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Whether to make decisions ön the flyŕegarding treatment for SARS-CoV-2 infection☆

Tomar o no tomar «decisiones en caliente» respecto al tratamiento de la infección por SARS-CoV-2

Dear Director,

The outbreak of the COVID-19 pandemic is a challenge of enormous dimensions for healthcare professionals, public health, and politicians.

As of April 5, 2020, official figures revealed that there were 135,032 people infected, 13,055 deaths, and 59,662 patients hospitalized (https://covid19.isciii.es/). We lived through convulsive days in which treatment protocols for COVID-19 infection were modified practically daily based on new evidence and the need to optimize the scarce therapeutic arsenal available.

Just three weeks ago, we learned the results of a clinical trial that compared lopinavir/ritonavir to supportive treatment in severe patients hospitalized with COVID-19 infection whose primary outcome was time until clinical improvement.[1] The poor overall results in terms of clinical response and mortality led, in just a few hours, to a rare wave of pessimism among the groups of professionals in charge of making decisions in many hospitals. This was reflected in heated discussions via WhatsApp and other forums, leading to the abrupt removal of lopinavir/ritonavir from the treatment protocols of several large centers in our country.

Nevertheless, the result of the information from a trial such as that one must be taken cautiously and analyzed with a critical, rigorous eye. The work suffers from various methodological problems in the design and in patient recruitment related to the urgent nature of the work. The authors themselves recognize these aspects in the discussion. Patient assignment was not blind and the desirable placebo control was not able to be established for patients who did not receive the drug in said study. Likewise, plasma levels of lopinavir/ritonavir were not able to be determined and could have been compromised in critical patients.

On the other hand, the study lacks power for outcomes that are secondary in the design, but which are important, such as mortality. Assuming the same premises as for the principal variable, between 200 and 860 additional patients would have been needed in each arm to demonstrate differences. In addition, although the overall benefit was weak, a close reading allows for observing how the use of lopinavir/ritonavir could point towards a trend in mortality reduction if it is used in the first 12 days. Among patients

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treated earlier, the primary objective was indeed achieved, with respective mortality of 15% versus 27% in each arm. What's more, the other secondary aims, such as a stay in the intensive care unit (5 days of difference) and the percentage of patients who developed ARDS (12% versus 24%), were also improved.

In our opinion, the fundamental issue is that patients were treated too late (median of 13 days from onset of symptoms) and in monotherapy. Therefore, although it did not achieve the primary aim, the results indicate that the treated group could progress better. Therefore, it remains to be determined if the use of lopinavir/ritonavir in the earliest phases and/or in combination with other potentially active drugs would benefit patients or not.

Nevertheless, we are aware of the lack of trust that protease inhibitors and their limited in vitro activity generate and in their clinical efficacy in this novel coronavirus and in others (SARS-CoV, MERS-CoV).[2,3] The controversial results of this study had already in part been anticipated in another Chinese study,[4] which did not demonstrate a benefit to treatment with lopinavir/ritonavir and abidol. Furthermore, Janssen has reported unpublished data on the inefficacy of darunavir/cobicistat in the treatment of 30 patients with COVID-19.[5]

Even so, while awaiting new evidence or consolidated alternative therapies, it seems prudent to continue using the optimize form of the few drugs we do have available.

In catastrophic times, it is important to keep a cool head and even keel when it comes to making decisions that may determine a patient's prognosis.

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