## Recent Clinical Data on Use of Remdesivir for COVID-19

**Updated 8/24/2020**

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<td>Grein et. al. [1]</td>
<td>By median follow-up of 18 days after 1st dose, 36 (68%) had improvement in oxygen support and 8 (15%) showed worsening; 17 (57%) stopped invasive mechanical ventilation; 7 (13%) died (6 of whom were receiving mechanical ventilation); 25 (47%) discharged</td>
<td>Lack of randomized control group, small cohort size (no sample size calculation performed for analysis), 8 patients excluded from analysis and only 40 received intended therapy duration, 95% CI not adjusted for multiple comparisons, short follow-up duration, potential for missing data, limited collection of laboratory data; Gilead funded compassionate use (CU) program was open to all patient types, not just children and pregnant women.</td>
<td>Compassionate use (CU) program results from 25 January 2020 to 7 March 2020. <strong>Note:</strong> This CU program was funded by Gilead.</td>
<td>61 (results from 53 reported, 40 received full 10-day course of remdesivir)</td>
<td>N/A</td>
<td>200 mg IV x1 on day 1, then 100 mg IV daily X 9 days</td>
<td>Oxygen saturation ≤94% on ambient air OR receiving oxygen support; 30 (57%) mechanical ventilation; 4 (8%) ECMO</td>
<td>United States, Europe, Canada, Japan</td>
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<tr>
<td>Author(s)</td>
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<td>Design</td>
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<td>Pasquini et al. [2]</td>
<td>Assess remdesivir efficacy for COVID-19</td>
<td>Retrospective, observational study</td>
<td>60 patients were evaluated and 51 were included in the study. The 9 patients who were excluded either died within 48 hours after ICU admission or were transferred to other facilities.</td>
<td>Remdesivir started a median of 18 days (15-20) after symptom onset and it is unknown if earlier treatment would have been beneficial. Viral load data not collected due to resource scarcity. Study occurred during first 3 weeks of the epidemic when needs for ventilators, doctors,</td>
<td>Severe respiratory failure with need for mechanical ventilation in ICU. Patients who died within 48 hours after ICU admission were excluded. Patients did not receive remdesivir if they had ALT/AST &gt;5 times the upper limit of normal or CrCl&lt; 30 mL/min, or need for inotropic support.</td>
<td>Kaplan-Meier curves showed significantly lower mortality in patients treated with remdesivir (56% vs 92%, P&lt;0.001). Cox regression analysis showed use of remdesivir was associated with improved survival (OR, 3.506; 95% CI 1.768-6.954, P&lt;0.001). Death occurred at a median of 17 days (13-20) after ICU admission in the remdesivir and 10 days (8-13) in the control group. Cox regression analysis also showed that Charlson Comorbidity Index was the only factor with significant association with increased mortality (OR 1.184; 95% CI 1.027-1.365; P=0.020). Univariate analysis factors related to mortality included time from symptom onset and ICU admission, Charlson Comorbidity Index, platelet count, and need for CRRT during ICU stay. Treatment with remdesivir and tocilizumab were associated with higher survival.</td>
<td>Single ICU in Pesaro, Italy Between 29 February and 20 March 2020.</td>
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and nurses were mostly unmet and ICU capacity was stressed.

- Overall study mortality of 75% is among the highest reported in literature to date; however, the study had a longer follow-up period than many other studies (median 52 days), which terminated while some patients were still receiving mechanical ventilation.

- Patients may have received other therapies for COVID-19 including hydroxychloroquine, lopinavir/ritonavir, and tocilizumab.

Wang Y, et al.

The primary outcome of this study was time to clinical improvement up to 28 days, as defined by a 2 point drop on a 6-point ordinal scale ranging from 1=discharge to 6=death.

In the intent-to-treat (ITT) population, time to clinical improvement was 21 days with remdesivir [IQR 13-28] less ill than compassionate use group, with 0.4% of patients on mechanical ventilation or ECMO.

Note: Primary analysis completed in ITT population; Safety analysis in patients who started assigned therapy.

Numerical time to improvement was faster in the remdesivir group (18 days) compared to placebo (23 days) (HR 0.95[0.95-2.43]).

- Adverse events were common in both the remdesivir group (102 pts, 66%) and placebo (50, 64%); however, more patients discontinued therapy due to remdesivir AE's (18 patients, 12%) compared to placebo (4 patient, 5%). The main reasons for remdesivir discontinuation were respiratory failure and ARDS.

- Mortality at 28 days was 22 (14%) in remdesivir arm and 10 (13%) in placebo arm; difference 1.1% (95% CI -8.1 – 10.3). No deaths were attributed to remdesivir by investigators.
Remdesivir was superior to placebo in shortening recovery time in hospitalized adults with COVID-19 (11 days (95% CI 9-12) vs. 15 days, 95% CI 13-19, ), (rate for recovery, 1.32; 95% CI, 1.12 – 1.55; \( P < 0.001 \)). Kaplan-Meier mortality estimates by 15 days were lower for remdesivir (7.1% vs. 11.9% HR 1.23[0.87-1.75]).

The primary endpoint was modified by statisticians prior to trial release due to updated external knowledge indicating that COVID-19 had a longer course of illness than accounted for in initial trial design. Differences in clinical outcomes - study enrollment declined in mid-March due to decreased cases and restrictions on patients being admitted to hospital who were later in their disease course and not eligible for the study.

Limited data on virus recovery and reduced remdesivir susceptibility available to investigators. Lack of knowledge of optimal dose and duration of therapy for remdesivir in COVID-19.

Clinical status at day 15 was evaluated. Grade 3 and 4 adverse events also occurred less frequently with remdesivir (28.8% vs. 33%). The most common remdesivir included: decreased hemoglobin or anemia, AKI, decreased eGFR or CrCl, increased Scr.

**Biegel et. al. [4]**

<table>
<thead>
<tr>
<th>Event</th>
<th>Description</th>
<th>Sample Size</th>
<th>Results</th>
<th>Source</th>
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<tr>
<td>Differences in clinical outcomes</td>
<td>-Study enrollment declined in mid-March due to decreased cases and restrictions on patients being admitted to hospital who were later in their disease course and not eligible for the study. -Limited data on virus recovery and reduced remdesivir susceptibility available to investigators. -Lack of knowledge of optimal dose and duration of therapy for remdesivir in COVID-19.</td>
<td>943 (88.7%)</td>
<td>843 (87%)</td>
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<td>15-day outcomes may not represent the full course of COVID-19</td>
<td></td>
<td>541 randomized</td>
<td>512 randomized</td>
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<td>8-category ordinal scale ranks at enrollment: 7-272 (25.6%); 6-197 (18.5%); 5-421 (39.6%); 4-127 (11.9%)</td>
<td></td>
<td>3 missing data</td>
<td>5 missing data</td>
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<td>The median days between symptom onset and randomization was 9 (IQR, 6-12);</td>
<td></td>
<td>Remdesivir 200 mg IV on day 1, then 100 mg IV daily on days 2-10 vs. Matching placebo</td>
<td>Remdesivir 200 mg IV on day 1, then 100 mg IV daily on days 2-10 vs. Matching placebo</td>
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<td>Primary outcome was time to recovery which was defined as the first day during the 28 days after enrollment when the patient satisfied category 1, 2, or 3 on and 8-category ordinal scale*.</td>
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<td>60 trial sites: US (45 sites), Denmark (8), UK (5), Greece (4), Germany (3), Korea (2), Mexico (2), Spain (2), Japan (1), Singapore (1)</td>
<td>60 trial sites: US (45 sites), Denmark (8), UK (5), Greece (4), Germany (3), Korea (2), Mexico (2), Spain (2), Japan (1), Singapore (1)</td>
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<td>Additional outcomes included 14 and 28 day mortality. 28-day mortality was not reported.</td>
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<td>Clinical status at day 15 was evaluated.</td>
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- 15-day outcomes may not represent the full course of COVID-19.
- The primary endpoint was modified by statisticians prior to trial release due to updated external knowledge indicating that COVID-19 had a longer course of illness than accounted for in initial trial design.
for death, 0.70; 95% CI, 0.47 – 1.04), but not statistically significant.

Serious adverse events (AEs) were less common in patients randomized to remdesivir (21.1% vs. 27%).

Recovery rates for patients randomized in the first 10 days after symptom onset had a rate ratio for recovery of 1.28 (95% CI, 1.05-1.57; 664 patients), and those randomized more than 10 days after symptom onset had ratio for recovery of 1.38 (95% CI, 1.05-1.81; 380 patients)

Patients receiving remdesivir had higher odds of improvement in clinical status by day 15 than those receiving placebo (OR 1.5, 95% CI: 1.18-1.91)

The authors caution that to fully understand the efficacy of remdesivir, full statistical analysis of the entire trial

-Placebo arm had sicker patients than remdesivir arm with ordinal scale score of 7* of 28.2% vs. 23.1%

-Missing data

-28-day mortality outcomes were not reported since patients had not all completed 29-day visits.

-538 included in analysis

1 missing data

521 included in analysis

Co-morbidities of were common: one (27%), two or more (52.1%)

pyrexia, increased blood glucose, increased ALT and/or AST.

Serious AEs occurred in remdesivir group less frequently than placebo (21.1% vs. 27%): 4 events were judged by investigators to be therapy-related. No deaths attributed to therapy
population is needed. They also share that due to high mortality rates in the remdesivir arm, treatment with combination therapy may be warranted for future studies.

**Randomized, open-label trial experience**

Goldman et al. [5] found no significant difference between 5-day and 10-day courses of remdesivir in patients with severe COVID-19 who do not require mechanical ventilation. At day 14, clinical improvement of ≥2 points on a 7-point ordinal scale** occurred for 64% of patients receiving 5-day courses and 54% of patients on 10-day courses. Once patients were adjusted for the poorer baseline clinical status in the 10-day group, clinical status at day 14 was similar among the two groups (P=0.14), as well as time to clinical improvement, recovery, and mortality. Authors caution that the magnitude of the impact cannot be fully evaluated due to a lack of a placebo arm. Additional studies are needed to evaluate the ideal duration of remdesivir in patients with COVID-19 who need mechanical ventilation.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Randomized, open-label, phase 3 trial</th>
<th>197 patients received remdesivir for 10 days</th>
<th>200 patients received remdesivir for 5 days</th>
<th>200mg IV on day 1, then 100 mg IV daily for days 2-5 or 2-10 based on treatment arm</th>
<th>Severe COVID-19, not requiring intubation; included hospitalized patients with oxygen saturation ≤94% on ambient air or patients receiving supplemental oxygen, radiologic evidence of pneumonia, age ≥12 years and SARS-CoV-2 established by PCR within 4 before randomization.</th>
<th>55 hospitals in the US, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, Taiwan</th>
<th>Enrolled between March 6 to March 26, 2020</th>
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<tbody>
<tr>
<td>groups were balanced by demographics and not baseline characteristics. The 10-day group had significantly worse clinical status at baseline than the 5-day group (P=0.02).</td>
<td>1:1 randomization, not stratified</td>
<td>(These patients were included in safety and efficacy analysis)</td>
<td>(These patients were included in safety and efficacy analysis)</td>
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<td>-Missing data: The most recent assessment was recorded for missing values at day 14. Due to low numbers of patients receiving mechanical ventilation prior to treatment, these findings may not be generalizable to critically ill patients. Findings cannot be used to establish remdesivir efficacy due to lack of placebo control.</td>
<td>86 in the 10-day arm completed the full course of therapy</td>
<td>172 in the 5-day arm completed the full course of therapy</td>
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<td>64% in 5-day vs. 54% in 10-day (baseline-adjusted difference in proportions -6.3% [95% CI, -15.4 – 2.9]). Median time to recovery was 10 days (IQR 6-18) for the 5-day group and 11 days (IQR 7 to not possible to estimate) for the 10-day group.</td>
<td>Time to modified recovery (defined as improvement from baseline score of 2-5 to a score of 6-7): similar to median time to recovery, all-cause mortality.</td>
<td>Time to recovery (defined as improvement from a baseline score of 2-5 to a score of 6-7): 64% in 5-day vs. 54% in 10-day (baseline-adjusted difference in proportions -6.3% [95% CI, -15.4 – 2.9]). Median time to recovery was 10 days (IQR 6-18) for the 5-day group and 11 days (IQR 7 to not possible to estimate) for the 10-day group.</td>
<td>Time to recovery (defined as improvement from baseline score of 2-5 to a score of 6-7): similar to median time to recovery, all-cause mortality.</td>
<td>Post-hoc analysis tried to determine if patients in the 5-day arm who were still hospitalized on day 14, as measures on a 7-point ordinal scale**.</td>
<td>Secondary endpoint was the proportion of patients with AEs on or up to 30 days after remdesivir administration. AEs were similar among groups (70% vs. 74%), serious AEs (21% vs. 35%), and AEs grade 3 or higher (30% vs. 43%), among 5-day and 10-day groups. The most common AEs noted with remdesivir include: nausea (9%), constipation (7%), elevated ALT (7%), worsening respiratory failure (8%).</td>
<td>Other exploratory endpoints include: time to clinical improvement (defined as 2-point improvement on a 7-point scale**): At day 14, 16 patients (8%) in the 5-day arm and 21 patients (11%) in the 10-day arm had died and 120 patients (60%) in the 5-day arm were discharged and 103 (52%) in the 10-day arm were discharged.</td>
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</table>
are intubated at baseline, immunocompromised, and other high risk groups.

- The trial allowed for hospital discharge prior to completion of therapy; therefore, 44% of patients in the 10-day arm did not complete their full course.
- 95% CI wasn’t adjusted for multiplicity and should not be used to infer effects for endpoints outside the primary endpoint.

| Spinner et al [6] | In patients with moderate COVID-19, patients who received a 5-day course had statistically significant odds of a better clinical distribution status on a 7-point ordinal scale** at 11 days compared to standard of care; however, the clinical importance of this difference is unknown. Patients who received a 10-day course did not have statistically significant difference in clinical status after 11 days compared with standard of care. | Randomized, open-label trial with 1:1:1 randomization to 5-day remdesivir course, up to a 10-day remdesivir course, or standard of care | 197 randomized to up to a 10-day course and 193 received therapy and included in primary analysis, 73 completed full treatment duration | 200 randomized to standard of care and all were included in full treatment analysis | Remdesivir 200 mg on day 1, then 100 mg daily for the remainder of the course infused over 30-60 minutes | Moderate COVID-19 pneumonia with pulmonary infiltrates and room-air oxygen saturation >94%. Patients were excluded if ALT or AST was > 5 times the upper limit of normal or if CrCl was <50 mL/min. | Note: 12% of patients in the 10-day arm, 16% in the 5-day arm, and 19% in the standard of care arm received supplemental oxygen on day 1 due to deteriorating clinical status after randomization. Median duration of hospitalization was 2 days (IQR 1-3 days) before study day 1 for all 105 hospitals in the US, Europe, and Asia between March 15, 2020 and April 18, 2020. Follow-up completed by May 20, 2020. | Primary outcome was clinical status by day 11 on a 7-point ordinal scale: - Patients in the 5-day remdesivir group had higher odds of improved clinical status distribution compared to standard of care (OR, 1.65; 95% CI, 1.09-2.48, P=0.02) - Patients in the 10-day remdesivir group did not have statistically significant clinical status distribution compared to standard of care (P=0.18 by Wilcoxon rank sum test) The secondary endpoint was adverse events: Adverse events occurred in all 3 group with 51% of patients in the 5-day group experiencing an adverse event; 59%, 10-day remdesivir group; 47%, standard of care. Adverse events that were more frequent in remdesivir-treated patients than in the standard of care group include nausea (10% vs. 3%), hypokalemia (6% vs. 2%), and headache (5% vs. 3%). Serious adverse events were less common in the remdesivir group (5% in both) compared to the standard care group (9%). No deaths were attributed to remdesivir. Additional prespecified exploratory endpoints showed no significant differences between the 5-day remdesivir group, 10-day remdesivir group, and standard of care group: 1) Time to recovery (defined as improvement on the ordinal scale from a baseline score of 2-5 to a score of 6-7 or improvement from a baseline score of 6 to a score of 7).
### 10-day remdesivir group had a negative impact on outcomes.

- Ordinal scales may not be ideal for detecting differences in oxygen requirements in patients with moderate COVID-19.
- Some patients received concurrent therapies.
- The protocol was amended on 15 March 2020 to change the following items due to new understandings about COVID-19:
  - Age limit for eligibility lower from 18 years to 12 years
  - Minimum temperature requirement eliminated
  - Primary endpoint changed from proportion of patients discharged by study day 14 to clinical status improvement on a 7-point ordinal scale by day 11
  - Nonrandomized extension phase added to include up to 1000 more patients that could be enrolled to receive remdesivir (data groups. In standard of care arm, the median duration of patient symptoms was 9 days (IQR 6-11 days) before study day 1; in the remdesivir arms, 8 days (IQR, 5-11 days).

39% (227) women Co-morbidities were common: 56% cardiovascular disease, 42% hypertension, 40% diabetes

### 2) Time to modified recovery (defined as improvement from baseline score of 2-4 to a score of 5-7; 5, to 6-7; 6, to 7)

3) Time to clinical improvement (defined as a 22-point improvement on the 7-point ordinal scale).

4) Time to 1-point or larger improvement

5) Time to discontinuation of any oxygen support

6) Hospital length of stay

7) At day 28, the Kaplan-Meier all-cause mortality was 1% (95% CI, 0.0% - 2.6%) for the 5-day remdesivir group (log-rank P=0.43 vs. standard of care), 2% (95% CI, 0.0% - 3.6%) for the 10-day remdesivir group (log-rank P=0.72 vs. standard of care) and 2% (95% CI, 0.1% - 4.1%) for the standard of care.
will be part of a later report)
- statistical plan was modified on 26 June 2020 prior to database lock (see study for details)

*Eight-category ordinal scale: 1-not hospitalized, no limitations on activities 2- not hospitalized, limitation of activities, home oxygen requirement, or both 3-hospitalized, not requiring supplemental oxygen and no longer requiring on-going medical care; 4-hospitalized, not requiring supplemental oxygen but requiring medical care for COVID-19 or other medical condition; 5-hospitalized, requiring supplemental oxygen; 6-hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices; 7-hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 8-death.

**7-point ordinal scale: 1-death, 2-hospitalized, receiving invasive mechanical ventilation or ECMO; 3-hospitalized, requiring high-flow oxygen or noninvasive ventilation; 4- hospitalized, requiring low-flow oxygenation; 5 - hospitalized, not requiring supplemental oxygen, but receiving ongoing medical care (both related and unrelated to Covid-19); 6 - hospitalized, requiring no supplemental oxygen and no ongoing medical care (other than protocol-driven interventions for the study); 7 - not hospitalized

References