Remdesivir and COVID-19: Justified in Emergency Use Authorization?

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May 20, 2020

Abstract

Since the advent of COVID-19 as a pandemic, multiple therapeutic options have been looked into as possible options for the management of COVID-19 disease. Remdesivir, a broad-spectrum anti-viral, has since been given Emergency Use Authorization by the US Food and Drug Agency (FDA). While cohort studies have shown benefit in the use of Remdesivir, the only Randomized Controlled Trial showed no statistically significant clinical benefit, and the other results from a trial by the NIH has only shown some benefit in reducing hospital admission in early results prior to peer review. In this scenario, with data lacking, is it justified for Remdesivir to be given Emergency Use Authorization?

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Keywords: COVID-19, Infectious Diseases, Therapeutics, General Medicine, Epidemiology

Word Count: 1171

Introduction

The novel coronavirus 2019 (2019-nCoV), officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a newly-emerged human infectious beta-coronavirus. Since December 2019, it has spread rapidly, firstly in China, and then worldwide. By early May, over 4 million confirmed cases were found worldwide, with over 280,000 deaths. Due to the novel nature of the virus, there were no proven therapeutics. Multiple conventional anti-viral medications were trialled. However, during clinical treatment of the COVID-19, it has been found that neuraminidase inhibitors (oseltamivir, peramivir, zanamivir), ganciclovir, acyclovir and ribavirin were not effective [1]. However, an unlisted broad-spectrum antibiotic, Remdesivir, has found quite some attention in recent times, with it being given Emergency Use Authorization by the US Food and Drugs Agency (FDA). The drug, manufactured by US pharmaceutical company Gilead has been commissioned for multiple drug trials in the US, UK and Singapore [2].

Pharmacology of Remdisivir

Remedisivir, an adenosine analogue, incorporates itself into viral RNA chains resulting in pre-mature termination [3]. It has been described as a potential antiviral medication against a broad variety of RNA viruses, including SARS and MERS, in animal models [4,5] . Remdisivir also inhibited virus infection in a human cell line that is susceptible to SARS-CoV-2 [6]. Remdesivir has also been shown to reduce viral load of

MERS-CoV in the lung tissue of infected mice. Moreover, it enhanced lung function and reduced damage to the lung tissue. [7] Among the various therapeutic candidates, it showed success both in vivo and in vitro against coronaviruses in general. [8]

Observational Studies on Remdesivir

Tested initially against Ebola, SARS-CoV and MERS-CoV [2], Remdesivir has been used in the dose that was used during the Ebola trials- 200 mg IV on day 1 followed by 100 mg for 9 days [8].

It was used in the first case of COVID-19 managed in the US [9], showing presumably good response. The patient presented with a 4-day history of fever and cough. On day 7 of hospitalization the patient deteriorated and were then given IV Remdesivir under compassionate use access with no adverse events observed on infusion [9]. Clinical improvement followed the next day. However, the patient was also concurrently given Paracetamol, Ibuprofen, Guaifenesin, Vancomycin and Cefepime. This acts as a confounder and does not allow for interpretation of the direct effect of Remdesivir on disease process.

Between January 20, 2020, and February 5, 2020 12 more patients were infected with SARS-CoV2 [10]. Three of the patients received Remdisivir on compassionate use access after deteriorating clinical condition. The first signs of adverse effects were seen in this case series as all patients experienced gastrointestinal symptoms (nausea, vomiting, gastroparesis or rectal bleeding) after the initial dose. However, treatment was not stopped until improvement in respiratory symptoms, with all patients reporting resolution of symptoms by February 22, 2020[10]. However, the sample size is incredibly small and there was no randomization, thus it is difficult to determine efficacy and, importantly, efficacy in light of the reporting of adverse effects.

Gilead sponsored a study into patients who were given compassionate use access of Remdesivir in critically unwell patients with COVID-19 [11]. A total of 53 patients- 22 were in the United States, 22 in Europe or Canada, and 9 in Japan were observed in this study. 30 patients (57%) were receiving mechanical ventilation and 4 (8%) were receiving extracorporeal membrane oxygenation at the start of compassionate use. During follow-up (median-18 days), 36 patients (68%) showed improvement in oxygen-support class. 17 of the 30 patients (57%) on mechanical ventilation were extubated. 25 patients (47%) were discharged, and 7 patients (13%) died. Among those receiving invasive ventilation, mortality was 18% (6 of 34). It was 5% among those not receiving invasive ventilation (1 of 19). [11] While 36 out of 53 (68%) showed clinical improvement, this study did not have a comparative control arm, was on a very small cohort of patients and crucially there was no adjustments for the level of care that each patient received- providing the doorway for multiple confounders.

Randomized Controlled Trials for Remdesivir

An early randomized controlled trial of Remdesivir trial in China [12], was forced to stop early because of difficulty recruiting COVID-19 patients as the outbreak in the country was brought under control. 237 patients aged over 18 from 10 hospitals in Wuhan were included in the study. Patients were randomly assigned to a treatment group (158 to remdesivir and 79 to placebo). The primary endpoint was time to clinical improvement. Remdesivir, unfortunately, was not associated with a difference in time to clinical improvement (hazard ratio 1·23 [95% CI 0·87–1·75]). Adverse events were reported in 102 (66%) of 155 remdesivir recipients versus 50 (64%) of 78 placebo recipients. Remdesivir was stopped early because of adverse events in 18 (12%) patients versus four (5%) patients who stopped placebo early [12]. However, it is difficult to imply that Remdesivir is not useful against COVID-19 based on this study alone.

The National Institute of Allergies and Infectious Diseases (NIAID), NIH initiated the Adaptive COVID-19 Treatment Trial (ACTT), a double-blind, randomized, placebo-controlled phase 3 trial to evaluate the safety and efficacy of Remdesivir compared with a placebo (NCT04280705) [13]. 1063 patients have been recruited in US, UK and Singapore. The primary endpoint has been defined as being well enough for hospital discharge or returning to normal activity level with multiple other secondary endpoints [2]. While official results have not been published, the NIH announced that preliminary results have indicated that patients who received Remdesivir had a 31% faster time to recovery than those who received placebo ($p<0.001$). The median time

to recovery was 11 days for patients on Remdesivir compared with 15 days for those on placebo. Moreover, mortality was 8% for the group receiving Remdesivir versus 11.6% for those in the placebo arm (P=0.059) [14].

Conclusions

As the pandemic reaches to every corner of the globe, the search for potential therapeutics and vaccines goes on. However, while Remdesivir has so far reported clinical benefit both in vitro and in vivo [8]. Based on this and on findings from recent observational [11] and randomized [14] studies, the US Food and Drug Administration (FDA) has issued an Emergency Use Authorization for the emergency use of remdesivir for the treatment of hospitalized COVID-19 patients. This is the first FDA authorization of an investigational drug for use in treating SARS-CoV-2 [8]. However, question marks remain over the strength of the studies and further research is needed before Remdesivir can be classed as a definite option in managing COVID-19 patients. It is unclear as to why Emergency Use Authorization has been granted for a drug which has as of yet no Randomized Clinical Trial showing any clear significant benefit.

Multiple other studies are currently ongoing for different therapeutics that may work in COVID-19, including Remdesivir. The WHO has started the largest such trial, the SOLIDARITY trial, a four-arm trial comparing remdesivir, lopinavir/ritonavir, lopinavir/ritonavir with interferon-β1a, and chloroquine or hydroxychloroquine [15]. The world waits on as the race to find an appropriate therapeutic goes on.

Contributorship Statement

Dr. Raiiq Ridwan drafted this manuscript after literature review

Funding

This paper received no funding sources

Competing Interests

The author describes no competing interest

Acknowledgement

None

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