Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Microbiology, Immunology and Infection (2020) 53, 674—675

Available online at www.sciencedirect.com

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journal homepage: www.e-jmii.com

Perspectives

Lopinavir/ritonavir use in Covid-19 infection: is it completely non-beneficial?

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Received 23 April 2020; accepted 17 May 2020
Available online 25 May 2020

KEYWORDS
Lopinavir-ritonavir;
COVID-19

Abstract Covid-19 infection caused by the novel coronavirus SARS-COV-2 continues to be a major global health challenge. Till date, no drug has been approved for the treatment of this infection. A number of medications have been proposed and there are ongoing clinical trials around the world to find a suitable treatment. A recent randomised control trial compared lopinavir/ritonavir with standard care among 199 patients with severe Covid-19 infection and concluded that there was no significant reduction in mortality rate with lopinavir/ritonavir. However, there are a few important lessons which may be learnt from the study apart from the statistical reduction in mortality rate. There was a numerical reduction in mortality rate, less intensive care unit stay and less complications in the lopinavir-ritonavir group. This article points out some of those important lessons with some suggestions for future clinical trials.

Finding the right treatment for the novel coronavirus SARS-COV-2 which causes Covid-19 infection continues to be a major challenge. Infection and mortality rates are increasing on a daily basis. As at 23rd April 2020, there are over 2.7 million reported cases with over 189,000 deaths worldwide.[1] A few candidate medications have been evaluated but none has been approved so far with clinical trials still going on in different parts of the world.

One of the medications which has been proposed is lopinavir-ritonavir which is a combination of protease inhibitors commonly used in the treatment of HIV infection. There was a recent publication of a randomised control trial (RCT) by Cao et al.[2] which compared lopinavir-ritonavir with standard care in the treatment of hospitalised adults with severe Covid-19 infection. The investigators did a brilliant and commendable job of planning and executing this RCT and recruiting 199 patients within a short time in such a difficult and challenging time.

The study reported that treatment with lopinavir-ritonavir was not associated with a difference in time to clinical improvement when compared with standard care and that mortality was similar in both groups. The study therefore concluded that there was no benefit observed

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https://doi.org/10.1016/j.jmii.2020.05.014

with lopinavir-ritonavir beyond standard care in hospitalised patients with severe Covid-19 infection.

Lopinavir-ritonavir is a readily available and relatively cheap medication. It is on the World Health Organisation's list of essential medicines. It was previously shown to be effective against SARS infection in humans and MERS-CoV infections in animal models.[3,4] The findings of this study may be a discouragement for the off-label use of lopinavir-ritonavir in the current pandemic. However, before we abandon the use of lopinavir-ritonavir based on the evidence from this study, there are a few lessons to be learnt which can influence clinical decision making and direct the focus of future research.

Although there was no statistically significant difference in mortality rates between the two groups, the lopinavir-ritonavir group had a numerically lower mortality rate which was 5.8% lower than the standard care group. A closer look at the data showed that 5 of the 99 patients randomised to the lopinavir-ritonavir group did not actually receive the medication with 3 of them dying within 24 h of enrolment. With a modified intention-to-treat analysis, mortality rate in the lopinavir-ritonavir group could actually be lower by up to 8.3%. While the 5.8% reduction in mortality rate is not statistically significant among 199 patients, if 1000 patients had been recruited and the same result obtained, this would have been significant. Given the high rate of mortality from the current pandemic, the finding of a 5.8% (or potentially 8.3%) lower mortality rate cannot be overlooked.

Another important finding of the trial was that patients in the lopinavir-ritonavir group had a shorter stay in the intensive care unit (ICU) with a median of 6 days compared to 11 days for the standard care group. This is certainly important in the current pandemic, given the fact that resources and ICU beds are currently being stretched to the limits. Equally important is that patients in the lopinavir-ritonavir had shorter hospital stays. It is also noteworthy that there were fewer patients with serious complications such as acute kidney injury, secondary infections and respiratory failure in the lopinavir-ritonavir group. These findings are important and mean that use of lopinavir-ritonavir is likely to free up more human and material resources.

Gastrointestinal adverse events were more common among patients in the lopinavir-ritonavir group and in fact, treatment had to be stopped early in some patients due to these side effects. Lopinavir-ritonavir is known to have gastrointestinal side effects but it is generally well tolerated. It is possible though that some of the gastrointestinal symptoms experienced could be attributable to the infection as evolving evidence suggests.[5]

This particular cohort of patients had a high mortality rate of 22.1% suggesting that they were very ill. Indeed, the criteria for enrolment into the study suggest this. The median time from onset of symptom to randomisation was 13 days, meaning that theoretically, patients eventually assigned to the lopinavir-ritonavir received standard care in the first 2 weeks of the illness before their randomisation. We speculate that clinical outcome may have been better if patients were commenced on treatment earlier. This hypothesis will hopefully to be investigated in future clinical trials.

Curiously, countries with a high number of HIV infections have not reported particularly high rates of Covid-19 infection or its associated high mortality rates. There may be a number of explanations for this. However, it is known that people who have co-morbidities or who are immunosuppressed are at risk of worse outcomes with Covid-19 infection. While HIV infected patients are particularly prone to having opportunistic lung infections and many have other co-morbidities, could the effect of lopinavir-ritonavir be contributive to the lower infection and mortality rates in these countries? This remains to be determined.

While we do not support jettisoning evidence-based medicine, there are a few lessons to be learnt from this study beyond the statistical difference in mortality rates. Before an appropriate treatment is found, we suggest that patients should be given all the information available and allowed to make informed decisions. We also suggest that clinicians using lopinavir-ritonavir as an off-label treatment for Covid-19 should consider starting it earlier rather than later in the course of the illness. The results from other clinical trials would also be useful to decide whether or not to abandon the use of lopinavir-ritonavir in Covid-19 infections.

Declaration of Competing Interest

None declared.

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