SARS-CoV-2 and COVID-19

Treatment: Remdesivir

David H. Spach, MD
Professor of Medicine
Division of Infectious Diseases
University of Washington

Gretchen Snoeyenbos Newman, MD
Senior Fellow
Division of Infectious Diseases
University of Washington
Remdesivir (formerly GS-5734)
Remdesivir

Chemical structure drawing by Kenton Unruh, Ph
Remdesivir (GS-5734)

- Adenosine nucleotide analogue prodrug
- Broad-spectrum against several RNA viruses
- Requires phosphorylation for activation triphosphate form
- Competes for incorporation with adenosine triphosphate (ATP)
- Does not act as classic chain terminator
- Possible delayed chain termination (similar to entecavir)
- Selectivity of ATP versus Remdesivir
  - Ebola RNA-dependent RNA polymerase $\sim 4:1$
  - RSV RNA-dependent RNA polymerase $\sim 3:1$
  - Human mitochondrial RNA polymerase $\sim 500:1$

Remdesivir (GS-5734)

- **Class**: Adenosine nucleotide analogue prodrug
- **Approval Status**: investigational
- **Mechanism**:
  - Competes for incorporation with adenosine triphosphate (ATP)
  - Does not act as classic chain terminator
  - Possible delayed chain termination (similar to entecavir)
- **Dose (Intravenous): Per Study Protocol**
  - 200 mg on day 1, followed by 100 mg daily for various time courses
- **Adverse Events**:
  - Elevated LFTs (typically 2-3x normal), unclear significance
  - GI symptoms (nausea, vomiting, gastroparesis, rectal bleeding)
Remdesivir (GS-5734) IC$_{50}$ and MERS-CoV

Percent Inhibition of MERS-CoV in 2B4 Cells

IC$_{50}$ = 0.03 µM

Measuring Antiviral Efficacy

• **EC\textsubscript{50} – Effective Concentration**
  - The concentration of an antiviral agent at which virus replication is inhibited by 50% in a cell-based assay
  - Conceptually similar to the MIC (minimum inhibitory concentration) for an antibacterial agent

• **CC\textsubscript{50} – Cytotoxic Concentration**
  - Concentration of an antiviral agent required to kill 50% of cells in uninfected culture

• **SI – Selectivity Index**
  - Ratio between the CC50 and EC50 (CC50/EC50)
  - A higher number signals a theoretically more safe and effective drug
Antiviral Drugs  Effective Concentration 50 (EC50)

EC\textsubscript{50} = The concentration of an antiviral agent at which virus replication is inhibited by 50% in a cell-based assay
Remdesivir EC50 and SARS-CoV-2

Activity Against SARS-CoV-2 (2019-CoV): Vero E6 Cells

Remdesivir EC50 and SARS-CoV-2

Activity Against SARS-CoV-2 (2019-CoV): Vero E6 Cells

Remdesivir in Adults with Severe COVID-19: A Randomized, Double-blind Trial (China)

Published Data — Randomized, double-blind, placebo-controlled trial

Remdesivir Randomized Controlled Trial in Adults with Severe COVID-19: Design

**Study Design**

- **Background**: A randomized, double-blind, placebo-controlled, multicenter trial of remdesivir in adults with severe COVID-19 conducted between February 6, 2020 and March 12, 2020.

- **Location**: 10 hospitals in Hubei, China.

- **Inclusion Criteria (intended n = 453; actual n = 237)**
  - Age ≥18 years
  - PCR positive test for SARS-CoV-2 infection
  - Pneumonia on chest imaging
  - SpO2 ≤94% on room air or PaO2:FiO2 <300mmHg
  - Symptom onset ≤12 days prior to enrollment

- **Exclusion Criteria**
  - Pregnant or breastfeeding
  - Cirrhosis or AST/ALT > 5x upper limit of normal
  - GFR <30mL/min per 1.73 m² or renal replacement therapy
  - Treatment with another investigational drug in the 30 days before screening

- **Duration of follow up**
  - 28 days or until discharge

Arms and Interventions (2:1 randomization)

**Remdesivir***
- 200 mg IV on day 1, followed by 100 mg IV on days 2–10 as single daily infusion (n = 158)

* or *

**Placebo***
- Equivalent volume given on day 1 and on days 2–10 as single daily infusions (n = 78)

* Patients in both groups were allowed to receive concomitant lopinavir-ritonavir, interferons, and/or corticosteroids as part of standard care

## Remdesivir Randomized Controlled Trial in Adults with Severe COVID-19: Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics*</th>
<th>Remdesivir (n = 158)</th>
<th>Placebo (n = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (IQR)</td>
<td>66.0 (57.0–73.0)</td>
<td>64.0 (53.0–70.0)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>89 (56%)</td>
<td>51 (65%)</td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td>112 (71%)</td>
<td>55 (71%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>72 (46%)</td>
<td>30 (38%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>40 (25%)</td>
<td>16 (21%)</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>15 (9%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Adjunctive Therapies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Receiving interferon alfa-2b</td>
<td>29 (18%)</td>
<td>15 (19%)</td>
</tr>
<tr>
<td>Receiving lopinavir–ritonavir</td>
<td>27 (17%)</td>
<td>15 (19%)</td>
</tr>
<tr>
<td>Antibiotic treatment</td>
<td>121 (77%)</td>
<td>63 (81%)</td>
</tr>
<tr>
<td>Corticosteroids therapy</td>
<td>60 (38%)</td>
<td>31 (40%)</td>
</tr>
</tbody>
</table>

Remdesivir Randomized Controlled Trial in Adults with Severe COVID-19: Baseline Characteristics

<table>
<thead>
<tr>
<th>Six-Category Scale on Day 1*</th>
<th>Remdesivir (n = 158)</th>
<th>Placebo (n = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2—hospital admission, not requiring supplemental oxygen</td>
<td>0</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>3—hospital admission, requiring supplemental oxygen</td>
<td>129 (82%)</td>
<td>65 (83%)</td>
</tr>
<tr>
<td>4—hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation</td>
<td>28 (18%)</td>
<td>9 (12%)</td>
</tr>
<tr>
<td>5—hospital admission, requiring extracorporeal membrane oxygenation or invasive mechanical ventilation</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>6—death</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Scale used to define clinical status: 1 = discharged or having reached discharge criteria (defined as clinical recovery [e.g. normalization of pyrexia, respiratory rate, O2 saturation >94% on room air, and relief of cough], all maintained for at least 72 hours). Note clinical status 1 (discharged) not applicable for this baseline table.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Remdesivir (n = 158)</th>
<th>Placebo (n = 78)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to clinical improvement, days</td>
<td>21.0 (13.0 to 28.0)</td>
<td>23.0 (15.0 to 28.0)</td>
<td>1.23 (0.87 to 1.75)</td>
</tr>
<tr>
<td>Day 28 mortality</td>
<td>22 (14%)</td>
<td>10 (13%)</td>
<td>1.1% (−8.1 to 10.3)</td>
</tr>
<tr>
<td>Duration of invasive mechanical ventilation, days</td>
<td>7.0 (4.0 to 16.0)</td>
<td>15.5 (6.0 to 21.0)</td>
<td>−4.0 (−14.0 to 2.0)</td>
</tr>
<tr>
<td>Duration of oxygen support, days</td>
<td>19.0 (11.0 to 30.0)</td>
<td>21.0 (14.0 to 30.5)</td>
<td>−2.0 (−6.0 to 1.0)</td>
</tr>
<tr>
<td>Duration of hospital stay, days</td>
<td>25.0 (16.0 to 38.0)</td>
<td>24.0 (18.0 to 36.0)</td>
<td>0.0 (−4.0 to 4.0)</td>
</tr>
</tbody>
</table>

Remdesivir Randomized Controlled Trial in Adults with Severe COVID-19: Results, Undetectable Viral RNA

Remdesivir Randomized Controlled Trial in Adults with Severe COVID-19: Results, Clinical Improvement Rates

Remdesivir Randomized Controlled Trial in Adults with Severe COVID-19: Results, Mortality

Remdesivir Randomized Controlled Trial in Adults with Severe COVID-19: Results

- Authors were unable to enroll nearly half the planned number of participants due to resolution of the COVID-19 outbreak in Hubei, China
- There were no differences in the rates of:
  - Time to clearance of virus
  - Clinical benefits
  - Mortality

Interpretation: “In this study of adult patients admitted to hospital for severe COVID-19, remdesivir was not associated with statistically significant clinical benefits. However, the numerical reduction in time to clinical improvement in those treated earlier requires confirmation in larger studies.”
Compassionate Use of Remdesivir for Patients with Severe COVID-19 (International)

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

<table>
<thead>
<tr>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Background:</strong> Case series of 61 patients diagnosed with severe COVID-19 infection who received remdesivir through compassionate use from January 25, 2020 to March 7, 2020 in multiple international sites</td>
</tr>
<tr>
<td><strong>Evaluation:</strong> Incidence of key clinical endpoints (multiple)</td>
</tr>
<tr>
<td><strong>Inclusion Criteria (enrolled, n = 61; final analysis, n =53)</strong></td>
</tr>
<tr>
<td>- PCR positive for SARS-CoV-2 in nasopharyngeal sample</td>
</tr>
<tr>
<td>- SpO2 ≤94% on room air, or need for oxygen support</td>
</tr>
<tr>
<td>- Creatinine clearance &gt;30 mL per minute</td>
</tr>
<tr>
<td>- AST and ALT &lt;5x the upper limit of normal</td>
</tr>
<tr>
<td><strong>Exclusion Criteria</strong></td>
</tr>
<tr>
<td>- Use of other investigational agent for COVID-19</td>
</tr>
<tr>
<td><strong>Planned Treatment</strong></td>
</tr>
<tr>
<td>- Remdesivir: 200 mg IV loading dose on day 1, then 100 mg IV daily x 9 days (total 10 days)</td>
</tr>
<tr>
<td>- Standard supportive care</td>
</tr>
<tr>
<td><strong>Duration of follow up</strong></td>
</tr>
<tr>
<td>- 28 days</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Baseline Characteristics*</th>
<th>Invasive Ventilation (n = 34)</th>
<th>Non-Invasive O2 Support (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, IQR, years)</td>
<td>67 (56 - 72)</td>
<td>53 (41-68)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>27 (79)</td>
<td>13 (68)</td>
</tr>
<tr>
<td>Coexisting conditions, n (%)</td>
<td>25 (74)</td>
<td>11 (58)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9 (26)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8 (24)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>6 (18)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Asthma</td>
<td>5 (15)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Duration of symptoms prior to remdesivir (median, IQR, days)</td>
<td>11 (8 – 15)</td>
<td>13 (10 – 14)</td>
</tr>
</tbody>
</table>

*Of the 61 patients approved for compassionate use remdesivir, 7 were excluded from analysis due to lack of baseline information and 1 was excluded due to an error in remdesivir dosing

Compassionate Use of Remdesivir for Patients with Severe Covid-19: Baseline Oxygen Support

<table>
<thead>
<tr>
<th>Baseline Characteristics*</th>
<th>Invasive Ventilation (n = 34)</th>
<th>Non-invasive O2 Support (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen Support Category, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>30 (88)</td>
<td>NA</td>
</tr>
<tr>
<td>Extracorporeal membrane oxygenation (ECMO)</td>
<td>4 (12)</td>
<td>NA</td>
</tr>
<tr>
<td>Noninvasive positive-pressure ventilation</td>
<td>NA</td>
<td>2 (11)</td>
</tr>
<tr>
<td>High-flow oxygen</td>
<td>NA</td>
<td>5 (26)</td>
</tr>
<tr>
<td>Low-flow oxygen</td>
<td>NA</td>
<td>10 (53)</td>
</tr>
<tr>
<td>Ambient air</td>
<td>NA</td>
<td>2 (11)</td>
</tr>
</tbody>
</table>

*Of the 61 patients approved for compassionate use remdesivir, 7 were excluded from analysis due to lack of baseline information and 1 was excluded due to an error in remdesivir dosing

Compassionate Use of Remdesivir for Patients with Severe Covid-19: Results (Overall)

Clinical improvement defined as decrease of ≥2 points on 6-point ordinal scale or live discharge

Compassionate Use of Remdesivir for Patients with Severe Covid-19: Results (Baseline O2 Support)

Clinical improvement defined as decrease of ≥2 points on 6-point ordinal scale or live discharge

Compassionate Use of Remdesivir for Patients with Severe Covid-19: Results (Baseline O2 Support)

Clinical improvement defined as decrease of ≥2 points on 6-point ordinal scale or live discharge

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

- 32 patients (60%) reported adverse events most commonly:
  - Increased hepatic enzymes
  - Diarrhea
  - Rash
  - Renal impairment
  - Hypotension

- 4 patients (8%) discontinued remdesivir:
  - 1 due to worsened renal failure
  - 1 due to multiorgan failure
  - 2 due to elevated aminotransferase levels

Compassionate Use of Remdesivir for Patients with Severe Covid-19: Authors’ Conclusions

Conclusions: “In this cohort of patients hospitalized for severe Covid-19 who were treated with compassionate-use remdesivir, clinical improvement was observed in 36 of 53 patients (68%). Measurement of efficacy will require ongoing randomized, placebo-controlled trials of remdesivir therapy.”

Remdesivir Prophylaxis and Therapy in Rhesus Macaque Model of MERS-CoV Infection

Remdesivir Therapy and Prophylaxis of in Animal Model of MERS-CoV Infection

**Study Design**

**Background:** Three-arm study testing efficacy of remdesivir prophylaxis and treatment of MERS-CoV in rhesus macaque model

**Primary Endpoints:**
- Clinical status
- Virologic clearance
- Chest radiograph data
- Lung histopathology

**Study Design:**
- Three arms (treatment, prophylaxis, control)
- Animals monitored clinically and with CXR
- All animals sacrificed on day 6
- All animals necropsied

**Vehicle Control**
Placebo IV given 12 hrs after or 24 hrs prior to inoculation (n = 6)

**Prophylaxis**
Remdesivir 5 mg/kg IV 24 hrs prior to inoculation and 1x/day until day 6 (n = 6)

**Treatment**
Remdesivir 5 mg/kg IV 12hrs after inoculation and 1x/day until day 6 (n = 6)

Remdesivir Therapy and Prophylaxis of in Animal Model of MERS-CoV Infection

Reduction of Lung Tissue MERS-CoV Load in Remdesivir-Treated Macaques

Viral Loads in Respiratory Tracts of Necropsy Samples in Six Lung Lobes

Favorable Lung Histology Scores in Animals Receiving Prophylactic Remdesivir for MERS-CoV Infection

Lesion Score in Lung Tissue (each lung rated 0 to 4)

Favorable Lung Histology in Animals Receiving Remdesivir

Vehicle control  Prophylactic remdesivir  Therapeutic remdesivir

Representative H&E Image of Lung Tissue, magnification 100x

Staining of lung sample with polyclonal α-MERS-CoV antibody, magnification 200x

Remdesivir Therapy and Prophylaxis of MERS-CoV in Animal Model: Conclusions

• Monkeys given remdesivir either prophylactically or as treatment had better clinical scores and fewer infiltrates on chest radiographs than controls

• There was lower viral load of MERS-CoV in respiratory tract of monkeys given prophylactic remdesivir

• Lung examination revealed gross (visible) lesions covering less of the lung in animals treated with remdesivir and no gross lung lesions in those given prophylactic remdesivir

• Histologic evaluation showed normal tissue in animals treated prophylactically and less severe pneumonia in those given treatment dosing

Conclusions: “The data presented here support testing of the efficacy of remdesivir treatment in the context of a MERS clinical trial. It may also be considered for a wider range of coronaviruses, including the currently emerging novel coronavirus 2019-nCoV.”

Clinical Benefit of Remdesivir in Rhesus Macaques Infected with SARS-CoV-2

# Clinical Benefit of Remdesivir in Rhesus Macaques Infected with SARS-CoV-2: Study Design

## Study Design

**Background:** Blinded, placebo-controlled study to evaluate the effect of remdesivir on SARS-CoV-2 infection using a rhesus macaque model

**Primary Endpoints:**
- Clinical status
- Viral load and infectious virus measure
- Chest radiograph data
- Lung histopathology

**Study Design:**
- Two arms: (1) treatment, (2) control
- Animals monitored clinically and with CXR
- All animals sacrificed on day 7
- All animals necropsied

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**Remdesivir Group**
10 mg/kg IV 12 hours after inoculation, then 5 mg/kg daily through day 6 (n = 6)

**Vehicle Solution (Control Group)**
Vehicle solution IV 12 hours after inoculation and then daily through day 6 (n = 6)

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Clinical Benefit of Remdesivir in Rhesus Macaques Infected with SARS-CoV-2: Study Design

Clinical Benefit of Remdesivir in Rhesus Macaques Infected with SARS-CoV-2: Results, Clinical Benefit

Clinical scores: based on weight, temperature, pulse oximetry, blood pressure, respiration rate, and chest radiographs

• Remdesivir metabolite was detected throughout the lungs

• Clinical, radiologic, and pathologic disease scores were lower in remdesivir treated animals than in controls

• Viral load and infectious virus in the nose, throat, and rectum were not different between remdesivir and control groups through the duration of the study

Clinical Benefit of Remdesivir in Rhesus Macaques Infected with SARS-CoV-2: Authors’ Conclusions

**Conclusions:** “Therapeutic remdesivir treatment initiated early during infection has a clear clinical benefit in SARS-CoV-2-infected rhesus macaques. These data support early remdesivir treatment initiation in COVID-19 patients to prevent progression to severe pneumonia.”