

## EDITORIALS



## Covid-19 — The Search for Effective Therapy

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Covid-19 is spreading rapidly through Europe and North America, but we have few specific tools to control the growing epidemic and treat those who are sick. We rely on quarantine, isolation, and infection-control measures to prevent disease spread and on supportive care for those who become ill. What we lack is a specific antiviral agent to treat the infected and, optimally, decrease viral shedding and subsequent transmission.

One antiviral-drug candidate is a combination of the HIV protease inhibitors lopinavir and ritonavir. Lopinavir, which acts against the viral 3CL protease, has modest antiviral activity against SARS-CoV-2.<sup>1</sup> Together with ritonavir, which increases drug bioavailability, it is in clinical trials, along with the immunomodulator interferon beta-1b, for the treatment of Middle East respiratory syndrome (MERS) (ClinicalTrials.gov number, NCT02845843). What makes lopinavir–ritonavir particularly attractive is that it is widely available and manufacturable to scale and that it could be prescribed immediately. In fact, there are several case reports and case series where this agent is being used against Covid-19. But does it work?

This is the question that motivated Cao and colleagues to perform an urgent randomized clinical trial of the efficacy of lopinavir–ritonavir in patients with Covid-19 in Wuhan, China, the epicenter of the outbreak.<sup>2</sup> On January 18, the first patient was enrolled in this open-label trial, about a week after SARS-CoV-2 had been identified and sequenced. The investigators recruited patients who had an oxygen saturation of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen to the

fraction of inspired oxygen of less than 300 mm Hg and who were receiving a range of ventilatory support modes, from nothing to mechanical ventilation or extracorporeal membrane oxygenation (ECMO). Enrollment was stratified according to the severity of illness as indicated by the level of ventilatory support administered. All the patients received standard care, and half were randomly assigned to receive lopinavir–ritonavir for 14 days. The primary end point was the time to clinical improvement, defined as the time from randomization to either discharge from the hospital or improvement on a multifactorial set of prespecified criteria, whichever came first. The trial aimed to enroll 160 patients.

This was a heroic effort. Health care workers in Hubei province have provided patient care in an overwhelming epidemic while they themselves are one of the highest risk groups for development of disease. As we saw during the 2014 Ebola outbreak in West Africa, obtaining high-quality clinical trial data to guide the care of patients is extremely difficult in the face of an epidemic, and the feasibility of a randomized design has been called into question.<sup>3</sup> Yet Cao's group of determined investigators not only succeeded but ended up enrolling a larger number of patients (199) than originally targeted.

Unfortunately, the trial results were disappointing. No benefit was observed in the primary end point of time to clinical improvement: both groups required a median of 16 days. But the results for certain secondary end points are intriguing. A slightly lower number of deaths was seen in the lopinavir–ritonavir group, although this observation is difficult to interpret, given

the small numbers and the fact that the standard-care group appears to have been sicker at baseline. Removing deaths in the lopinavir–ritonavir group that occurred after randomization but before the first dose of drug was given would provide a more encouraging result, but such a change is debatable, since no such removal occurred in the control group. On the other hand, the trial was an open-label one, and since the end points were being evaluated or influenced by clinicians who were aware of treatment assignment, they were susceptible to potential bias. It is important to note that both groups were heterogeneous and received various additional treatments, including other pharmacologic interventions such as interferon (11%) and glucocorticoids (34%).

The secondary end points provide both reason for hope and reason for discouragement. The number of deaths was somewhat lower in the group that received lopinavir–ritonavir. Tellingly, though, there was no discernible effect on viral shedding. Since the drug is supposed to act as a direct inhibitor of viral replication, the inability to suppress the viral load and the persistent detection of viral nucleic acid strongly suggest that it did not have the activity desired. Thus, although some effect of the drug is possible, it was not easily observed.

Why isn't lopinavir–ritonavir more effective? Two major factors may be in play. First, the authors chose a particularly challenging population. The patients recruited for the study were late in infection and already had considerable tissue damage (as evidenced by compromised lung function and 25% mortality in the control group). Even highly active antibacterial agents have limited efficacy in advanced bacterial pneumonia. Second, lopinavir simply isn't particularly potent against SARS-CoV-2. The concentration necessary to inhibit viral replication is relatively high as compared with the serum levels found in patients treated with lopinavir–ritonavir.<sup>1,4</sup> We currently know little about drug concentrations in the tissues where SARS-CoV-2 is replicating.

The fact that this trial began within days after the virus was identified and that testing for

infection was developed and deployed very rapidly means that test characteristics had not been fully defined. Notably, 35% of those who screened positive for SARS-CoV-2 by nasopharyngeal swab then tested negative at the day 1 visit by oropharyngeal swab. Was this due to differences in site of assessment, time of illness, testing characteristics, or just the natural evolution of the disease? In addition, 42% of the patients were viral load-positive at day 28, but the quantitative data at that point show that the levels were low, probably near the threshold of detection. Since the test detects nucleic acid, positive results do not necessarily indicate the production of infectious virus. These data suggest that assessing transmissibility after recovery from severe disease will be a priority to help control transmission.

Despite the fact that lopinavir–ritonavir does not seem to be highly effective in patients with Covid-19, there are many important takeaways from this study. The investigators appropriately prioritized speed, designing a trial that could rapidly produce an answer. What we've learned from their work can help inform the design of new trials. And it is clear that rapidly initiated, high-quality randomized clinical trials are possible in epidemic conditions, even in the trying circumstances that prevailed in Wuhan. The results of such trials, providing either convincing positive or convincing negative findings, will be central to clinical care as the dangerous coronavirus outbreak continues.

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

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