Journal pre-proof

DOI: 10.1016/j.medj.2020.04.002

What is the best drug to treat COVID-19? The need for randomized controlled trials

Silvia Ottaviani[1], Justin Stebbing[1,*]

[1] Department of Surgery and Cancer, Imperial College, London W12 0NN, UK

*Correspondence to: j.stebbing@imperial.ac.uk

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 and minimize mortality, decrease pressures on intensive care units and health systems and optimally they should decrease subsequent transmission.

At the time of writing, there are no licensed drugs to treat COVID-19 and a search on 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,[4,5] and newer entities but both categories should be given in the context of clinical trials. In Wuhan, China, then the epicentre of the pandemic, Cao *et al*. 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 (ChiCTR2000029308). Patients were randomly assigned 1:1 to receive either lopinavir–ritonavir (400 mg and 100 mg, respectively) twice daily for 14 days, or standard care alone. The primary end point was the time to clinical improvement, defined as the time from randomization to either an improvement of two points on a seven-category ordinal scale or discharge from the hospital, whichever came first.[6] Even though their study showed no benefits with lopinavir–ritonavir treatment beyond standard care, this is exactly the sort of study that best informs our treatment options.

Following this, we were surprised to see the New England Journal of Medicine publishing a single arm study on 61 patients who received at least one dose of remdesevir, again with similar entry criteria of SaO2 <94% on air.[7] Unlike the randomised trial by Cao *et al*., there was no accompanying editorial, but there was a subsequent an open letter discussing remdesevir 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 remdesevir 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.

Randomised 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 very high cure rates. Clearly, recruiting patients recently diagnosed will have 'cure rates' usually in the high 90s%, unless one focuses on recruiting hospitalised 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 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 randomised 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 observed[11] 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 randomised studies in which it is included, and we suggest again that comparisons between different therapies or placebo are likely to yield more informative results than randomised

studies comparing 10 days of intravenous remdesevir 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 randomised 86 individuals with mild-to-moderate COVID-19 in a 2:2:1 design, to either lopinavir/ritonavir, arbidol (a broad spectrum viral infusion inhibitor[12]) or placebo (NCT04252885). 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 genes, and positive and negative controls were used at each batch. Negative conversion required 2 separate real time RT-PCR tests separated by 24 hours, and the entry criteria for the definition of mild-to-moderate including the absence of pneumonia are entirely appropriate. Baseline criteria between the 3 groups were well-matched (a criticism of one of the hydroxychloroquine randomised studies is this was not the case[13]) 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, randomised, 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 randomised trial of the anti-viral favipravir versus arbidol in 240 adults has shown no difference in clinical recovery at 7 days, but cough and pyrexia were improved on favipravir.[14] These authors and Li *et al*. should be applauded for their efforts to add a useful randomised trial to the literature, albeit one that is negative. It is critical to publish such studies. International multicentre trials, such as Discovery (NCT04315948) and Solidarity (EudraCT Number 2020-000982-18), will randomise 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 randomisation. 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 forwards.

Authors' contributions:

S.O. and J.S. wrote the manuscript and approved the final version.

Role of the funding source:

None.

Declaration of interests:

J.S. conflicts can be found at https://www.nature.com/onc/editors but none are relevant to this piece. S.O. reports no conflicts.

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