Is It Time to Revisit Remdesivir Use for Severe COVID-19?

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During the coronavirus disease-2019 (COVID-19) pandemic, early reports from China,[1] subsequently Italy[2] and other countries suggested that patients with pre-existing cardiovascular diseases, hypertension, and diabetes were at a greater risk of developing severe disease and requiring intensive care unit (ICU) admission. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus was also found to affect the cardiovascular system resulting in endothelial dysfunction and myocardial damage.[3,4] The mechanism of damage has been attributed to either direct injury by the viral invasion of cells or indirect injury *via* inflammatory cytokines.

The direct injury was attributed to infiltration of the myocardium by the virus resulting in lysis of the myocyte, subsequent inflammation, and myocarditis. However, autopsy data has shown conflicting results. Systematic reviews of postmortem histopathological data showed that while cardiac abnormalities were common in patients dying due to COVID-19, specific changes of acute myocarditis were extremely uncommon.[5,6] While the viral invasion ranges from 47–60% of the cases, typical features of myocarditis are infrequent. The data from early 2020 has indicated that myocardial edema and myocardial necrosis are among the most common postmortem features.[5,6] The most common acute findings have been found to be thrombosis, cardiac ischemia[5] and the presence of microthrombosis.[6] The increased incidence of coronary events has been attributed to rupture of pre-existing plaques, procoagulant state, and endothelial dysfunction resulting in coronary blockage and occurrence of acute ischemic cardiac events. There have been reports of elevated troponin levels at admission and their association with the severity of disease and mortality.[3,4]

An indirect injury has been attributed to cardiac stress as a result of a severe inflammatory systemic response which can add to cardiac inflammation, worsened by the presence of respiratory failure and hypoxia. This is further aggravated by supply–demand mismatch and vasospasm.[6]

Specific therapies such as aspirin and therapeutic anticoagulation have been used in an attempt to reduce the morbidity associated with the pro-thrombotic and procoagulant state in COVID-19. The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial showed no significant 28-day mortality benefit with aspirin use in patients hospitalized with COVID-19. However, there was a small increase in being discharged alive at 28 days.[7] Therapeutic anticoagulation also showed no significant benefit in reducing 28-day mortality in COVID-19.[8] Neither of these therapies is currently recommended due to insufficient evidence of benefit.

While corticosteroids have shown a significant mortality benefit in COVID-19,[9] questions have been raised regarding the safety profile of steroids in patients with heart failure. A retrospective

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cohort study showed that the use of steroids in COVID-19 patients with heart failure was associated with greater in-hospital mortality and adverse outcomes.[10] Steroids have also been used in patients with COVID-19-related myocarditis;[11] however, there are no large studies to support this indication for their use.

Thus, despite gaining insight into the pathophysiology of the cardiac manifestations of COVID-19, no targeted therapies have been developed.

Remdesivir was given emergency authorization for use in severely ill COVID-19 patients on 1 May 2020. Since then, while some studies have shown reduced time to recovery,[12] the World Health Organization (WHO)-sponsored Solidarity trial[13] and subsequent meta-analysis[14] have showed no mortality benefit and no impact on clinically important outcomes, respectively.

The retrospective study conducted by Panda et al.[15] looks primarily at the effect of Remdesivir on the occurrence of Major Adverse Cardiac Events (MACE) in critically ill patients with COVID-19. This has not been addressed in the previous studies. The study shows a significant reduction in mortality due to MACE with Remdesivir use. The study also highlights the increased mortality seen in patients who suffer from MACE in the presence of severe COVID-19. The study concludes that Remdesivir administration results in mortality benefit and reduced MACE; its findings, while encouraging, must be treated with caution. The retrospective nature of the study means there may be unknown confounders affecting the outcome of the study. While there was a reduction in MACE-related deaths, there was no significant difference in overall deaths between the two groups. There was also significant heterogeneity between groups with respect to the presence of chronic diseases such as chronic kidney disease and chronic obstructive pulmonary disease (COPD).

There are still proponents of Remdesivir who feel that its benefit is related to its timing.[16,17] The median time to Remdesivir was 9 days in the Adaptive COVID-19 Treatment Trial-1 (ACTT-1) trial and around 43% of patients were enrolled more than 10 days

following the onset of symptoms.[12] This data is not available for the Solidarity trial. In a retrospective study, Mehta et al. analyzed outcomes with Remdesivir use with respect to symptom onset to Remdesivir treatment (SORT). They reported that patients with SORT time of below or equal to 9 days had lower all-cause mortality.[17] It is pertinent to note that in the study by Panda et al the mean time from onset of symptoms to ICU admission was 5.9 ± 3.5 days in the Remdesivir group. Even if we assume that all of them received Remdesivir on the day of admission, to conclude that early Remdesivir resulted in improved outcomes, would be a matter of pure conjecture. Future large trials focused on these aspects of Remdesivir use, that is, the timing of administration and impact on MACE and mortality are necessary to answer these questions.

Remdesivir received its approval in India for use in the treatment of severe COVID-19 patients on 20 June 2020. Following this and the subsequent increase in the number of COVID-19 cases, there was a sudden surge in demand resulting in a massive shortage and desperate attempts to procure the drug from any possible source, giving rise to black marketing of the drug.[18] This was despite the fact that its adverse effect profile was not well-characterized as its use till then had been extremely limited. In the aftermath of the early days of the pandemic, Jung et al. analyzed data from Vigibase, a WHO global database of individual case safety reports (ICSRs), which is the largest pharmacovigilance database. They found a greater prevalence of bradycardia, hypotension, and cardiac arrest with the use of Remdesivir as compared to other COVID-19-related drugs.[19] This has been attributed to its metabolite, which is an adenosine analog. Adenosine can result in transient atrioventricular (AV) block and may have possible arrhythmogenic potential. It can also cause vasodilatation and subsequent hypotension.[20] It is pertinent to note that cardiac manifestations seen in severe COVID-19 may be potential confounders while monitoring for cardiovascular toxicity of Remdesivir. Even so, the possible cardiac side effects of Remdesivir should be kept in mind while deciding to administer the drug.

This study raises some important questions regarding Remdesivir use in severe COVID-19. However, large, randomized, prospective trials with the use of advanced imaging tests like cardiac magnetic resonance imaging (MRI) and biopsies when indicated, are necessary to fully understand the role of Remdesivir. This is necessary to gain further insight regarding the effect of Remdesivir on mitigating adverse cardiovascular events and resultant mortality due to COVID-19.

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