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Timing of anti-viral therapy in COVID-19: key to success

To the Editor

Since the onset of the current coronavirus disease 2019 (COVID-19) pandemic, there have been attempts to identify medications for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As there have been no antivirals available for the treatment of this disease, repurposing of drugs has started and various classes of drugs are being tried. Some of the candidate drugs include remdesivir (recently approved by Food and Drug Administration), ivermectin, and interferon β-1b. There is emerging evidence regarding the efficacy of these drugs; however, no definite conclusions are available. A recent study by Shi et al. reported results about the efficacy of antiviral therapies in patients with coronavirus disease 2019 (COVID-19) in China and found no significant impact on improvement [1]. Similar results were reported in a recently published randomized controlled trial (RCT) about the use of interferon β-1a in patients with severe coronavirus disease 2019 (COVID-19) and found no significant difference in the time to clinical response in the experimental arm as compared to the control arm [2]. However, there are a few aspects regarding the timing of the initiation of antivirals which require discussion. In both of these studies, the authors have not reported the timing of initiation of antiviral therapy, which is crucial to patient outcomes. We all understand that the host's immune response plays a crucial role in the prevention as well as containment of any infection; however, when an antiviral agent is sought for patients with disease or for patients who are at risk of severe disease, it should be done in a timely manner [3]. COVID-19 has an initial virological phase which leads the patients into a host inflammatory response phase where they tend to develop a cytokine storm [4]. Based on the report by Wölfel et al. [5] which states that the virus cannot be isolated beyond day 8, it is also likely that antivirals may not be efficacious beyond this time. Thus, it would be best to use antiviral medications relatively early in the illness and anti-inflammatory drugs later. Using antiviral drugs later in the disease course may add to the adverse effects rather than yielding clinical benefits. In the study by Effat *et al.* [2], the mean (standard deviation, SD) duration of starting treatment in the interferon arm was 11.7 (5.71) days. This late initiation of antiviral therapy may be the reason behind no difference in time to clinical response, which was the primary endpoint. However, there was a difference with respect to the percentage of patients being discharged by day 14, favouring the interferon group. Such a result may be owed to the properties of interferon, which endorses more than just an antiviral mechanism (i.e. decreasing vascular leakage and inflammatory biomarkers like IL-6) [6, 7]. They also reported that starting interferon treatment early in the course of the disease showed mortality benefit (odds ratio, 13.5; 95% confidence interval 1.5 to 118) which further emphasizes the importance of early initiation of therapy [2].

Table 1 enlists some noteworthy trials in COVID-19 regarding the use of antiviral medications and timing of treatment initiation for the outcome reported. Remdesivir showed no benefit when treatment was started after ten days of illness. Instead, it was associated with higher

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Table 1. List of studies with use of antivirals and outcomes reported

Author	Drug	Number of patients	Study design	Day of initiation of treatment from symptom onset	Outcome in comparison to control or standard of care
Wang *et al.* [8]	Remdesivir	237	RCT	11	No benefit Patients started on treatment within 10 days had decreased mortality (11%) vs patients having treatment started after 10 days (14%)
Spinner *et al*. [9]	Remdesivir	584	RCT	8	Higher odds of a better clinical outcome with those randomized to standard care (OR 1.65; 95% CI 1.09–2.48; p = 0.02)
Beigel *et al*. [10]	Remdesivir	1063	RCT	9	The remdesivir group had a shorter time to recovery (median, 11 days, as compared with 15 days; rate ratio for recovery, 1.32; 95% CI 1.12 to 1.55; p < 0.001)
Cao *et al*. [11]	Lopinavir-ritonavir	199	RCT	13	No benefit
Hung *et al.* [12]	Interferon beta-1b, lopinavir–ritonavir, and ribavirin	127	RCT	5	Significantly shorter median time from start of study treatment to negative nasopharyngeal swab in treatment group (7 days [IQR 5–11]) than the control group (12 days [8–15]; HR 4·37 [95% CI 1.86–10.24], p = 0.0010) Clinical improvement was better in the combination group
Zhou *et al.* [7]	Interferon alpha	77	Non randomized	8	Significant accelerated viral clearance (p = 0.002), and reduced circulating levels of IL-6 ($p = 5.7 \times 10^{-10}$) and CRP (p = 0.002)

CI — confidence interval; CRP — C-reactive protein; HR — hazard ratio; Il-6 — interleukine 6; IQR — interquartile range; OR — odds ratio; RCT — randomized clinical trial

mortality than the control arm [8]. However, when used within ten days, it tended to show benefits in other trials [9, 10]. Most other trials tend to start antivirals late and have reported no clinical benefits with their use.

This brings us to essential questions of whether these drugs, if initiated early, can lead to clinical benefits, and whether or not these negative trials are giving us a false portrayal of their efficacy. Based on the available evidence, we suggest that antivirals should be initiated within the first ten days of illness, especially in research settings. In this COVID era, with the limited therapeutic options available to physicians, the appropriate and timely use of therapy can help save lives.

Conflict of interest

None declared.

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