Viewpoint
What Is the Best Drug to Treat COVID-19? The Need for Randomized Controlled Trials

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is currently the biggest public health challenge to the biomedical community of the last century. Despite multiple public health measures,1-3 there remains an urgent need for pharmacologic therapies to treat infected patients, minimize mortality, and decrease pressures on intensive care units and health systems and optimally, they should also decrease subsequent transmission.

At the time of writing this Viewpoint, there are no licensed drugs to treat COVID-19, and a search on https://www.clinicaltrials.gov using “COVID-19” as the input term yielded 657 studies. Drug-based interventions currently fall into categories including off label use, which includes repurposed drugs,4-6 and newer entities, but both categories should be given in the context of clinical trials. In Wuhan, China, then the epicenter of the pandemic, Cao et al.,6 under heroic circumstances, conducted a randomized, controlled, open-label trial involving 199 hospitalized patients with confirmed SARS-CoV-2 infection, including as an entry criteria oxygen saturation (SaO2) of 94% or less on air.7 Unlike the randomized trial by Cao et al., there was no accompanying editorial, but there was a subsequent open letter discussing remdesivir studies from the CEO and Chairman of Gilead (https://www.gilead.com/stories/articles/an-open-letter-from-our-chairman-and-ceo). One presumes that the patients in the remdesivir single-arm study, and several included in an earlier Lancet paper,8 were recruited in perhaps easier conditions than those in Wuhan earlier this year.

Randomized trials are designed to precisely answer questions regarding toxicity and efficacy beyond standard of care and in the absence of an effective therapy, it remains entirely reasonable and ethical at this point to perform a trial versus placebo. They are much more informative than single-arm studies which result in claims, perhaps borne from hope and/or desperation, that drugs work,9 and such claims include those from physicians stating “cure rates” usually in the high 90% range, unless one focuses on recruiting hospitalized patients and/or the elderly, frail, those with co-morbidities, or a high body mass index, to name a few examples.

A well-known French microbiologist on social media has promoted the use of chloroquine to treat or prevent COVID-19. The FDA has approved it, although at the time of writing they haven’t explained the rationale behind the approval, and as a consequence, patients, institutions and the worried public have demanded immediate chloroquine for all. The resulting rush on chloroquine has led to severe shortages of the drug, and patients taking regular chloroquine or hydroxychloroquine for lupus or other systemic diseases had to stop their treatment due to a lack of supply. This drug has well known, often serious, toxicities;10 we note one small study that was stopped due to potential cardiac complications (https://www.nytimes.com/2020/04/12/health/chloroquine-coronavirus-trump.html), and we suggest it should only be taken in the context of a randomized or other clinical study. This is not to suggest single-arm studies are not helpful: they inform subsequent trials including dosage, duration, and appropriate endpoints. For example, we have observed11 that use of baricitinib for 10 days is associated with viral rebound in nasopharyngeal swabs in rapidly recovered and discharged patients and thus have recommended longer use in the large randomized studies in which it is included; we suggest again that comparisons between different therapies or placebo are likely to yield more informative results than randomized studies comparing 10 days of

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intravenous remdesivir with 5 days (https://benevolent.ai/news/potential-treatment-for-covid-19-identified-by-benevolentai-using-artificial-intelligence-enters-clinical-testing-and https://investor.lilly.com/news-releases/news-release-details/lilly-begins-clinical-testing-therapies-covid-19).

With this in mind, we thoroughly congratulate the authors from Guangzhou, China, who successfully randomized 86 individuals with mild-to-moderate COVID-19 in a 2:2:1 design to lopinavir/ritonavir, arbidol (a broad-spectrum viral infection inhibitor12), or placebo (NCT04252885)13. Because they included only mild-to-moderate patients, the pre-defined primary endpoint was the conversion at day 21 of positive-to-negative PCR tests for SARS-CoV-2 from nasopharyngeal swabs. The real-time reverse-transcriptase PCR (RT-PCR) method used was indeed appropriate as it was performed simultaneously on two target genes, ORF1ab and N, and positive and negative controls were used at each batch. Negative conversion required two separate real time RT-PCR tests separated by 24 h, and the entry criteria for the definition of mild-to-moderate including the absence of pneumonia are entirely appropriate. Baseline criteria between the three groups were well-matched (a criticism of one of the hydroxychloroquine randomized studies is this was not the case13) and follow up was appropriate. Their data helpfully shows there was no difference between any of the groups in the primary endpoint.

In the continuing search for safe and effective new therapies to treat patients with COVID-19, we require well-conducted ethical studies including prospective, randomized, placebo-controlled clinical studies such as this. Although many drugs have predicted in vitro activity against the virus, the proposal that such drugs might provide more benefit than harm is not appropriate with no evidence base supporting efficacy in any patients infected with SARS-CoV-2. A preprint reporting results from a randomized trial of the anti-viral favipiravir versus arbidol in 240 adults has shown no difference in clinical recovery at 7 days, but cough and pyrexia were improved on favipiravir.15 These authors and Li et al. should be applauded for their efforts to add a useful randomized trial to the literature, albeit one that is negative. It is critical to publish such studies. International multicenter trials, such as Discovery (NCT04315948) and Solidarity (EudraCT number 2020-000982-18), will randomize patients with COVID-19 to receive different drugs in adaptive study designs. Such initiatives will provide the best and most relevant data to guide management of patients with COVID-19.

Whether antiviral, immunomodulatory, or antimalarial drugs could be effective in changing the disease course in patients with either mild or severe COVID-19 remains unknown. When patients take these off-label and recover it is not known whether the drug was helpful in the disease course without randomization. Similarly, when patients deteriorate, we do not know if they should be continued or considered clinically ineffective and stopped. Assessing viral loads by PCR on nasopharyngeal swabs, as performed in the trial here, will help clarify the roles of these medicines going forward.

DECLARATION OF INTERESTS

J.S. declares his conflicts of interest at https://www.nature.com/onc/editors (none are relevant here).

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