Remdesivir (GS-5734)

A Review of Pertinent Drug Information for SARS-CoV-2

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Society of Infectious Diseases Pharmacists
Remdesivir (GS-5734)

Mechanism of Action: Interference with viral RNA-dependent RNA polymerase; premature termination of viral RNA transcription

Status: Investigational, COVID-19 Phase III trials ongoing

Formulation: Intravenous only

Dosing: 200 mg IV loading dose, then 100 mg IV daily for 5-10 days
Pediatric Dosing: 5 mg/kg IV loading dose (max 200 mg), then 2.5 mg/kg IV daily (max 100 mg)

Manufacturer: Gilead Sciences

*Optimal duration currently under investigation
Remdesivir Structure Activity Relationship

Monophosphoramidate 1’Cyano C-adenosine Nucleoside Analog

Siegel; ACS 2017.
Remdesivir Structure Activity Relationship

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C-Adenosine Analog  Monophosphate Form  Remdesivir

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Remdesivir Structure Activity Relationship

C-Adenosine Analog
Rate limiting phosphorylation

Monophosphate Form

Remdesivir

Siegel; ACS 2017.
Remdesivir Structure Activity Relationship

C-Adenosine Analog
Rate limiting phosphorylation

Monophosphate Form
Charge reduces permeability

Remdesivir

Siegel; ACS 2017.
Remdesivir Structure Activity Relationship

C-Adenosine Analog
Rate limiting phosphorylation

Monophosphate Form
Charge reduces permeability

Remdesivir
Neutral charge, bypasses rate limiting step

Siegel; ACS 2017.
Remdesivir Structure Activity Relationship

Monophosphoramidate 1’Cyano C-adenosine Nucleoside Analog

Siegel; ACS 2017.
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C-Adenosine Analog
Poor selectivity, highly cytotoxic

Remdesivir

Remdesivir Structure Activity Relationship

Siegel; ACS 2017.
Remdesivir Structure Activity Relationship

C-Adenosine Analog
Poor selectivity, highly cytotoxic

Remdesivir
1’Cyano modification confers selectivity

Siegel; ACS 2017.
Remdesivir (GS-5734) Pharmacokinetics

- **Distribution**: Unbound 12.1%; Widely distributed
  - Bladder, kidneys, liver, prostate gland, salivary gland (mandibular), pancreas
  - Seminal vesicle, epididymis, testes
  - Poorly crosses blood-brain barrier

- **Metabolism**: Phosphoramidate prodrug activated by esterases; CYP3A4 substrate

- **Elimination**: Renal 63%, biliary 27.8%

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Remdesivir (GS-5734)</th>
<th>Nucleoside Metabolite (GS-441524)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$</td>
<td>2.6 µg/mL</td>
<td>0.14-0.15 µg/mL</td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>-</td>
<td>2.75-4 hr</td>
</tr>
<tr>
<td>Half-life</td>
<td>0.84-1.04 hr</td>
<td>20.4-25.3 hr</td>
</tr>
</tbody>
</table>

Safety

• Multiple-dose, 5-14 days
  • Any TEAE - 56-72%; All Grade 1-2
  • ALT/AST increase
    • Onset 5-25 days; resolution 3-47 days
• Phlebitis
• Constipation
• Dyspepsia
• Extremity pain
• Headache
• Nausea

• Ebola RCT
  • Single patient experienced hypotension and cardiac arrest after RDV initiation; cannot be distinguished from fulminant Ebola
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Sulfobutylether-beta Cyclodextrin (SBECD)

Remdesivir 150 mg solution - 9 g
Remdesivir 150 mg lyophylized powder - 4.5 g
Voriconazole 400 mg - 6.4 g
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### Sulfobutylether-beta Cyclodextrin (SBECOD)

- Remdesivir 150 mg solution - 9 g
- Remdesivir 150 mg lyophylized powder - 4.5 g
- Voriconazole 400 mg - 6.4 g

Does **NOT** meet NIOSH/ASHP criteria for hazardous compound

Consult updated pharmacy instructions from Gilead for additional information

**In vitro Activity**

**Filoviridae**
- Ebola
- Marburg

**Paramyxoviridae**
- Measles
- Mumps
- Nipah
- Hendra

**Pneumoviridae**
- Respiratory Syncytial Virus
- Human Metapneumovirus

**Orthocoronaviridae**
- HCoV-NL63
- HCoV-OC43
- HCoV-229E
- HCoV-HKU1
- MERS
- SARS-CoV-1
- SARS-CoV-2

HCoV = Human Coronavirus; MERS = Middle East Respiratory Syndrome; SARS = Severe Acute Respiratory Syndrome
## In vitro Activity

<table>
<thead>
<tr>
<th>Virus</th>
<th>EC50 (cells)</th>
<th>CC50 (cells)</th>
<th>Selectivity Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>SARS-CoV-2</td>
<td>0.77 µM (Vero E6)</td>
<td>&gt;100 µM (Vero E6)</td>
<td>&gt;130</td>
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<tr>
<td>SARS-CoV-1</td>
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<td>&gt;10 µM (HAE)</td>
<td>&gt;144</td>
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<td>0.086 µM (MCr)</td>
<td>6.1 (Hep-2)</td>
<td>N/A</td>
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</table>

EC50 = 50% effective concentration; CC50 = 50% cytotoxic concentration; Selectivity Index = CC50/EC50; Vero E6 = African monkey kidney cells; HAE = human airway epithelial cells; MCr = macrophages; Hep-2 = human epithelial type 2 cells.
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SARS-CoV-2 EC₅₀

**Ribavirin 109.5 µM**

**Penciclovir 95.96 µM**

**Favipiravir 61.9 µM**

**Hydroxychloroquine 0.77 µM**

**Chloroquine 1.13-5.47 µM**


Sheahan; Sci Transl Med 2017.

Agostini; Am Soc Micro 2018.

Yao; CID 2020.
Coronaviruses and Proofreading

Ribavirin	Penciclovir	Favipiravir

Removed by proofreading

Remdesivir

Maintains activity; high fitness cost

Agostini; mBio 2018.
Jordan; AAC 2018.
## In vivo Animal Prophylaxis

<table>
<thead>
<tr>
<th>Virus</th>
<th>Virologic</th>
<th>Clinical/Pathologic</th>
<th>Survival</th>
</tr>
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<tbody>
<tr>
<td>SARS-CoV-1</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>MERS</td>
<td>✓</td>
<td>✓</td>
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*MERS-infected mice showed improved survival; rhesus macaques euthanized day 6 post-infection unable to determine survival impact of remdesivir*

## In vivo Animal Treatment

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<th>Clinical/Pathologic</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>SARS-CoV1</td>
<td>✓</td>
<td>✓</td>
<td>✓ (Day 1)✗ (Day 2)</td>
</tr>
<tr>
<td>MERS</td>
<td>✓</td>
<td>✓</td>
<td>✗ *</td>
</tr>
<tr>
<td>Ebola</td>
<td>✓</td>
<td>✓</td>
<td>---</td>
</tr>
</tbody>
</table>

*MERS-infected mice did not show improved survival; rhesus macaques euthanized day 6 post-infection unable to determine survival impact of remdesivir; Macaques in Ebola model were euthanized if deemed clinically moribund

De wit E; Proc Natl Acad Sci 2020.
Sheahan; Nat Comm 2020.
Sheahan; Sci Transl Med 2017.
“A drug that inhibits viral replication may be of little use once virus replication has reached its peak...”
Randomized, Controlled Ebola Trial

- Standard of Care +
  - ZMapp (Control)
    - Triple monoclonal antibody
  - Remdesivir (RDV)
    - 200 mg load
    - 100 mg daily x9-13d
  - REGN-EB3
    - Triple monoclonal antibody
  - MAb114
    - Single Ebola survivor monoclonal

1:1:1:1
Stratified on cycle-threshold (i.e. viral load)
1º Outcome: 28 day mortality
Randomized, Controlled Ebola Trial

• Similar duration of symptoms (~5.5 days)/viral load
  • Per day OR 1.12 (1.00-1.24)
• Baseline characteristics generally well matched
  • Higher SCr/LFTs in ZMapp/RDV (sicker?)
• ZMapp and RDV arms halted; mortality signal

Mulangu; NEJM 2019.
Randomized, Controlled Ebola Trial

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  - Per day OR 1.12 (1.00-1.24)
- Baseline characteristics generally well matched
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Started too late? (latest start day 3)
Flaw in animal model?
Standard of care/resources?
Compassionate Use Case Series

61 Patients

8 Excluded:
- 7 No post-baseline data
- 1 Erroneous start date

53 Patients

10 days: n = 40; 75%
5-9 days: n = 10; 19%
< 5 days: n = 3; 6%

Median follow-up 18 days (IQR 13-23)
Compassionate Use Case Series

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53 Patients

10 days: n = 40; 75%

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<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR) – yr</td>
<td>64 (48-71)</td>
</tr>
<tr>
<td>Male sex – no. (%)</td>
<td>40 (75)</td>
</tr>
<tr>
<td>Invasive ventilation – no. (%)</td>
<td>34 (64)</td>
</tr>
<tr>
<td>ECMO – no. (%)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Median Sx before RDV (IQR) – days</td>
<td>12 (9-15)</td>
</tr>
<tr>
<td>Coexisting conditions* – no. (%)</td>
<td>36 (68)</td>
</tr>
</tbody>
</table>

*Specific conditions – n (%): hypertension 13 (25), diabetes 9 (17), hyperlipidemia 6 (11), asthma 6 (11); ECMO = extracorporeal membrane oxygenation; Sx = symptoms; RDV = remdesivir

Grein; NEJM 2020.
Compassionate Use Case Series

No pre-specified endpoints

1 - Discharged
2 – Ambient air
3 – Low-flow
4 – High-flow/NIPPV
5 – MV/ECMO
6 – Death

MV = mechanical ventilation; NIPPV = non-invasive positive pressure ventilation
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Improvement/Discharge
N= 36/53 (67.9%)

Worsening
N= 8/53 (15.1%)

Mortality
N= 7/53 (13%)
Mean age 74.5 (range 68-79)
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Worsening
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Mortality
N= 7/53 (13%)
Mean age 74.5 (range 68-79)

28-day/discharge/death data unavailable
N= 17/53 (32.1%)
8 MV, 1 ECMO at last time-point

Grein; NEJM 2020.
### Compassionate Use Case Series

<table>
<thead>
<tr>
<th>Adverse Events*</th>
<th>Patients – n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>32 (60)</td>
</tr>
<tr>
<td>ALT/AST increase</td>
<td>12 (23)</td>
</tr>
<tr>
<td>Renal impairment/AKI</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Rash</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Multi-organ dysfunction syndrome</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

*Adverse events listed with >5% patients

Four patients discontinued for the following:
1. Worsening renal function
2. Multi-organ dysfunction
3. Transaminitis/rash
4. Transaminitis

“No new safety signals were detected in this compassionate use cohort of short-term remdesivir therapy.”
Compassionate Use Case Series

Take home points:

• Difficult to interpret without control group
  • Natural course vs. remdesivir effects
  • Historical comparisons of limited value
  • No pre-specified endpoints
  • Median start day 12 of illness; no quantitative PCR to evaluate viral load progression

• High risk of bias
  • Selection – patients screened for compassionate use
  • Sampling – unclear if consecutive patients, not all compassionate use patients included
  • Reporting – 8 patients excluded for erroneous/lack of data, high proportion without endpoints

• Safety profile consistent with previous data
  • Toxicity vs. underlying disease
• Current data insufficient to draw definitive conclusions
• Clinical trials and compassionate use ongoing
• High quality evidence paramount for meaningful conclusions
<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Population</th>
<th>Intervention</th>
<th>Completion*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adaptive</td>
<td>NIAID</td>
<td>n = 440</td>
<td>RDV vs. PCB; Adaptive</td>
<td>4/1/2023</td>
</tr>
<tr>
<td>Moderate</td>
<td>Gilead</td>
<td>SpO₂ ≥ 94%; n = 1600</td>
<td>5 vs. 10 days RDV vs. SOC; Extension</td>
<td>5/2020</td>
</tr>
<tr>
<td>Severe</td>
<td>Gilead</td>
<td>SpO₂ &lt; 94%; n = 6000</td>
<td>5 vs. 10 days RDV; Extension &amp; MV arms</td>
<td>5/2020</td>
</tr>
<tr>
<td>Mild/Mod (Ch)</td>
<td>CMU</td>
<td>SpO₂ &gt; 94%; n = 308</td>
<td>RDV vs. PCB</td>
<td>4/27/2020</td>
</tr>
<tr>
<td>Severe (Ch)</td>
<td>CMU</td>
<td>SpO₂ &lt; 94%; n = 453</td>
<td>RDV vs. PCB</td>
<td>5/1/2020</td>
</tr>
<tr>
<td>DisCoVeRy</td>
<td>Inserm</td>
<td>SpO₂ &lt; 94%; n = 3100</td>
<td>RDV vs. HCQ vs. IFN-β vs. LPV/r vs. SOC</td>
<td>3/2023</td>
</tr>
<tr>
<td>Solidarity</td>
<td>WHO</td>
<td>Hospitalized; n = 700</td>
<td>RDV vs. HCQ vs. SOC</td>
<td>11/2020</td>
</tr>
</tbody>
</table>

RDV = remdesivir; PCB = placebo; HCQ = hydroxychloroquine; LPV/r = lopinavir/ritonavir; IFN-β = interferon beta; *Estimated completion; Current as of 4/15/2020, subject to change; Source: ClinicalTrials.gov
Gilead is transitioning the provision of emergency access to remdesivir from individual compassionate use requests to expanded access programs. This approach will both accelerate access to remdesivir for severely ill patients and enable the collection of data from all participating patients. These programs are currently under rapid development in conjunction with national regulatory authorities worldwide. More details on how to participate in the expanded access programs will be forthcoming.

During this transition period, we are unable to accept new individual compassionate use requests due to an overwhelming demand over the last several days. We are focused now on processing previously approved requests and anticipate the expanded access programs will initiate in a similar expected timeframe that any new requests for compassionate use would have been processed.

Exceptions will be made only for pregnant women or children less than 18 years of age with confirmed COVID-19 and severe manifestations of disease.

Given the importance of data generation, we urge you to enroll patients in clinical trials if reasonably possible rather than pursue an emergency treatment request. Please refer to the links below for information on current clinical trials investigating the use of remdesivir in COVID-19:

- NCT04280705
- NCT04292730
- NCT04292899
- 2020-000936-23
References

References

21. Chin-Hong, Peter (PCH_SF). We have fielded a lot of requests from around the country for our experience with getting #compassionateuse #remdesivir from #Gilead for critically ill #COVID19 pts. Pearls:1)~72 hrs if approved 2)Many steps but doable 3)Model of #interprofessional ID/IDPharm aloha. We are all in.” 3/16/20:20:16. Tweet.
Updates Log

3/24/2020 – v1 Original version posted
4/5/2020 – v2 Community transmission case report; ongoing trial info updated
4/12/2020 – v3 Compassionate use case series added; ongoing trial info updated
4/17/2020 – v4 Updated trial info
Questions

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