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# Remdesivir, a remedy or a ripple in severe COVID-19?

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**ABSTRACT**

**Introduction:** In clinical trial for the Ebola virus, the broad-spectrum anti-viral agent remdesivir was shown to have a good safety profile. Remdesivir is now being tested in severe COVID-19.

**Areas covered:** The Gilead Sciences SIMPLE trial suggests that the short-term use of remdesivir probably does not increase mortality dramatically or have serious short-term toxicity when used to treat severe COVID-19. The Adaptive COVID-19 treatment trials (ACTT1) trial showed that remdesivir may shorten recovery and decrease mortality in severe COVID-19 without increasing adverse effects.

**Expert opinion:** It seems to me that we have learnt very little from the SIMPLE trial, and this would be predicted from a trial that has no control or placebo group. The results of ACTT1 were reported early after an interim analysis showed that a higher than expected number of recoveries had occurred. There was an indication that remdesivir may be reducing mortality, but this was no statistical significance. The trial is continuing, and the final data are eagerly awaited to determine whether remdesivir is a game-changing remedy or a ripple in the ongoing search for a medicine for the treatment of COVID-19.

## 1. Introduction

This evaluation is of two clinical trials of remdesivir in severe COVID-19 that have recently been published [1,2]. The first is the SIMPLE trial compared the efficacy and safety of treating subjects with severe COVID-19 for 5 or 10 days with remdesivir [1]. The second is Adaptive COVID-19 treatment trial (ACTT1) ACTT-1 was a randomized, placebo controlled of remdesivir in hospitalized subjects with COVID-19 [2].

The background to these trials is that emergence of new viruses, such as the coronavirus SARS-CoV-2 (COVID-19), requires both vaccines for the prevention and medicines for the treatment of the infection. As a vaccine is still at least a year away, medicines for the treatment of the symptoms of COVID-19 are urgently needed. Broadly, there are two approaches to the development of new medicines for COVID-19; firstly, to reposition medicines approved for other conditions for COVID-19 and secondly, to develop new medicines for COVID-19. The first approach may be quicker, but both approaches will require extensive preclinical testing followed by clinical trials. Remdesivir falls between these two approaches, as it is not a new medicine, but an investigational drug, which has not been approved for clinical use [3]. Remdesivir was being developed to treat the Ebola virus disease. In clinical trial for the Ebola, it was shown to have a good safety profile but was less effective than monoclonal antibodies [4]. Due to this lack of efficacy, the clinical development of remdesivir for Ebola was stopped.

Remdesivir (GS-5734) is a prodrug of an adenosine analog. It is a broad-spectrum antiviral agent, which inhibits viral RNA dependent RNA polymerase [5]. This makes remdesivir effective against a range of coronaviruses [5] including severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) [6], and COVID-19 [7]. The first published clinical trial of remdesivir in severe COVID-19 did not show a mortality benefit [8].

## 2. Gilead sciences SIMPLE trial

The SIMPLE trial [1] compared the efficacy and safety of treating subjects with severe COVID-19 for 5 or 10 days with remdesivir. It was an international trial but was not placebo controlled. The trial was sponsored by Gilead Sciences, the makers of remdesivir, and the company collected the data, monitored the trial, and undertook the statistical analysis.

SIMPLE enrolled subjects with COVID-19, radiographic evidence of pulmonary infiltrates, and (i) oxygen saturation of 94% or less while breathing ambient air or (ii) were receiving supplemental oxygen. Subjects were excluded if they were receiving mechanical ventilation and extracorporeal membrane oxygenation (ECMO). The enrolled subjects (397) had a mean age of ~ 61, and were predominantly white, and half had hypertension, and about a quarter had diabetes and/or hyperlipidemia. At the start, ~ 55% of subjects were at point 4 on the 7-point ordinal scale, and ~ 27% at point 3:

  (i) Death
 (ii) Hospitalized, receiving invasive mechanical ventilation or ECMO
(iii) Hospitalized, receiving noninvasive ventilation or high-flow oxygen devices
(iv) Hospitalized, requiring low-flow supplementary oxygen

(v)   Hospitalized, not requiring supplemental oxygen but receiving ongoing medical care
(vi)  Hospitalized, requiring neither supplemental oxygen not ongoing medical care
(vii) Not hospitalized

Subjects received 200 mg remdesivir iv on day 1 and then 100 mg iv for 4 or 9 days. More subjects completed the 5-day course of remdesivir (172/200, 86%) than the 10-day course (86/197, 44%) mainly because more subjects were discharged during the 10- (68/197, 35%) than 5-day course (16/200, 8%).

The primary outcome was point improvement on the ordinal scale on day 14, and this was at least 2 points for 64% of subjects, who received the 5-day course of remdesivir, and (after adjustment for difference in status at the start) 54% of subjects after the 10-day course. Also, similar between the two courses was duration of hospitalization, proportion that recovered, and time to recovery. Numerically mortality was lower in the 5-day group (8% vs 11%), and more were discharged from hospital in the 5- than 10-day group (60% vs 52%).

The secondary outcome was adverse events, and the overall occurrence was similar in both groups. However, acute respiratory failure was more common in the 10-day group (9% vs 5%).

In their discussion [1], the authors emphasize that

(i)   There was no difference in efficacy between the 5-day and 10-day course of remdesivir.
(ii)  As the study did not enroll subjects with mechanical ventilation, the results cannot be extrapolated to this group.
(iii) As there was no placebo group, the study did not test efficacy.
(iv)  Data on liver enzymes were inconclusive.

The authors mention [1], without reference, that transient elevations in liver enzymes were observed in phase 1 trials of remdesivir in healthy volunteers. Also unpublished in a refereed journal is that remdesivir, at high concentrations in preclinical testing, had renal toxicity. In the SIMPLE trial in 2.5% and 3.6% of subjects in the 5-day and 10-day group had elevated aminotransferase elevation leading to discontinuation. There were also decreases in creatinine clearance with remdesivir in the SIMPLE trial. However, as COVID-19 itself is associated with liver and kidney injury, it is unknown whether it is remdesivir or the virus that led to the elevated aminotransferases and decreased creatinine clearance.

## 3. Adaptive Covid-19 treatment trial (ACTT1)

ACTT-1 [2] was a randomized, placebo controlled, international trial of remdesivir in hospital subjects with COVID-19 with the subjects predominantly coming from North America (80%) followed by Europe (15%). To be included subjects with COVID-19 had to have at least one of radiographic infiltrates by imaging, clinical assessment (evidence of rales/crackles) and $SpO_2 \leq 94\%$ or requiring mechanical ventilation and/or supplementary oxygen.

The mean age of subjects was 59 years, and most were white (53%). Many of the subjects had preexisting conditions such hypertension (50%), obesity (37%), and type 2 diabetes (30%). Subjects (1063) were randomized to a loading dose of 200 mg iv, followed by a maintenance dose of 100 mg iv from day 2–10 or until hospital discharge or death, or placebo.

In an interim analysis, the data and safety monitoring board reported that as a higher than expected number of recoveries had occurred, the data should be reported. At this time, only 731 subjects had completed the study through day 29 with another 301 were continuing treatment and not recovered when the database closed. The number of subjects that discontinued due to adverse events was similar in both groups (~38).

The primary outcome was the time to recovery within 28 days of enrollment to

(i)   Not hospitalized, no limitation of activities
(ii)  Not hospitalized, limitation of activities and/or home oxygen requirement
(iii) Hospitalized, not requiring supplemental oxygen, and no longer requiring ongoing medical care (used if hospitalization was extended for infection control reasons)

and this was shorter with remdesivir (11 days) than with placebo (15 days). After 27 days, 87% had recovered in the remdesivir group, compared to 82% in the placebo group.

The secondary outcomes used an ordinal scale

(i)   Death
(ii)  Hospitalized, no invasive mechanical ventilation or ECMO (extracorporeal membrane oxygenation)
(iii) Hospitalized, on noninvasive ventilation or high-flow oxygen devices
(iv)  Hospitalized, requiring supplemental oxygen
(v)   Hospitalized, not requiring supplemental oxygen
(vi)  Not hospitalized, limitation on activities
(vii) Not hospitalized, no limitation on activities

and the percentage of recoveries was higher with remdesivir (62%) than with placebo (52%). Although the deaths at 14 days were lower with remdesivir (32/7.1%) than with placebo (54/11.9%), this did not reach significance. There was no excess of adverse effects with remdesivir, and this included no excess in liver or kidney toxicity.

The authors clarify that the trial is ongoing and will be reported when complete in order to fully understand the efficacy of remdesivir in COVID-19 [2]. The authors discuss the reasons for the difference in their findings and a previous study showing no benefit with remdesivir in COVID-10 [2], and this is discussed in section 5.3.

## 4. Conclusions

The SIMPLE trial suggests that short-term treatment with remdesivir does not increase mortality dramatically or have serious short-term toxicity when used to treat COVID-19. The ACTT1 trial showed that remdesivir may shorten recovery and

decrease mortality in COVID-19 without increasing adverse effects.

## 5. Expert opinion

### 5.1. The SIMPLE trial

It seems to me that we have learnt very little from the SIMPLE trial [1], and this would be predicted from a trial that has no control or placebo group. Even in the extraordinary COVID-19 times, I am surprised that an uncontrolled trial was undertaken, and even more surprised that it has been published in a prestigious journal.

### 5.2. The ACTT1 trial

In the ACTT1 trial, an interim analysis was undertaken, which led to early reporting of the data due to higher than expected recoveries with remdesivir. Interim findings leading to early reporting always have pros and cons. The pro, in this case, is that remdesivir will be more widely used in COVID-19 for its likely benefit. The con is that the early analysis is probably the reason that the trial did not give a significant finding on mortality. Fortunately, the trial is going to be completed [2], which should give us definitive data on the effect of remdesivir on the mortality in COVID-19.

Based on the findings of the ACTT1 trial, the Food and Drug Administration (FDA) have licensed remdesivir for the emergency use of remdesivir for hospitalized subjects with COVID-19 [9].

### 5.3. The first placebo-controlled trial of remdesivir in severe COVID-19

The first randomized, double-blind, placebo-controlled trial of remdesivir in severe COVID-19 was performed in Wuhan, China, and did not find a recovery benefit with remdesivir [8]. This trial was terminated early when the outbreak of COVID-19 in Wuhan was curtailed, and this limited the numbers enrolled and statistical power of the study [8]. At termination, 158 subjects with COVID-19 had been treated with remdesivir, compared to 78 in the placebo group, and the time to clinical improvement was similar in remdesivir group (21 days) and placebo group (23 days) [8].

Due to the lack of statistical power in this Wuhan trial, there seems to have been a tendency to dismiss its finding of no benefit with remdesivir after the positive findings in the ACTT1 trial were released. Another approach is to compare the trials to see if there are other differences than statistical power. The population of subjects enrolled in the two studies was different; in the Wuhan trial, 82% of subjects were requiring supplemental oxygen, whereas only 40% were in this category in the ACTT1 trial. In the ACTT1 trial, remdesivir did show benefit in those requiring supplemental oxygen, but the number of subjects was too low to reach statistical significance. Thus, it could be argued that the findings in this category in both studies were statistically similar.

In the Wuhan trial, subjects with severe COVID-19 continued their other treatments including ~39% who were taking a corticosteroid, and this trial did not show any benefits with remdesivir [8]. In the ACTT1 trial, other experimental treatments or off-label use of marketed medications were prohibited, and remdesivir shortened recovery [2]. Thus, it is possible that the different findings between the studies may be related to the use of a corticosteroid in the Wuhan, but not the ACTT1 trial.

### 5.4. Potential treatments with remdesivir

On autopsy, severe COVID-19 is associated with diffuse alveolar damage, inflammatory infiltrates, and coagulopathy. Dexamethasone, an anti-inflammatory corticosteroid, reduces mortality and time to discharge in subjects with COVID-19 requiring invasive mechanical ventilation or oxygen alone but not among those receiving no respiratory support [10]. Anticoagulants, such as heparin, are used to prevent the coagulopathy with severe COVID-19, and it has been suggested that low molecular weight heparin reduces mortality in subjects with severe COVID-19 and coagulopathy [11]. To test whether the use of dexamethasone and/or anticoagulants affects the findings with remdesivir, placebo-controlled trials of remdesivir need to be undertaken in the presence of dexamethasone and/or anticoagulants.

### 5.5. Other potential treatments for severe COVID-19

In addition to dexamethasone, other medicines may have the potential for the treatment of severe COVID-19. The SOLIDARITY open-label clinical trial was launched by the WHO to compare chloroquine/hydroxychloroquine, remdesivir, lopinavir/ritonavir, or interferon beta-1a with local standard of care in subjects hospitalized COVID-19. The chloroquine/hydroxychloroquine and lopinavir/ritonavir arms were stopped when the International Steering Committee recommended this, as interim results showed little or no reduction in mortality in COVID-19 with either of these combinations [12]. The exclusion of lopinavir/ritonavir from SOLIDARITY is supported by the LOTUS China (the Lopinavir Trial for Suppression of SARS-Cov-2 in China) trial in hospitalized subjects with COVID-19, which showed no benefits but increased gastrointestinal adverse effects [13].

Remdesivir is included in SOLIDARITY because it 'generated promising results in animal studies for Middle East Respiratory Syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS) … '[14]. One of the limitations of the SOLIDARITY trial is that it is open label, making it difficult to obtain conclusive results.

Tocilizumab is not included in the SOLIDARITY trial. In a preliminary trial tocilizumab, which is monoclonal antibody, directed against the interleukin-6 receptor, was shown to possibly reduce the risk of invasive mechanical ventilation or death in subjects with severe COVID-19 pneumonia [15]. Thus, perhaps, tocilizumab should be added to the SOLIDARITY trial, and needs further testing in severe COVID-19.

### 5.6. Ordinal scales differ between studies

The ordinal scales used for severe COVID-19 in the SIMPLE trial [1], the ACTT1 trial [2], and the Wuhan trial [8] with remdesivir

are different, and this makes it difficult to compare the trials. Also, a 2-point improvement may occur more commonly on a 7-point scale [1,2] than a 6-point scale [8]. It is suggested that a guideline be set for the ordinal scale to be used in severe COVID-19 to allow easier comparisons between trials.

## 5.7. Remdesivir, a remedy or a ripple in severe COVID-19?

The ACTT1 trial is continuing, and the final data is eagerly awaited to determine whether remdesivir is a game-changing remedy or a medicine that has a borderline benefit (a ripple) in the treatment of COVID-19.

## Funding

## Declaration of interest

## Reviewer disclosures

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