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[Intervention Review]

Remdesivir for the treatment of COVID-19

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ABSTRACT

Background

Remdesivir is an antiviral medicine with properties to inhibit viral replication of SARS-CoV-2. Positive results from early studies attracted media attention and led to emergency use authorisation of remdesivir in COVID-19. A thorough understanding of the current evidence regarding the effects of remdesivir as a treatment for SARS-CoV-2 infection based on randomised controlled trials (RCTs) is required.

Objectives

To assess the effects of remdesivir compared to placebo or standard care alone on clinical outcomes in hospitalised patients with SARS-CoV-2 infection, and to maintain the currency of the evidence using a living systematic review approach.

Search methods

We searched the Cochrane COVID-19 Study Register (which comprises the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, and medRxiv) as well as Web of Science (Science Citation Index Expanded and Emerging Sources Citation Index) and WHO COVID-19 Global literature on coronavirus disease to identify completed and ongoing studies without language restrictions. We conducted the searches on 16 April 2021.

Selection criteria

We followed standard Cochrane methodology.

We included RCTs evaluating remdesivir for the treatment of SARS-CoV-2 infection in hospitalised adults compared to placebo or standard care alone irrespective of disease severity, gender, ethnicity, or setting.

We excluded studies that evaluated remdesivir for the treatment of other coronavirus diseases.

Data collection and analysis

We followed standard Cochrane methodology.

To assess risk of bias in included studies, we used the Cochrane RoB 2 tool for RCTs. We rated the certainty of evidence using the GRADE approach for outcomes that were reported according to our prioritised categories: all-cause mortality at up to day 28, duration to liberation from invasive mechanical ventilation, duration to liberation from supplemental oxygen, new need for mechanical ventilation (high-flow oxygen, non-invasive, or invasive mechanical ventilation), new need for invasive mechanical ventilation, new need for non-invasive mechanical ventilation or high-flow oxygen, new need for oxygen by mask or nasal prongs, quality of life, serious adverse events, and adverse events (any grade).

Main results

We included five RCTs with 7452 participants diagnosed with SARS-CoV-2 infection and a mean age of 59 years, of whom 3886 participants were randomised to receive remdesivir. Most participants required low-flow oxygen (n=4409) or mechanical ventilation (n=1025) at baseline. Studies were mainly conducted in high- and upper-middle-income countries. We identified two ongoing studies, one was suspended due to a lack of COVID-19 patients to recruit.

Risk of bias assessments were considered to be some concerns or high risk for clinical status and safety outcomes because participants who had died did not contribute information to these outcomes. Without adjustment, this leads to an uncertain amount of missing values and the potential for bias due to missing data.

Effects of remdesivir in hospitalised individuals

Remdesivir probably makes little or no difference to all-cause mortality at up to day 28 (risk ratio (RR) 0.93, 95% confidence interval (CI) 0.81 to 1.06; risk difference (RD) 8 fewer per 1000, 95% CI 21 fewer to 7 more; 4 studies, 7142 participants; moderate-certainty evidence). There was limited evidence for a beneficial effect of remdesivir on mortality in a subset of 435 participants who received low flow oxygen at baseline in one study (RR 0.32, 95% CI 0.15 to 0.66). We could not confirm this finding due to restricted availability of relevant subgroup data from other studies.

Remdesivir may have little or no effect on the duration to liberation from invasive mechanical ventilation (2 studies, 1298 participants, data not pooled, low-certainty evidence). We are uncertain whether remdesivir increases or decreases the chance of clinical improvement in terms of duration to liberation from supplemental oxygen at up to day 28 (3 studies, 1691 participants, data not pooled, very low-certainty evidence).

We are very uncertain whether remdesivir decreases or increases the risk of clinical worsening in terms of new need for mechanical ventilation at up to day 28 (high-flow oxygen or non-invasive ventilation or invasive mechanical ventilation) (RR 0.78, 95% CI 0.48 to 1.24; RD 29 fewer per 1000, 95% CI 68 fewer to 32 more; 3 studies, 6696 participants; very low-certainty evidence); new need for non-invasive mechanical ventilation or high-flow oxygen (RR 0.70, 95% CI 0.51 to 0.98; RD 72 fewer per 1000, 95% CI 118 fewer to 5 fewer; 1 study, 573 participants; very low-certainty evidence); and new need for oxygen by mask or nasal prongs (RR 0.81, 95% CI 0.54 to 1.22; RD 84 fewer per 1000, 95% CI 204 fewer to 98 more; 1 study, 138 participants; very low-certainty evidence). Remdesivir may decrease the risk of clinical worsening in terms of new need for invasive mechanical ventilation (67 fewer participants amongst 1000 participants; RR 0.56, 95% CI 0.41 to 0.77; 2 studies, 1159 participants; low-certainty evidence).

None of the included studies reported quality of life.

Remdesivir probably decreases the serious adverse events rate at up to 28 days (RR 0.75, 95% CI 0.63 to 0.90; RD 63 fewer per 1000, 95% CI 94 fewer to 25 fewer; 3 studies, 1674 participants; moderate-certainty evidence). We are very uncertain whether remdesivir increases or decreases adverse events rate (any grade) (RR 1.05, 95% CI 0.86 to 1.27; RD 29 more per 1000, 95% CI 82 fewer to 158 more; 3 studies, 1674 participants; very low-certainty evidence).

Authors' conclusions

Based on the currently available evidence remdesivir probably has little or no effect on all-cause mortality at up to 28 days in hospitalised adults with SARS-CoV-2 infection. We are uncertain about the effects of remdesivir on clinical improvement and worsening. There were insufficient data available to examine the effect of remdesivir on mortality across subgroups defined by respiratory support at baseline.

Future studies should provide additional data on efficacy and safety of remdesivir for defined core outcomes in COVID-19 research, especially for different population subgroups. This could allow us to draw more reliable conclusions on the potential benefits and harms of remdesivir in future updates of this review. Due to the living approach of this work, we will update the review periodically.

PLAIN LANGUAGE SUMMARY

Remdesivir to treat people with COVID-19

Is remdesivir (an antiviral medicine) an effective treatment for COVID-19?

Key messages

• For adults hospitalised with COVID-19, remdesivir probably has little or no effect on deaths from any cause up to 28 days after treatment compared with placebo (sham treatment) or usual care.

• We are uncertain whether remdesivir improves or worsens patients' condition, based on whether they needed more or less help with breathing.

• Researchers should agree on key outcomes to be used in COVID-19 research, and future studies should investigate these areas. This would allow future updates of this review to draw more certain conclusions about the use of remdesivir to treat COVID-19.

What is remdesivir?

Remdesivir is a medicine that fights viruses. It has been shown to prevent the virus that causes COVID-19 (SARS-CoV-2) from reproducing. Medical regulators have approved remdesivir for emergency use to treat people with COVID-19.

What did we want to find out?

We wanted to know if remdesivir is an effective treatment for people in hospital with COVID-19 and if it causes unwanted effects compared to placebo or usual care.

People with COVID-19 are given different kinds of breathing support, depending on how severe their breathing difficulties are. We used the types of breathing support people received as a measure of the success of remdesivir in treating COVID-19. Types of breathing support included:

• for severe breathing difficulties: invasive mechanical ventilation, when a breathing tube is put into patients' lungs, and a machine (ventilator) breathes for them. Patients are given medicine to make them sedated whilst they are on a ventilator.

• for moderate to severe breathing difficulties: non-invasive mechanical ventilation through a mask over the nose and/or mouth, or a helmet. Air or oxygen is pushed through the mask. Patients are generally awake for this treatment.

• for moderate breathing difficulties: oxygen via a mask or prongs that sit in the nostrils. Patients can still breathe room air.

We were interested in the following outcomes:

• deaths from any cause in the 28 days after treatment;

• whether patients got better after treatment, measured by how long they spent on mechanical ventilation or oxygen;

• whether patients' condition worsened so that they needed oxygen or mechanical ventilation;

• quality of life;

• any unwanted effects; and

• serious unwanted effects.

What did we do?

We searched for studies that investigated remdesivir to treat adults with COVID-19 compared to placebo or standard care. Patients were hospitalised with COVID-19 and could be of any gender or ethnicity.

We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found 5 studies with 7452 people hospitalised with COVID-19. Of these, 3886 people were given remdesivir. The average age of patients was 59 years. Studies took place around the world, mainly in high- and upper-middle-income countries.

Main results

The included studies compared remdesivir to placebo or usual care in people hospitalised with COVID-19 for up to 28 days.

Deaths from any cause

• Remdesivir probably makes little or no difference to deaths from any cause (4 studies, 7142 people). In 1000 people, 8 fewer die with remdesivir compared to placebo or standard care.

Did patients get better with remdesivir?

• Remdesivir may have little or no effect on the length of time patients spent on invasive mechanical ventilation (2 studies, 1298 people).

• We do not know whether remdesivir increases or decreases time on supplemental oxygen (3 studies, 1691 people).

Did patients get worse with remdesivir?

• We do not know whether patients are more or less likely to need any mechanical ventilation (invasive or non-invasive) with remdesivir (3 studies, 6696 people).

• Patients may be less likely to need invasive mechanical ventilation (2 studies, 1159 people).

• We do not know whether patients are more or less likely to need non-invasive mechanical ventilation (1 study, 573 people).

• We do not know whether patients are more or less likely to need oxygen by mask or nasal prongs (1 study, 138 people).

Quality of life

• None of the included studies reported quality of life.

Unwanted effects

• We do not know whether remdesivir leads to more or fewer unwanted effects of any level (3 studies, 1674 people).

• Patients are probably less likely to experience serious unwanted effects with remdesivir than with placebo or standard care (3 studies, 1674 people). In 1000 people, 63 fewer would experience a serious unwanted effect compared to placebo or standard care.

What are the limitations of the evidence?

We are moderately confident in the evidence for deaths from any cause and serious unwanted effects; however, our confidence in the other evidence is limited because studies used different methods to measure and record their results, and we did not find many studies for some of our outcomes of interest.

How up-to-date is this evidence?

The evidence is current to 16 April 2021.