Letter to the Editor

Clinical Trials Approaching Antiviral Agents Use Against SARS-CoV-2: Reliable Studies or Drug’s Cemetery?

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The emergence of COVID-19 led to the development of various vaccines at an unprecedented rate. Due to massive vaccination, the pandemic has started to change, reducing the cases and deaths related to COVID-19. Despite the massive contribution of vaccines, drugs, such as antivirals, are still essential in the containment of severe cases and deaths from COVID-19. However, this same rapidity in vaccine development was not observed in the antiviral agents’ discovery against SARS-CoV-2.

Studies showed that viral load from upper respiratory tract specimen swabs in COVID-19 seems to decline during the first week of infection, extending the decline to the end of the second week, and may extend until the end of the third week. Nevertheless, successfully cultivating SARS-CoV-2 occurs between the first and the fifth days of symptom onset and peaks on the third day. Although a study has found a cultivable virus in 9% of the patients with severe COVID-19 after the second week of symptoms onset, this is not the only factor that explains the mortality since the mortality rates are 54.64% among severe COVID-19 cases and 5% among mild to moderate COVID-19.

Furthermore, antiviral drugs inhibit viral development, so treatment must be started during the viral replication period. Therefore, detection of viral load after a long period of symptom onset can mean viral debris instead of a virus competent for replication, making it impossible to assess the effectiveness of the antiviral drug.

Since the emergence of COVID-19, three hundred and eleven (311) randomized clinical trials approaching antivirals used to treat patients with COVID-19 have been registered on ClinicalTrials.gov until December 23, 2021. Of these, seventy-five (24.1%) describe eligibility criteria with confirmation of COVID-19 through a molecular test 2 to 14 days before randomization. However, the duration of symptoms is not clear. Finally, one hundred and six-four (52.7%) studies do not mention any time of the disease.

Some studies involving remdesivir use in patients with COVID-19 showed decreased clinical recovery time, especially when started within ten days of the symptoms onset, and a lower risk of serious adverse events with a certain degree of uncertainty and divergent results. However, if these studies diverged on the safety and clinical recovery of patients with COVID-19 infection, they are unanimous in concluding that the remdesivir group has no difference from the control group in mortality and viral load. If we observe, these studies have a significant variation in the duration of symptoms of the recruited patients (the mean duration of symptoms varied from 7 to 14 days).

Therefore, many clinical trials do not have well-established criteria for patient inclusion. This suggests that many patients started treatment with the antiviral agents after the virus replication period. Antivirals administration from the second week onwards would be helpful only for some patients with severe illnesses.

Studies approaching respiratory infectious diseases have shown that antiviral treatment increases viral clearance and clinical recovery when started within the first four days of illness. In addition, a randomized clinical trial that recruited unvaccinated adults with COVID-19 for treatment with molnupiravir started five days after the onset of signs or symptoms found a lower risk of death in the treatment group compared to the placebo. Another study involving hospitalized adults with COVID-19 treated with nirmatrelvir plus ritonavir within three days after symptom onset showed decreased progression to severe disease and quickly reduced SARS-CoV-2 viral load.

Thus, studies that assess the efficacy or effectiveness of antiviral drugs against SARS-CoV-2 or other future respiratory infectious diseases should establish defined criteria regarding the duration of patients’ symptoms. Randomized controlled trials to assess antiviral agents’ efficacy in COVID-19 patients should at least recruit an arm within five days of symptom onset.

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Abbreviations: COVID-19, coronavirus disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Conflict of interest

The author declares that there are no competing interests.

Author contributions

PRB: conceptualization, literature search, study design, data collection, manuscript preparation, and manuscript review.

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