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Editorial

Remdesivir: Remedy the world is waiting for?

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As the world grimly attained a somber landmark of 10 million cases and nearly 500,000 coronavirus disease 2019 (COVID-19) deaths globally on June 29, 2020, there is a desperate race for a specific antiviral drug. In the beginning of May 2020, the United States Food and Drug Administration (US FDA) issued an emergency use authorization for the investigational antiviral drug remdesivir for the treatment of suspected or laboratory-confirmed COVID-19 in hospitalized adults and children with severe disease.[1] The existing evidence about the safety and efficacy of remdesivir use in hospitalized patients with COVID-19 is scant and evolving, although recently reported analysis of preliminary data depicted the shortening of the time to recovery. Remdesivir was discovered and developed by Gilead Sciences in 2016 for treatment of Ebola infection. Remdesivir is a monophosphoramidate prodrug and an adenosine analog and is known to possess broad-spectrum antiviral activity.[2] The active metabolite GS-441524, which is a triphosphate analog, competes for incorporation into nascent RNA chains owing to severe acute respiratory syndrome coronavirus (SARS-CoV) 2 RNA-dependent RNA polymerase activity, resulting in delayed chain termination during viral RNA replication.[3] The drug is also known to evade the intrinsic viral proofreading mechanism owing to exonuclease activity, causing decreased viral RNA production.[3] The anti−SARS-CoV activity of remdesivir is demonstrated by various in vitro studies, with the inhibition of different coronaviruses such as SARS-CoV, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), Bat Coronaviruses, and the circulating contemporary human CoV.[3,4] Moreover, an *in vitro* study has demonstrated the antiviral activity of remdesivir against various strains of Ebola virus;[5] a similar effect has also been demonstrated in non-human models (rhesus monkey) of Ebola virus disease.[6] Furthermore, the broad-spectrum antiviral effect of remdesivir has been reported against various other viruses such as Marburg virus, the Paramyxoviridae group of viruses (viz, Nipah virus, Hendra virus, measles virus, mumps virus, and parainfluenza type 3 virus), and the Pneumoviridae group of viruses (viz, respiratory syncytial virus).[7] However, the benefit of *in vitro* data need not necessarily translate into clinical efficacy as substantiated by a randomized controlled trial that demonstrated significant worse mortality in the group treated with remdesivir (53% vs 35%, respectively) compared with the group treated with three different antibody treatments. The investigators attributed the increased mortality in the remdesivir arm to the enrollment of more patients with severe condition at the baseline.[8]

Among the clinical studies, the earliest evidence for the use of remdesivir in COVID-19 was reported in a placebo-controlled trial from China, in which a total of 237 patients older than 18 years from 10 hospitals in the city of Wuhan were recruited. The investigators concluded that "remdesivir was not associated with statistically significant clinical benefits." The authors also reported numerically more (66% vs 64%) adverse events such as constipation, hypoalbuminemia, and hypokalemia among the patients in the remdesivir group;[9] however, the study was prematurely terminated owing to difficulty in recruiting new patients with COVID-19 as the outbreak in China came under control.[9]

The developer of remdesivir Gilead Sciences has reported the short-term outcomes of the compassionate remdesivir use program from three continents. In more than 20 hospitals, 53 patients with COVID-19 were treated with at least one dose of a 10-day course of intravenous remdesivir. At the baseline, patients with severe disease were either on ventilator (30 patients) or extracorporeal membrane oxygenation (4 patients). After a median of 18 days, 47% (25/53) of patients were discharged, and 13% (7/53) of patients succumbed to disease. But the patients with milder disease, who were not on ventilator support, showed lesser mortality (5%). The overall probability of improvement of patients was about 68% by 18 days. Around

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60% (32/53) of the study patients had at least one adverse event, and 23% (12/53) experienced serious adverse events.[10] It is pertinent to note that this is a collated data from the compassionate use program in which remdesivir was provided free of cost by the drug manufacturer. Various factors such as small cohort size, short duration of follow-up, potential missing data considering the nature of the drug usage in the program, and non-randomized uncontrolled setup are the serious limitations of outcome data.[10] Another open-label phase 3 trial (SIMPLE) by the same manufacturer on patients with severe COVID-19 demonstrated similar improvement with 10-day treatment course of remdesivir compared with a 5-day regimen (odds ratio = 0.75 [95% confidence interval {CI} = 0.51–1.12]).[11]

The recent double-blind randomized, placebo-controlled trial funded by National Institute of Allergy and Infectious Diseases, which assessed the effect of intravenous remdesivir in 1059 patients (538 patients assigned to the remdesivir group and 521 assigned to the placebo group), has provided the more reliable evidence for remdesivir safety and efficacy. The preliminary results showed that those who received remdesivir showed a median recovery time of 11 days compared with 15 days in those who received placebo ($p < 0.001$). There is indication of survival benefit by 14 days, as shown by a mortality of 7.1% with remdesivir and 11.9% with placebo (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04, $p = 0.059$). Serious adverse events were reported in 21% of the patients in the remdesivir group compared with 27% in the placebo group. This is the first randomised control trial (RCT) to report the superiority of remdesivir over placebo in shortening the time to clinical recovery in hospitalized adult patients with COVID-19 and lower respiratory tract infection.[12]

The safety profile of remdesivir has not been studied adequately; apart from the RCT mentioned previously, there is no other literature investigating the adverse drug profile and drug–drug interactions. The manufacturer safety data indicate the dosage needs to be adjusted in hepatorenal impairment, although no study has been conducted in this regard. Robust clinical trials are designed and being conducted across the world, many of which comprise valid safety end points; these studies may provide credible data on safety.

The more recent World Health Organization interim guidance on clinical management of COVID-19 released on May 27, 2020, clearly mentions that many drugs under investigation including remdesivir should not be used for treatment and prophylaxis outside the purview of clinical trials, unless the national authorities or local expert bodies suggest it as per the adequate preclinical or clinical data available.[13] In the wake of high need for specific chemotherapy, on June 1, 2020, the Drug Regulatory Authority of India has granted the "restricted emergency approval usage" in hospitalized patients with COVID-19, with a condition of 5-dose administration.[14] The latest dynamic national guidance document on COVID-19 clinical management published on July 3, by Ministry of Health and Family Welfare mentions remdesivir as investigational therapy to be considered in patients with moderate disease (those on oxygen) as a 5-day intravenous administration.[15]

Although the earliest evidence that emerged was not so favorable for remdesivir, the more recent interim data from a well-designed study indicated the promising efficacy in terms of clinical recovery. Few countries including India have granted the emergency use of remdesivir in hospitalized patients. Henceforth, the wider use of this drug in patients with moderate/severe disease is expected to generate abundant empirical data. Various ongoing clinical trials are also expected to provide robust evidence.[16,17,18] Albeit cautious optimism should be the cornerstone in these unprecedented times of emergency usage of this drug, overwhelming reactions and responses to interim data analyses and preliminary published results are warranted as new, robust, and clear-cut evidence is expected to emerge in the next few weeks.

Disclosure of competing interest

The authors have none to declare.

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