Have we found the panacea to COVID-19 with remdesivir, an old but newly packaged drug?

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Title: Compassionate Use of Remdesivir for Patients with Severe Covid-19

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Summary

Investigators provided open-label remdesivir on a compassionate-use basis to patients hospitalised with severe COVID-19, an illness caused by infection with SARS-CoV-2. Severity was defined as an oxygen saturation of 94% or less while patients were breathing ambient air or receiving oxygen support. Patients with contraindications for remdesivir, including creatinine clearance below 30 ml/min and elevated liver enzymes beyond five times upper limit of normal, were excluded. Patients received a 10-day course of intravenous remdesivir, starting with loading dose of 200 mg administered intravenously on day one, followed by 100 mg daily for the remaining nine days.

Other supportive therapies including dialysis and extracorporeal membrane oxygenation (ECMO) were provided at the discretion of clinicians. The study outcome was based on incidence of key clinical events, especially oxygen requirement, discharge and mortality at 28 days' follow-up.

Of the 61 patients receiving remdesivir, 53 were suitable for analysis (8 patients were excluded for missing data or erroneous remdesivir start date). Most patients (22/52) were from the USA, with two-thirds being male, and a median age of 64-years old. At baseline, 64% were already receiving invasive ventilation and 8% were on ECMO. The median time from symptoms to initiation of remdesivir was 12 days.

Over a follow-up median period of 18 days, 68% showed improvement in the need for oxygen support, of which 17 out of 30 (57%) ventilated patients were extubated and 75% stopped ECMO. A total of 25 patients (47%) were discharged while 7 patients (13%) died. Mortality did not differ between those with vs without invasive ventilation, but the risk of death was greater in patients above 70-years old and those with higher creatinine levels at baseline. At 28 days' follow-up, cumulative incidence of clinical improvement was seen in 84%, and less improvement was observed in those receiving invasive ventilation and in patients above 70-years old. More than half (60%) reported adverse events and 23% were serious adverse events. About 8% of patients needed to stop remdesivir prematurely due to safety reasons.

In conclusion, this is the first amongst the several trials around the world on remdesivir in COVID-19, and the current study has observed a clinical improvement in 68% of patients.

Opinion

We are at the most unprecedented of times. The COVID-19 pandemic has been gaining momentum since the first report came from Wuhan, China in December 2019. As of 12 May 2020, 4,425,094 people have been infected with SARS-CoV-2 with deaths reaching 297,723.[1] Doctors are desperately looking for an effective drug, and there have been a number of candidates on trial; one of them, remdesivir, is probably the most exciting of all. This is the drug developed for the Ebola

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Table 1 Current and past clinical trials* of remdesivir

No.	Status*	Study Title	Conditions	Intervention	Main Country
1	Suspended	A trial of remdesivir in adults with mild and moderate COVID-19	COVID-19	Remdesivir Placebo	China
2	Recruiting	Study to evaluate the safety and antiviral activity of remdesivir (GS-5734™) in participants with severe COVID-19	COVID-19	Remdesivir Standard of care	USA
3	Recruiting	Study to evaluate the safety and antiviral activity of remdesivir (GS-5734™) in participants with moderate COVID-19 compared to standard of care treatment	COVID-19	Remdesivir Standard of care	USA
4	Terminated	A trial of remdesivir in adults with severe COVID-19	COVID-19	Remdesivir Placebo	China
5	Available	Expanded access treatment protocol: remdesivir (RDV; GS-5734) for the treatment of SARS-CoV-2 Infection	COVID-19	Remdesivir	USA
6	Recruiting	The efficacy of different anti-viral drugs in COVID-19-infected patients	COVID 19	Hydroxychloroquine Remdesivir Standard of care	Norway
7	Recruiting	Adaptive COVID-19 Treatment Trial (ACTT)	COVID-19	Remdesivir Placebo	USA
8	Available	Expanded access remdesivir (RDV; GS-5734™)	COVID-19	Remdesivir	USA
9	Recruiting	Trial of treatments for COVID-19 in hospitalised adults	COVID-19	Remdesivir Lopinavir/ritonavir Interferon Beta-1A	France
10	Recruiting	Investigational therapeutics for the treatment of people with Ebola virus disease	Ebola	ZMapp Remdesivir MAb114 REGN-EB3	USA; Democratic Republic of Congo

*Based on data extracted from www.clinicaltrials.gov (accessed 29/04/2020)

epidemic in 2015, but it was found to be less effective in clinical trials than in in vitro studies. Is remdesivir the panacea for COVID-19? In this clinical opinion, we critically appraised the article published in NEJM on the compassionate use of remdesivir in severe COVID-19.

Remdesivir or GS-5734, is the monophosphoramidate prodrug of C-adenosine nucleoside analogue GS-441524, developed and marketed by Gilead Sciences (Foster City, USA). In contrast to the interest shown in COVID-19, little is known of remdesivir in human trials of Ebola virus other than case reports[2] and ongoing multicentre phase-III randomised controlled trials (RCT)[3] (Table 1). Overall, from in vitro studies, the compound seems to have a broad-spectrum anti-CoVs activity including SARS-CoV and MERS-CoV, the close cousins of SARS-CoV-2.[4] For example, SARS-CoV has been shown to be inhibited effectively by remdesivir in the primary human airway epithelial cell cultures.[5] Based on a recent study in the rhesus macaque, data has shown that remdesivir prevented clinical disease from MERS-CoV when administered 24h before.[6] In addition, compared to controls, the macaque treated with remdesivir 12h after infection had less severe disease, lower viral loads in the lung and less lung damage.

The encouraging preclinical data seem to have translated into several small clinical studies, and larger multicentre RCTs are ongoing. Before RCTs, there have been approvals from Gilead Sciences for prescription of remdesivir on compassionate grounds in severe COVID-19 disease. Those with severe COVID-19 are most likely to have respiratory complications, increased need for respiratory support, intensive care and a higher rate of mortality. From the Wuhan experience,[7] 3.2% of patients with COVID-19 required mechanical ventilation, but recent data from New York reported a higher rate of 12.2%.[8]

In the New York report, out of those patients needing mechanical ventilation, about a quarter died and two-thirds remained in the hospital. This is where remdesivir benefits the most. Overall, over a median follow-up of 18 days, Grein et al.[9] reported that 68% (36/53) on remdesivir needed less oxygen support including all patients on ambient air and 71% (5/7) who were receiving non-invasive oxygen support. More notable is that with remdesivir, 57% of those needing ventilation could be extubated and 75% stopped needing ECMO. The clinical improvement from remdesivir was translated into a greater hospital discharge rate of 47% (25/53), more days before mortality (interval between remdesivir initiation to death was 15 days) and a mortality rate of 13% (7/53).

The clinical benefits of remdesivir were better for those not receiving ventilation than those on ventilation (hazard ratio for improvement 0.33), and older age was the only determining factor for less clinical improvement despite being on remdesivir. On the other hand, the mortality benefits did not differ between those receiving invasive vs non-invasive ventilation; however, the risk of death was higher in the elderly (above 70-years old) and those with higher creatinine level at baseline.

The reported results are undoubtedly remarkable; however, several points or limitations need to be considered. Many have been described by the authors, including small sample size, limited duration of follow-up and the lack of a randomised control group. As with all open-label and uncontrolled studies, the remdesivir study is subjected to potential bias as it does not minimise the effect of knowledge of treatment allocation on reporting of key outcomes.[10] In addition, it may be of concern that a sizeable number of patients' data could not be analysed i.e. 13% of the cohort (including seven patients with no post-treatment data and one with a dosing error). Furthermore, some outcome data were omitted, for example in the patients labelled 1 to 4 and 11 to 18, where in spite improvement in oxygen support, the final outcome (discharge or death) was omitted. Similarly, the patients numbered 20, 24, 25, 29, 32–34 and 38 did not have their final outcome recorded. In all, these make up 37% (20/53) of 'unavailable' outcome data.

While on one hand there are no new safety events that we did not know about remdesivir, on the other hand, the reported 60% of adverse events, especially 23% elevation in liver enzymes and 23% of serious adverse events, should not be taken lightly. In addition, viral load data were not collected, information which would have helped the authors in correlating viral suppression with observed clinical and mortality benefits.

Also, the duration of remdesivir therapy was not entirely uniform across all patients, with only 19% (10/53) receiving 5–9 days of treatment and 6% (3/53) receiving less than 5 days' treatment. More controversial is the initial draft that was leaked to the press which mentioned that remdesivir was 'not associated with a difference in time to clinical improvement when compared to a standard of care as control'. The report in the press further stressed that 13.9% of the remdesivir patients had died compared to 12.8% of patients in the control arm.

As of 29 April 2020, preliminary results from the Adaptive COVID-19 Treatment Trial (ACTT) have been released.[11] This multicentre, adaptive, randomised double-blind controlled trial of the safety and efficacy of remdesivir for the treatment of non-severe COVID-19 involving 800 subjects has shown 'a clear-cut significant positive effect in diminishing time to recovery' from 15 days to 11 days. However, the mortality rate of remdesivir vs placebo arm i.e. 8% vs 11% in placebo arm was not statistically significant. Being the larger study, the preliminary results provide additional clinical reason for use of remdesivir, especially in having benefit to non-severe COVID-19 patients. However, finer details of the trial need to be explored before clinicians are convinced, especially in the light of recent negative study results reported in *The Lancet*.[12]

As a conclusion, while the encouraging preclinical and open-label studies seem to suggest a clinical benefit from remdesivir in severe COVID-19, remdesivir is not a panacea. There are many clinical aspects of COVID-19 treatment that are poorly understood, e.g. cytokine storm, which are not covered in this study. It will be interesting to see the results of a RCT trial[13] before the final judgement call on this compound can be made.

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