-19, hospital physicians should refrain from treating patients with promising drugs—because of scientific or political hype—in the absence of solid evidence for their efficacy and safety, but rather try and participate in large, simple, randomized trials aimed at obtaining such evidence. Secondly, despite potential limitations of adaptive designs (including the need of pre-specified rules for removing or adding treatments),[2] this type of trials offers the unquestionable advantage of rapidly testing several therapeutic strategies using the same controls, and quickly terminating ineffective drug regimens to start newer ones. When reviewing pandemic preparedness plans, governments should consider establishing and funding even larger multinational hospital networks than used by the Solidarity trial in order to shorten time-to-evidence and reduce statistical uncertainty of trial results. Finally, the disappointing results produced by four repurposed antiviral drugs clearly question the predictive value of currently available screening platforms and call for technological innovation in the field.

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