CADTH COVID-19 PANDEMIC

COVID-19 CADTH HEALTH TECHNOLOGY REVIEW

# Remdesivir

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To produce this report, CADTH used a modified approach to the selection, appraisal, and synthesis of the evidence to meet decision-making needs during the COVID-19 pandemic. Care has been taken to ensure the information is accurate and complete, but it should be noted that international scientific evidence about COVID-19 is changing and growing rapidly.


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## Is Remdesivir Effective in Treating COVID-19?

Comparative clinical trials evaluating the safety and efficacy of remdesivir are ongoing. The use of remdesivir for patients with COVID-19 outside of an approved clinical trial is not recommended at this time.

## Background

Remdesivir (development name GS-5734) by Gilead Sciences, Inc., is an antiviral medication with activity against ribonucleic acid (RNA) viruses such as the Coronaviridae.[1] It works by stopping the production of viral genetic material, thus preventing viral replication. Initially developed as a treatment for the Ebola virus, it is under investigation to treat the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19.[2,3]

Remdesivir is not approved for use in any country at this time. In Canada, remdesivir was previously available for individual compassionate use under Health Canada's Special Access Programme. As of April 6, 2020, access to remdesivir is limited to clinical trials only. Exceptions may be considered for pregnant women or children younger than 18 years of age with confirmed COVID-19 and severe disease.[4]

## Question of Interest

Is remdesivir effective in treating COVID-19?

## Summary of Findings

In vitro studies have shown that remdesivir can stop coronaviruses such as SARS-CoV-2 from multiplying.[5-7] Remdesivir has also been studied in vivo using mouse and non-human primate animal models.[6] To date, there are no completed clinical trials conducted in humans comparing remdesivir to placebo or other drugs for treating COVID-19.

### Case Series

The manufacturer of remdesivir recently published a case series of 61 hospitalized patients with severe COVID-19. These patients received remdesivir under Gilead Sciences' compassionate use program between January 25, 2020 and March 7, 2020.[8]

Remdesivir was administered intravenously for a total of 10 days, with an initial dose of 200 mg followed by 100 mg daily for nine days. Of the 61 patients who received remdesivir for compassionate use, 53 patients were included in the analysis. Data were not collected for seven patients and one patient was excluded from the analysis due to a dosing error. Patients were followed from the first dose of remdesivir up to 28 days or until discharge or death. A total of 40 patients (75%) were men with a median age of 64 years (range 23 years to 82 years), and 36 of the 53 patients (68%) had a coexisting condition of hypertension, diabetes, asthma, or hyperlipidemia.[8] Detailed information on the study and patient characteristics is outlined in Appendix A, Tables 1 and 2.

Clinical outcomes that were evaluated during the time period under study, and the results, are depicted in Appendix A, Table 3. Improvements were reported in most patients: The cumulative incidence of clinical improvement (a decrease of two points or more on the six-

point ordinal scale or live discharge)[1] was 84% (95% confidence interval [CI], 70 to 99). The number of patients discharged between the first dose and up to 28 days of follow-up was 25 of 53 patients (47%). During that same period, of the 30 patients on invasive mechanical ventilation, 17 patients (57%) were subsequently extubated. A total of seven of the 53 patients (13%) died during the study. The overall mortality rate from the date of admission was 0.56 per 100 hospitalization days (95% CI, 0.14 to 0.97).[8]

The study also collected information on the safety of remdesivir (Appendix A, Table 3). A total of 32 patients (60%) experienced one or more adverse events. Increased hepatic enzymes, diarrhea, rash, renal impairment, and hypotension were most commonly reported. A total of 12 patients (23%) reported one or more serious adverse events including multiple organ dysfunction syndrome, septic shock, acute kidney injury, and hypotension. Early study withdrawals were reported in four patients (8%). Reasons for stopping treatment included worsening renal failure (one patient), multiple organ failure (one patient), and elevated aminotransferase levels (two patients).[8]

This study is limited by its small sample size, its lack of a control group, and its short duration of follow-up. The benefits and harms of remdesivir need to be established in randomized controlled trials.

### Ongoing Clinical Trials

A review of ClinicalTrials.gov, a website hosted by the U.S. National Library of Medicine, shows that there are five ongoing, phase III, randomized controlled trials evaluating remdesivir in patients with mild, moderate, or severe COVID-19 (Appendix B, Table 4). Two trials have estimated study completion dates of May 2020.

### Terminated or Suspended Clinical Trials

On April 15, 2020, the manufacturer of remdesivir terminated a randomized controlled trial evaluating remdesivir in patients with severe COVID-19. It also suspended a randomized controlled trial evaluating remdesivir in patients with mild to moderate COVID-19 (Table 5). Both trials were conducted in China. The manufacturer cited challenges in recruiting patients given that the epidemic of COVID-19 is under control in China.[9,10]

## Conclusion

The efficacy and safety of remdesivir have not yet been clearly established in human clinical trials. One case series of 61 hospitalized patients with severe COVID-19 who received a 10-day course of intravenous remdesivir has recently been published. In particular, the lack of randomized comparison with a control group precludes the ability to make conclusions regarding remdesivir's safety and efficacy in COVID-19. There are two ongoing phase III randomized controlled trials with estimated completion dates of May 2020. Hence, at this time, the use of remdesivir is not recommended for patients with COVID-19 outside of approved clinical trials.

[1] The six-point scale consists of the following categories: (1) not hospitalized; (2) hospitalized, not requiring supplemental oxygen; (3) hospitalized, requiring supplemental oxygen; (4) hospitalized, requiring nasal high-flow oxygen therapy, non-invasive mechanical ventilation, or both; (5) hospitalized, requiring invasive mechanical ventilation, extracorporeal membrane oxygenation, or both; and (6) death.

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# Appendix A: Data From the Case Series as Part of Gilead Science's Compassionate Use Program for Remdesivir

## Table 1: Study Characteristics of the Case Series on Remdesivir [8]

| Study Information | Study Design | Population | Intervention |
|---|---|---|---|
| Sponsor:<br>Gilead Sciences, Inc.<br>Date of data capture: January 25, 2020 to March 7, 2020 | Multi-centre, open-label<br>(61 patients)<br>Patients included if received at least one dose of the study drug<br>Follow-up to 28 days after the beginning of treatment or until discharge or death | Hospitalized patients with confirmed SARS-CoV-2 infection, an oxygen saturation of ≤ 94% while breathing ambient air or receiving oxygen support<br>Creatinine clearance > 30mL per minute<br>Serum levels<br>of alanine aminotransferase and aspartate<br>aminotransferase < five times the upper limit of the normal range | Remdesivir 200 mg intravenously on day 1 followed by 100 mg intravenously once daily for 9 days<br>Supportive therapy at the discretion of the clinician |

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

## Table 2: Patient Disposition, Demographics, and Baseline Characteristics of the Case Series on Remdesivir[8]

| Patient Disposition | Demographics | Patient Baseline Characteristics |
|---|---|---|
| 53 patients included in the analysis<br>8 patients (13%) excluded<br>(7 patients with no post-dose data and 1 with dosing error)<br>Median follow-up = 18 days (interquartile range 13 to 23) | US = 22 patients<br>Canada = 1 patient<br>Europe = 21 patients<br>Japan = 9 patients | Men = 40 patients (75%)<br>Median age = 64 years<br>(interquartile range 48 to 71))<br>Invasive ventilation = 34 patients (64%)<br>Median duration of invasive mechanical ventilation before treatment = 2 days (interquartile range 1 to 8)<br>Median duration of symptoms before the initiation of treatment = 12 days (interquartile range 9 to 15)<br>Coexisting condition = 36 patients (68%) |

## Table 3: Results of the Case Series on Remdesivir[8]

| Outcomes | Results |
|---|---|
| **Mortality** | |
| Deaths | 7/53 patients (13%) |
| Deaths in patients receiving invasive ventilation | 6/32 patients (18%) |
| Overall mortality rate from the date of admission | 0.56 per 100 hospitalization days (95% CI, 0.14 to 0.97) |
| Risk of death in patients ≥70 years old compared with patients < 70 years old | HR = 11.34 (95% CI, 1.36 to 96.17) |
| **Clinical Outcomes[a]** | |
| Number of patients discharged | 25/53 patients (47%) |
| Number of patients receiving invasive mechanical ventilation who were extubated | 17/30 patients (57%) |
| Number of patients with improvement in the category of oxygen support[b] | 36/53 patients (68%) |
| Cumulative incidence of clinical improvement (a decrease of 2 points or more on the six-point ordinal scale or live discharge)[c] | 84% (95% CI, 70 to 99) |
| Clinical improvement in patients receiving invasive ventilation compared to patients receiving non-invasive ventilation | HR for improvement = 0.33 (95% CI, 0.16 to 0.68) |
| Clinical improvement in patients ≥ 70 years compared with patients < 50 years | HR for improvement = 0.29 (95% CI, 0.11 to 0.74) |
| **Safety** | |
| Number of patients with one or more adverse events | 32/53 (60%) |
| Number of patients with one or more serious adverse events | 12/53 (23%) |
| Number of patients stopping treatment early | 4/53 (8%) |

CI = confidence interval; HR = hazard ratio.

a Results reported during the 28 days after the beginning of treatment with remdesivir or until discharge or death.

b Change in oxygen support requirements (ambient air, low-flow oxygen, nasal high-flow oxygen, non-invasive positive pressure ventilation, invasive mechanical ventilation, and extracorporeal membrane oxygenation).

c The six-point scale consists of the following categories: (1) not hospitalized; (2) hospitalized, not requiring supplemental oxygen; (3) hospitalized, requiring supplemental oxygen; (4) hospitalized, requiring nasal high-flow oxygen therapy, non-invasive mechanical ventilation, or both; (5) hospitalized, requiring invasive mechanical ventilation, extracorporeal membrane oxygenation, or both; and (6) death.

# Appendix B: Clinical Trials on Remdesivir

## Table 4: Ongoing Phase III Randomized Controlled Trials

| Study Information | Study Design | Population | Interventions | Key Outcomes |
|---|---|---|---|---|
| Sponsor:<br>Gilead Sciences, Inc.<br>ClinicalTrials.gov Identifier: NCT04292899[11]<br>Date of trial completion:<br>May 2020 | Open-label, multi-centre (2,400 patients) | Hospitalized patients aged ≥ 18 years or aged ≥ 12 and < 18 years weighing ≥ 40 kg, with severe COVID-19 | Patients not mechanically ventilated: standard of care with remdesivir 200 mg IV on day 1 followed by 100 mg IV on days 2 to 5<br>Patients not mechanically ventilated: standard of care with remdesivir 200 mg IV on day 1 followed by 100 mg IV on days 2 to 10<br>Patients on mechanical ventilation: standard of care with remdesivir 200 mg IV on day 1 followed by 100 mg IV on days 2 to 10 | • Odds ratio for improvement on day 14<br>• Safety |
| Sponsor:<br>Gilead Sciences, Inc.<br>ClinicalTrials.gov Identifier: NCT04292730[12]<br>Date of trial completion:<br>May 2020 | 0pen-label, multi-centre (1,600 patients) | Hospitalized patients aged ≥ 12 years with moderate COVID-19 | Standard of care with remdesivir 200 mg IV on day 1 followed by 100 mg IV on days 2 to 5<br>Standard of care with remdesivir 200 mg IV on day 1 followed by 100 mg IV on days 2 to 10<br>Standard of care | • Odds ratio for improvement on day 14<br>• Safety |
| Sponsor:<br>National Institute of Allergy and Infectious Diseases<br>ClinicalTrials.gov Identifier: NCT04280705[13]<br>Date of trial completion:<br>April 2023 | Double-blind, placebo-controlled, multi-centre (440 patients) | Hospitalized adult patients diagnosed with COVID-19 | Remdesivir 200 mg IV on day 1 followed by 100 mg IV once daily for 9 days<br>Matching placebo | • Percentage of patients reporting each severity rating on an 8-point ordinal scale<br>• Change from baseline in various laboratory values (e.g., creatinine, platelets)<br>• Clinical status<br>• Safety |
| Sponsor: Oslo University Hospital | Open-label, multi-centre (700 patients) | Hospitalized adult patients with confirmed SARS-CoV-2 infection | Remdesivir 200 mg loading dose IV followed by 100 mg IV daily for the duration of the hospitalization and | • All-cause in-hospital mortality |

| | | | | |
|---|---|---|---|---|
| ClinicalTrials.gov Identifier: NCT04321616[14]<br>Date of trial completion:<br>November 2020 | | | up to 10 days total course<br>Oral hydroxychloroquine 800 mg x 2 loading doses followed by 400 mg x 2 doses every day for a total of 10 days<br>Standard of care | • Occurrence and duration of mechanical ventilation<br>• Occurrence and duration of intensive care unit treatment<br>• Duration of hospitalization |
| Sponsor:<br>INSER–Institut national de la santé et de la recherche médicale<br>ClinicalTrials.gov Identifier: NCT04315948[15]<br>Date of trial completion:<br>March 2023 | Open-label, multi-centre (3,100 patients) | Hospitalized adult patients with confirmed SARS-CoV-2 infection | Remdesivir 200 mg IV on day 1 followed by a 100 mg dose IV once daily for the duration of the hospitalization, up to 10 days<br>Oral lopinavir 400 mg/ritonavir 100 mg every 12 hours for 14 days<br>Oral lopinavir 400 mg/ritonavir 100 mg every 12 hours for 14 days with subcutaneous interferon beta-1a 44 mcg on day 1, day 3, and day 6<br>Oral hydroxychloroquine loading dose of 400 mg twice daily for one day followed by 400 mg once daily for 9 days<br>Standard of care | • Percentage of subjects reporting each severity rating on a 7-point ordinal scale<br>• Time to discharge<br>• Number of oxygenation-free days in the first 28 days |

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

## Table 5: Terminated or Suspended Phase III Randomized Controlled Trials

| Study Information | Study Design | Population | Interventions | Key Outcomes |
|---|---|---|---|---|
| Sponsor:<br>Capital Medical University<br>ClinicalTrials.gov Identifier: NCT04257656[9]<br>Date of trial completion:<br>terminated[a] | Double-blind, placebo-controlled, multi-centre<br>(453 patients) | Hospitalized adult patients with severe 2019-nCoV respiratory disease | Remdesivir 200 mg IV on day 1 followed by 100 mg IV once daily for 9 days<br>Matching placebo | • Time to clinical improvement<br>• Clinical status<br>• Time to hospital discharge<br>• All-cause mortality<br>• Safety |
| Sponsor:<br>Capital Medical University<br>ClinicalTrials.gov Identifier: NCT04252664[10]<br>Date of trial completion:<br>suspended[a] | Double-blind, placebo-controlled, multi-centre<br>(308 patients) | Hospitalized adult patients with mild and moderate 2019-nCoV respiratory disease | Remdesivir 200 mg IV on day 1 followed by 100 mg IV once daily for 9 days<br>Matching placebo | • Time to clinical improvement<br>• All-cause mortality<br>• Frequency of respiratory progression<br>• Time to defervescence<br>• Safety |

2019-nCoV = novel coronavirus.

[a] The epidemic of COVID-19 is under control in China; no eligible patients can be enrolled or recruited at present.