COVID-19 rapid evidence summary: Remdesivir for treating hospitalised patients with suspected or confirmed COVID-19

Evidence summary
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Key messages

The content of this evidence review was up-to-date on 4 June 2020. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information. For details on the date the searches for evidence were conducted see the search strategy

COVID-19 manifests as a predominantly respiratory illness, of widely varying clinical severity. At the most severe end of the spectrum it results in severe pneumonia and respiratory failure with the need for mechanical ventilation. Acute respiratory distress syndrome (ARDS) is often a pre-terminal event in patients with COVID-19 and is the leading cause of mortality.

This is a rapidly evolving pandemic globally, with countries facing different stages of the spread of disease. Initial hospital data from the UK suggest that increasing age over 50 years is a strong predictor of mortality in hospital (hazard ratio [HR] 4.02 for 50–69 years, 9.6 for 70–79 years and...
13.6 for 80 years or over; Docherty et al. 2020). Children and young people appear to be less affected by the virus, with low numbers of deaths and critical care admissions in this age group (Lu et al. 2020). UK primary care record data from 17.4 million patients showed death in hospital from COVID-19 was strongly associated with male gender, older age, Black or Asian ethnicity, deprivation, uncontrolled diabetes and severe asthma. Treatment options for COVID-19 are limited and there are trials underway to assess the efficacy of available medicines to manage the disease.

Remdesivir is an adenosine nucleotide prodrug that is metabolised intracellularly to form the pharmacologically active substrate remdesivir triphosphate. Remdesivir triphosphate inhibits SARS-CoV-2 RNA polymerase which prevents viral replication.

Remdesivir is the first COVID-19 treatment to receive a positive scientific opinion by the Medicines and Healthcare products Regulatory Agency (MHRA), based on advice from the Commission on Human medicines, under the rapid early access to medicines scheme (EAMS) by meeting the EAMS published access criteria. Remdesivir is indicated for the treatment of adults and young people aged 12 years and over and weighing at least 40 kg hospitalised with suspected or laboratory confirmed SARS-CoV-2 infection and severe disease.

This review aims to establish the clinical effectiveness, safety and cost effectiveness of remdesivir in adults, young people and children hospitalised with suspected or confirmed COVID-19.

The research questions are:

1. In adults, young people and children hospitalised with suspected or confirmed COVID-19 (COVID-19 is the acute clinical syndrome caused by SARS-CoV2 virus), what is the clinical effectiveness of remdesivir compared with placebo or standard care? (Standard care can vary according to country. In the UK standard care for COVID-19 is supportive treatment.)

2. In adults, young people and children hospitalised with suspected or confirmed COVID-19, what is the safety of remdesivir compared with placebo or standard care?

3. In adults, young people and children hospitalised with suspected or confirmed COVID-19, what is the cost effectiveness of remdesivir compared with placebo or standard care?

4. From the evidence selected, are there any subgroups of patients that may benefit or be harmed from remdesivir more than the wider population of interest?
5. From the evidence selected:

   1. what definitions have been used/developed to describe 'moderate' and 'severe' COVID-19?

   2. what is the duration of remdesivir treatment?

Three studies identified from the search are included in this evidence summary. Two studies (Beigel et al. 2020 and Wang et al. 2020) are phase 3 double-blinded, placebo-controlled randomised controlled trials (RCT) and 1 study is an observational study (Grein et al. 2020). A meta-analysis of the 2 included RCTs (Cochrane 2020) was also identified following the search and included.

Remdesivir when compared with placebo was associated with clinical improvements in some of the outcomes and fewer serious adverse events.

The findings in the review suggest that factors to consider when using remdesivir as a treatment option for COVID-19 in patients with mild or moderate, or severe disease include the timing of initiation of treatment at the onset of symptoms, disease severity (this includes the need for oxygen support, non-invasive ventilation, invasive ventilation or organ support, most of the patients in the studies had severe COVID-19) and the underlying clinical status of the patient and age. These may have important effects on the outcomes of treatment. Remdesivir should only be administered by intravenous infusion which may limit its use.

Factors for decision making

Effectiveness and safety

In terms of efficacy, the Cochrane (2020) meta-analysis reported fewer deaths with remdesivir compared with placebo and there was no significant difference for mortality at days 14 to 28. However, the meta-analysis reported remdesivir to be significantly better than placebo for reducing the need for supportive measures such as non-invasive ventilation/high flow oxygen or mechanical ventilation with or without additional organ support in patients on WHO progression score level 6/7 or above at days 14 to 28. Beigel et al (2020) reported that the time to recovery was significantly shorter (by 4 days) with remdesivir compared with placebo. Wang et al (2020) reported remdesivir was better in reducing the time to clinical improvement and the duration of invasive mechanical ventilation and oxygen support compared with placebo (not statistically significant for both). However, Wang et al (2020) reported no statistically significant difference between remdesivir and placebo in length of hospital stay, viral RNA load and viral RNA detectability. The study by Wang et al (2020) was not powered to assess significant difference in
the outcomes reported, consequently the findings should be interpreted with caution.

In terms of subgroup analyses, in patients receiving treatment within or after 10 days of symptom onset: Beigel et al (2020) reported that the remdesivir group recovered within a shorter time compared with placebo (statistically significant difference) in both subgroups; Wang et al (2020) reported that there was faster clinical improvement with remdesivir compared with placebo when starting treatment within 10 days of symptom onset (although not statistically significant), however no statistically significant difference was observed when treatment was started after 10 days of symptom onset; no statistically significant differences were seen for 28-day mortality when remdesivir was compared with placebo for these 2 subgroups. Beigel et al (2020) reported that patients with severe disease in the remdesivir group had a shorter time to recovery (statistically significant) and lower 14-day mortality (not statistically significant) compared with placebo, whereas no difference was reported in people with mild or moderate disease. Beigel et al (2020) found the time to recovery was statistically significantly shorter with remdesivir compared with placebo in patients for the following: from North America; of a white origin; aged from 18 to 39 years or aged 65 or over. Grein et al (2020) reported that clinical improvement was statistically significantly less common in patients receiving invasive ventilation compared with those receiving non-invasive ventilation. Grein et al (2020) reported that in patients on remdesivir, death was statistically significantly greater in patients aged 70 or over and in patients who had a higher serum creatinine at baseline (this was not defined by the authors). Subgroup analyses reported by Beigel et al (2020) and Grein et al (2020) should be interpreted with caution because the authors state that inferences on treatment effects cannot be made because of wide confidence intervals and presence of multiplicity.

In terms of safety, Cochrane (2020) found there were significantly fewer serious adverse events with remdesivir compared with placebo. The individual RCTs reported the common serious adverse events with remdesivir and placebo to be respiratory failure, acute respiratory distress syndrome and cardiopulmonary failure. Beigel et al (2020) reported that 4 of the 114 serious adverse events were thought to be due to remdesivir or placebo (2 in each group) which may indicate that the rest of the adverse events may have been related to COVID-19 or underlying comorbidities. It was unclear in Wang et al (2020) and Grein et al (2020) whether serious adverse events were related to COVID-19 or remdesivir. Adverse events relating to kidney and liver biomarkers were not significantly different when remdesivir was compared with placebo in the 2 RCTs. This may have been due to the studies excluding patients with impaired renal function and alanine aminotransferase or aspartate aminotransferase 5 times the upper limit of the normal range. Consequently, there are no data in patients with renal or liver impairment. Wang et al (2020) reported that a higher proportion of patients in the remdesivir group compared with placebo group had dosing prematurely stopped by the investigators because of adverse events, including
gastrointestinal symptoms (anorexia, nausea, and vomiting), aminotransferase or bilirubin
increases and worsened cardiopulmonary status.

The definition of severe COVID-19 disease differed in the included studies, the common feature
was having a peripheral oxygen saturation of 94% or less on room air. Of the included studies,
Beigel et al (2020) had a clear definition for both severe and mild or moderate COVID-19 disease.
Beigel et al (2020) described 'severe' as requiring invasive or non-invasive mechanical ventilation,
requiring supplemental oxygen, a peripheral oxygen saturation of 94% or less on room air, or a
respiratory rate 24 breaths per minute or more). Mild or moderate disease was defined by a
peripheral oxygen saturation of more than 94% and respiratory rate of less than 24 breaths per
minute without supplemental oxygen requirement. No average duration of remdesivir was
reported in the studies. All studies used a treatment duration of up to 10 days.

Discussion and limitations of the evidence

Remdesivir has not been studied in the paediatric population or in pregnant women with
COVID-19 and there are currently limited safety data. In addition, no data was found for the
outcomes of disease complications, ratio of arterial oxygen partial pressure to fractional inspired
oxygen (PaO$_2$/FiO$_2$) and cost-effectiveness. The included studies compared remdesivir with
placebo and no data are available for its effects compared with a different active comparator (as
there are limited treatment options for treating COVID-19).

Patients included in all the studies were hospitalised and required supplemental oxygen or other
supportive treatments such as invasive ventilation. Enrolled patients were, on average, older with
comorbidities such as hypertension and diabetes and were required to have stable renal and
hepatic function. The median time from symptom onset to starting treatment was between 9 and
12 days. Remdesivir dose was the same in all the included studies.

The Cochrane (2020) meta-analysis included results from 2 moderate quality RCTs (Beigel et al.
2020 and Wang et al. 2020) and both were assessed using Cochrane risk of bias 2 tool as having
'some concerns'. Overall, the quality and applicability of the meta-analysis reported by Cochrane
(2020) was considered as high and fully applicable to practice. The limitations of the meta-analyses
were not presented and it is unclear if these data reported by Cochrane (2020) have been formally
peer reviewed before publication.

Beigel et al (2020) was the larger study (n=1,063) of the individual studies included in this review
that had patients from 10 countries including the UK. This paper reported preliminary results up to
day 14 (total follow-up was reported to be 29 days) from a trial that is still ongoing and it is unclear
if it has been peer-reviewed. A short follow-up time may not be sufficient to assess treatment effects.

Wang et al (2020) was a small RCT (n=237) that was limited to a Chinese population. The limitations of this study that affect its applicability to clinical practice include insufficient power to detect assumed differences in clinical outcomes, remdesivir and placebo groups were not well matched for baseline characteristics, treatment was started late in COVID-19, and the absence of data on infectious virus recovery or on possible emergence of reduced susceptibility to remdesivir.

Grein et al (2020) was a small case series (n=53) that included patients from Europe (no UK patients), Canada and Japan. The limitations of this study that affect its applicability to clinical practice include small size, retrospective nature, missing data, lack of information on 8 patients that were initially treated, short follow-up of 28 days and lack of an active control arm.

Many trials are planned or underway to assess remdesivir for treating COVID-19, these include NCT04292899, NCT04292730, NCT04280705 and ISRCTN83971151.

Conclusion

The included studies in this review suggest some benefit with remdesivir compared with placebo for reducing supportive measures including mechanical ventilation and time to recovery in patients with mild or moderate, or severe COVID-19 disease who are on supplemental oxygen treatment. However, no statistically significant differences were found for mortality and serious adverse events (fewer reported with remdesivir compared with placebo). More treatment discontinuations were reported with remdesivir compared with placebo due to adverse events (Wang et al. 2020). A subgroup analysis reported in Beigel et al (2020) suggests that some groups may benefit more than others however this data needs to be interpreted with caution given the wide confidence intervals and lack of adjustment for multiplicity. Therefore this limits the applicability to clinical practice when assessing which patients are most likely to benefit from remdesivir.

See the full evidence review for more information.

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