CORRESPONDENCE

A Trial of Lopinavir–Ritonavir in Covid-19

TO THE EDITOR: After a review of the findings of Cao et al. (published in the *Journal* online on March 18),[1] many clinicians are abandoning the use of lopinavir–ritonavir for the treatment of Covid-19. We consider this action to be premature. It is crucial to realize that although this trial did not show that the time until clinical improvement was meaningfully better than standard care among patients with severe Covid-19 who received lopinavir–ritonavir, the trial was statistically underpowered to show this outcome. In addition, the analyses of secondary outcomes (which still require confirmation) suggested that lopinavir–ritonavir may be associated with substantial lowering of overall mortality (19% in patients in the lopinavir–ritonavir group vs. 25% in the standard-care group), the risk of severe adverse events (20% vs. 32%), and the risk of respiratory failure or acute respiratory distress syndrome (13% vs. 27%). Lopinavir–ritonavir has shown activity against SARS-CoV-1[2,3] and is available for immediate clinical use in many countries. Because there currently are no approved treatments for Covid-19,[4] and because the pandemic diffusion of SARS-CoV-2 is causing shortages of alternative drugs, we should not yet abandon lopinavir–ritonavir. We therefore advocate that therapeutic guidelines retain lopinavir–ritonavir as a treatment option against Covid-19, pending completion of the World Health Organization SOLIDARITY trial.[5]

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TO THE EDITOR: In a single-center, open-label, randomized, controlled trial, Cao and colleagues conclude that the administration of lopinavir–ritonavir did not result in a shorter time until clinical improvement, lower mortality, or lower SARS-CoV-2 RNA levels than standard care among patients with Covid-19. Antiviral drugs are most effective when they are administered early in an infection,[1] yet the patients in this trial underwent randomization a median of 13 days after disease onset. Initiating therapy earlier may be more effective, since systemic hyperinflammation rather than viral pathogenicity dominates later stages of SARS-CoV-2 infection.[2]

The enrolled population had severe disease, with an overall mortality of 22%, a factor that may have contributed to the poor effect associated with lopinavir–ritonavir and the high discontinuation rate (14%) because of adverse events. In addition, concurrent therapies were not controlled: one in three patients received glucocorticoids, although the use of these drugs is not recommended,[3] since they have been associated with a delay in clearance of other coronaviruses.[4] This use may have contributed to the absence of an observed effect on viral loads.

The lopinavir–ritonavir combination is relatively safe and could be easily mobilized against Covid-19. Given the urgent need for evidence-based pharmacotherapies, we should not shut the door on further randomized, controlled trials of the early use of this combination drug in other populations.

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TO THE EDITOR: Thomas Edison once said, "I have not failed, I only found another way that did not work." I thank Cao and colleagues for showing an intervention with lopinavir–ritonavir in Covid-19 management that did not work. Their study, undertaken in desperate times, arguably started patients on medication later than we would today (median, 13 days after symptom onset). In addition, their primary end point (speed to symptom resolution) may not be the best end point, given our knowledge of the natural history of SARS-CoV-2. The survival analysis in the lopinavir–ritonavir group included three patients who never received the medication; after the exclusion of these patients, there would be an absolute increase of almost 10 percentage points in 28-day survival. In addition, a shorter length of hospital stay and time until discharge was observed, although the finding was not statistically significant. With limited access to ventilators and shortages of personal protective equipment, decreasing the length of hospitalization, even by only a day or two, would bring benefits to a distressed health system. We will probably not find a magic bullet for Covid-19 soon, and we should work toward incremental clinical improvements from off-the-shelf interventions evaluated in similar trials.

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TO THE EDITOR: In the trial of lopinavir–ritonavir involving patients with severe Covid-19, Cao et al. conclude that no benefit was observed for the drug combination beyond standard care. This conclusion can certainly mislead clinicians, and a critical appraisal needs to be performed together with an exercise of logic. The results of a trial may have no statistical significance, but signals are important if the sample size is small. In this case, such signals among the patients who received lopinavir–ritonavir were a shorter stay by 5 days in the intensive care unit, a difference of 15.5 percentage points in clinical improvement by day 14, and a lower incidence of 28-day mortality by 5.8 percentage points. To know the appropriate sample size from the raw data of the trial, we must implement the formula for the comparison of two mortality rates.[1] Thus, a sample size of 800 patients would be needed to provide the trial with a statistical power of 80%. No strong conclusions can be made until a trial with the correct sample size has been performed.

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TO THE EDITOR: At this dire time in which the scientific community is fighting to mitigate the pandemic caused by SARS-CoV-2, Cao et al. conclude that lopinavir–ritonavir was not associated with clinical improvement over standard care. However, it must be pointed out that this conclusion is a classic example of "absence of evidence is not evidence of absence,"[1] unless we were to consider that a difference in survival of 17 percentage points (the lower limit of the confidence

interval for the between-group difference of 5.8 percentage points in 28-day mortality) is inconsequential. We digitalized and reanalyzed the data with a Bayesian Cox proportional-hazards model[2,3] and found that there was a 73% posterior probability of a clinical improvement of more than 15% and a 17% probability that the effect was in a region of practical equivalence. Since this trial was underpowered, the results do not sustain the conclusion that lopinavir–ritonavir was ineffective. This drug combination has a well-known safety profile, and in vitro data indicate that it is active against coronavirus.[4] At this critical time, even a modest advantage can entail greater availability of crucial material, such as respirators and beds in the intensive care unit.

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THE AUTHORS REPLY: Since the publication of the results of our lopinavir–ritonavir trial, we have received emails from around the world. In most of these messages, the correspondents mainly interpreted the results of our trial as showing that lopinavir–ritonavir did not have a beneficial effect. We appreciate the comments of the wise clinicians regarding the uncertainty that remains concerning the clinical effectiveness of lopinavir–ritonavir in Covid-19. Results that are based on different analyses of the data have shown dissimilarity for the primary outcome (time to clinical improvement), which suggests that we should be very cautious in the interpretation of our findings.

In the modified intention-to-treat analysis, after the exclusion of three patients who died within 24 hours after randomization and did not receive lopinavir–ritonavir, the time to clinical improvement in the lopinavir–ritonavir group was 1 day shorter than that in the control group. One of the underlying reasons for the lack of statistical significance in the intention-to-treat analysis may have been the small sample size. Furthermore, as several of the correspondents have pointed out, the patients whom we enrolled were severely ill, with a median interval of 13 days between symptom onset and drug administration. The treatment course and dose may not have been optimized. Judging from the preliminary observations in this trial that approximately 45% of the patients in the lopinavir–ritonavir group had positive RNA detected on day 14, we speculate that some patients may need an extended administration of antiviral drugs or that the negative conversion of RNA testing should be considered as a criterion for stopping antiviral treatment.

Given the complex nature of Covid-19, we recommend that clinicians review all the data about all the outcomes in our trial (including those provided in the Supplementary Appendix, available with the full text of our article at NEJM.org) before making any clinical decisions regarding treatment. On the basis of the results regarding different outcomes and alternative data analyses, lopinavir–ritonavir may still be a potential therapeutic agent against Covid-19. The World Health Organization is launching a large study with lopinavir–ritonavir as one of the treatments.[1] We believe that additional trials with a larger sample size involving patients with milder disease, earlier drug administration, and an extended treatment course may be helpful in further evaluating the effectiveness of lopinavir–ritonavir against Covid-19.

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Since publication of their article, the authors report no further potential conflict of interest.

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