# Supplementary Material*

Qaseem A, Yost J, Etxeandia-Ikobaltzeta I, et al; Scientific Medical Policy Committee of the American College of Physicians. Update alert: should remdesivir be used for the treatment of patients with COVID-19? Rapid, living practice points from the American College of Physicians (Version 2). Ann Intern Med. 13 July 2021. [Epub ahead of print]. doi:10.7326/L21-0389

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* This supplementary material was provided by the authors to give readers further details on their article. The material was reviewed but not copyedited.

ONLINE SUPPLEMENT: ACP Living Practice Points on the use of Remdesivir

**Key Questions**

*Key Question 1.* What are the effectiveness and harms of remdesivir in hospitalized patients with coronavirus disease 2019 (COVID-19)?

*Key Question 2*. Do effectiveness and harms in hospitalized patients with COVID-19 vary by symptom duration, disease severity, and treatment duration?

**Development Process for Living Practice Points Based on a Rapid Evidence Review**

For details on the development process of living practice points based on a rapid evidence review, please see the ACP's recently published methods paper (3).

*Table 1.* Evidence Gaps

- Additional studies are needed to assess the optimal treatment duration with remdesivir (i.e., 5-d vs. 10-d course) and to determine if there is variation in the optimal duration of treatment with remdesivir across different subgroups of patients.
- Additional studies are needed to assess if the effectiveness of remdesivir treatment for COVID-19 varies by severity (e.g., respiratory support requirements) of COVID-19.
- There is a need for studies assessing whether remdesivir treatment outcomes vary by symptom duration in patients with COVID-19.
- Studies are needed to determine the effectiveness of extending an initial 5-d course of remdesivir to 10 d and to identify subpopulations of patients with COVID-19 who may benefit from longer treatment.
- Future studies should consider evaluating additional critical and important clinical outcomes, such as respiratory failure or duration of invasive ventilation.

COVID-19 = coronavirus disease 2019.

*Table 2.* Clinical Considerations

- Remdesivir is currently only administered by IV infusion in hospital settings or in a facility that can provide care similar to an acute care hospital setting (1).
- 5-d course in adults is 200 mg IV on day 1 followed by 100 mg/d for a total of 5 d (5 doses).
- 10-d course in adults is 200 mg IV on day 1 followed by 100 mg/d for a total of 10 d (10 doses).
- The practice points do not apply to pregnant women or patients with severe renal or hepatic dysfunction because they were excluded from the studies included in the evidence review.
- The decision to initiate treatment with remdesivir in hospitalized patients with COVID-19 should be based on clinical judgment; remdesivir should not necessarily be initiated in patients hospitalized for a primary diagnosis unrelated to COVID-19 who have incidentally tested positive for severe acute respiratory syndrome coronavirus 2.

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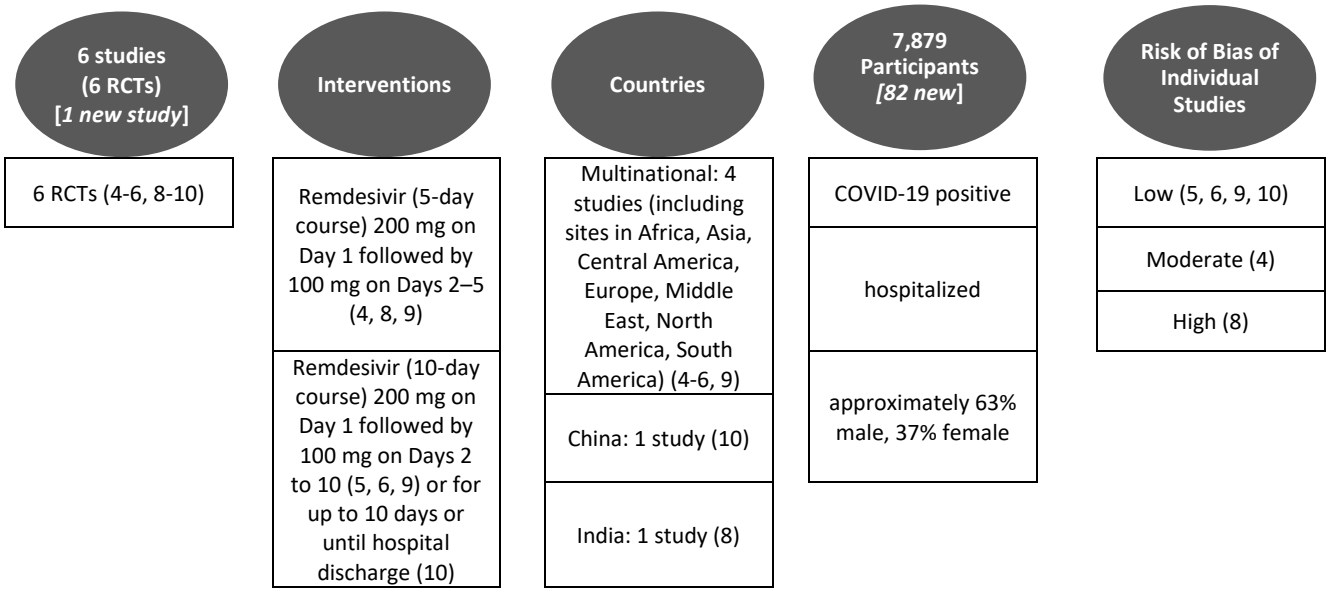
- For hospitalized patients with COVID-19 whose condition worsens within a 5-d course to require oxygen but not invasive ventilation extending the use of remdesivir should be based on clinical judgment and the balance of benefits and harms, because current evidence is insufficient to determine whether treatment beyond 5 d improves mortality among patients who are receiving noninvasive ventilation or supplemental oxygen or who are breathing ambient air* (4).
- The effectiveness of a 10-d course of remdesivir in reducing mortality (5) and time to recovery (6) may not vary by age, sex, or race in hospitalized patients with COVID-19.
- There was not enough information to determine what other treatment interventions, including experimental or off-label medications, were given in the trials.
- *UPDATED:* It is recommended that clinicians assess kidney and hepatic function at baseline and during treatment. Remdesivir should not be used in patients with an estimated glomerular filtration rate <30 mL/min/1.73 $m^2$ and the use of remdesivir should be discontinued if alanine aminotransferase levels (ALT) increase to >10 times the upper limit of normal or if alanine aminotransferase elevation is accompanied by signs or symptoms of liver inflammation (7).
- *UPDATED:* Common adverse events include nausea and serious adverse effects including hypersensitivity reactions (including infusion-related and anaphylactic reactions), increased serum alanine aminotransferase levels, increased aspartate aminotransferase levels, and hepatoxicity (7).

COVID-19 = coronavirus disease 2019; IV = intravenous; VA = U.S. Department of Veterans Affairs.
*Invasive ventilation is administering supplemental oxygen with positive pressure to the lungs via an endotracheal or tracheostomy tube. Non-invasive ventilation is administering supplemental oxygen with positive pressure to the lungs to deliver a fixed amount of oxygen, independent of the patient's breathing pattern [e.g. continuous positive airway pressure (CPAP), bi-level positive airway pressure (BIPAP), or high-flow oxygen]. Supplemental oxygen is administering oxygen without positive pressure to the lungs [e.g. low-flow nasal cannula, simple face mask].

**Figure. Updated Evidence Description***




RCT: randomized controlled trial.

*Evidence search and assessment conducted by the Veterans Administration (VA) Evidence Synthesis Program, Minneapolis, Minnesota (1, 2). Updated search for evidence updated through 10 May 2021 aimed to identify RCTs evaluating remdesivir for treatment of individuals with COVID-19.

*Table 3.* Updated Evidence Summary for the Use of Remdesivir as Treatment for Patients With COVID-19: What Information Does the Evidence Provide?

**What has changed in the evidence since the last version?**

- 5-day course vs. standard of care: 1 new study (8) added addressing the following outcomes: all-cause mortality and new need for invasive ventilation/ECMO.
- Changed the term mechanical ventilation to invasive ventilation to better reflect most of the patient populations informing the practice points and added a footnote to define invasive ventilation, non-invasive ventilation, and supplemental oxygen in Tables 3 and 4.
- Identified the quality of the individual studies and added a footnote to define quality in Tables 3 and 4.

| Outcome | Study Design (Patients, *n*): Quality* | Evidence | Certainty of Evidence† |
|---|---|---|---|
| **All-cause mortality** | | | |
| 5-d course vs. placebo/standard care | 2 RCTs (461): 1 RCT good quality (9); 1 RCT poor quality (8) | Remdesivir (5-d course) may slightly reduce mortality compared with standard care (8, 9) | Low |
| 10-d course vs. placebo/standard care | 4 RCTs (7142): 4 RCTs good quality (5, 6, 9, 10) | Remdesivir (10-d course) probably does not reduce mortality compared with placebo/standard care (5, 6, 9, 10)<br><br>*Note: The effect of remdesivir (10-d course vs. placebo/standard care) may vary by baseline respiratory support requirements‡ (5, 6, 9, 10). A 5-d course may not reduce mortality in patients not requiring supplemental oxygen at baseline, may result in a small reduction in mortality in patients requiring supplemental oxygen but not ventilation (non-invasive or invasive) at baseline, and may result in a modest increase in mortality in patients requiring ventilation (non-invasive or invasive)/ECMO at baseline§.*<br><br>*Note: The effect of remdesivir (10-d course vs. placebo) may not vary by symptom duration (≤10 vs. >10 d)† (10).* | Moderate |
| 5-d vs. 10-d course | 2 RCTs (781): 1 RCT fair quality (4); 1 RCT good quality (9) | Remdesivir 5-d course may slightly reduce mortality compared with a 10-d course (4, 9)<br><br>*Note: The evidence is very uncertain about the effect of remdesivir (5-d course) in patients who progress to requiring invasive ventilation/ECMO at day 5 ǂǀ (4): A 5-d course vs. a 10-d course may result in a large increase in mortality for patients who progressed to requiring invasive ventilation/ECMO at day 5, and there may not be a reduction in mortality for patients who were receiving non-invasive positive-pressure ventilation or high- or low-flow oxygen or who were breathing ambient air at day 5 (insufficient certainty of evidence).* | Low |

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|---|---|---|---|
| **Recovery**‖ | | | |
| 5-d course vs. placebo/standard care | 1 RCT (391): 1 RCT good quality (9) | Remdesivir (5-d course) may result in a modest increase in the proportion of patients who recovered compared with standard care (9) | Low |
| 10-d course vs. placebo/standard care | 3 RCTs (1682): 3 RCTs good quality (6, 9, 10) | Remdesivir (10-d course) probably results in a modest increase in the proportion of patients who recovered compared with placebo/standard care (6, 9, 10) | Moderate |
| 5-d vs. 10-d course | 2 RCTs (781): 1 RCT fair quality (4); 1 RCT good quality (9) | Remdesivir 5-d course may result in a modest increase in the proportion of patients who recovered compared with a 10-d course (4, 9) | Low |
| **Hospital length of stay**¶ | | | |
| 5-d course vs. placebo/standard care | NA | No evidence | NA |
| 10-d course vs. placebo/standard care | 2 RCTs (1299): 2 RCTs good quality (6, 10) | Remdesivir (10-d course) may result in a modest reduction in hospital length of stay compared with placebo (6, 10) | Low |
| 5-d vs. 10-d course | NA | No evidence | NA |
| **Serious adverse events**** | | | |
| 5-d course vs. placebo/standard care | 1 RCT (391): 1 RCT good quality (9) | Remdesivir (5-d course) may slightly reduce serious adverse events compared with standard care (9) | Low |
| 10-d course vs. placebo/standard care | 3 RCTs (1674): 3 RCTs good quality (6, 9, 10) | Remdesivir (10-d course) probably results in a modest reduction in serious adverse events compared with placebo/standard care (6, 9, 10) | Moderate |
| 5-d vs. 10-d course | 2 RCTs (781): 1 RCT fair quality (4); 1 RCT good quality (9) | Remdesivir 5-d course may result in a modest reduction in serious adverse events compared with a 10-d course (4, 9)<br><br>*Note: The effect of remdesivir 5-d course compared with a 10-d course may vary by baseline respiratory support requirements‡ (4, 9): There may be a large reduction in severe adverse events for patients hospitalized with reduced oxygen levels who did not require invasive ventilation at baseline (4), but there may not be a reduction in severe adverse events in patients without reduced oxygen levels on room air (9).* | Low |
| **Time to recovery**‖ | | | |
| 5-d course vs. placebo/standard care | 1 RCT (391): 1 RCT good quality (9) | Remdesivir (5-d course) may slightly reduce time to recovery compared with standard care (9) | Low |

| | | | |
|---|---|---|---|
| 10-d course vs. placebo/standard care | 2 RCTs (1455): 2 RCTs good quality (6, 9) | Remdesivir (10-d course) may result in a large reduction in time to recovery compared with placebo (6), but the effect is uncertain for remdesivir (10-d course) compared with standard care (9)<br><br>*Note: The effect of remdesivir (10-d course) may not vary by symptom duration or baseline respiratory support requirements*[§] *(6).* | Low |
| 5-d vs. 10-d course | 2 RCTs (781): 1 RCT fair quality (4); 1 RCT good quality (9) | Remdesivir 5-d course may slightly reduce time to recovery compared with a 10-d course (4, 9) | Low |
| **Clinical improvement**[††] | | | |
| 5-d course vs. placebo/standard care | 1 RCT (391): 1 RCT good quality (9) | Remdesivir (5-d course) may result in a modest increase in clinical improvement compared with standard care(9) | Low |
| 10-d course vs. placebo/standard care | 2 RCTs (629): 2 RCTs good quality (9, 10) | Remdesivir (10-d course) may result in a modest increase in clinical improvement compared with placebo/standard care (9, 10) | Low |
| 5-d vs. 10-d course | 2 RCTs (781): 1 RCT fair quality (4); 1 RCT good quality (9) | Remdesivir (5-d course) may result in a modest increase in clinical improvement compared with a 10-d course (4, 9) | Low |
| **Time to clinical improvement**[††] | | | |
| 5-d course vs. placebo/standard care | NA | No evidence | NA |
| 10-d course vs. placebo/standard care | 1 RCT (237): 1 RCT good quality (10) | Remdesivir (10-d course) may result in a modest reduction in time to clinical improvement compared with placebo (10)<br><br>*Note: The effect of remdesivir (10-d course) may not vary by symptom duration (≤10 vs. >10 d)*[§] (10). | Low |
| 5-d vs. 10-d course | NA | No evidence | NA |
| **Invasive ventilation/ECMO**[‡] | | | |
| 5-d course vs. placebo/standard care | 1 RCT (391): 1 RCT good quality (9) | Remdesivir (5-d course) may slightly reduce the proportion of patients on invasive ventilation/ECMO[‡] at follow-up compared with standard care (9) | Low |
| | 1 RCT (70): 1 RCT poor quality (8) | Very uncertain about the effect of remdesivir (5-d course) on the new need for invasive ventilation[‡ǀ] compared to standard care (8) | Insufficient |
| 10-d course vs. placebo/standard care | 3 RCTs (1686): 3 RCTs good quality (6, 9, 10) | Remdesivir (10-d course) may slightly reduce the proportion of patients on invasive ventilation/ECMO[‡] at follow-up compared with placebo/standard care (6, 9, 10) | Low |

| | | | |
|---|---|---|---|
| | 1 RCT (4964): 1 RCT good quality (5) | Remdesivir (10-d course) probably does not reduce the proportion of patients with a new need for ventilation (non-invasive or invasive) or ECMO) ‡ in those not ventilated at baseline compared with standard care (5) | Moderate |
| 5-d vs. 10-d course | 2 RCTs (781): 1 RCT fair quality (4); 1 RCT good quality (9) | Remdesivir 5-d course may slightly reduce the proportion of patients on invasive ventilation/ECMO‡ at follow-up compared with a 10-d course (4, 9)<br><br>*Note: The effect of a 5-d course of remdesivir compared with a 10-d course may vary by baseline respiratory support requirements† ‡ (4, 9): There may be a modest reduction in the proportion of patients on invasive ventilation/ECMO among patients hospitalized with reduced oxygen levels who did not require invasive ventilation at baseline (4) but there may not be a reduction in the proportion of patients on invasive ventilation/ECMO among patients without reduced oxygen levels on room air at baseline(4, 9).* | Low |
| **Any adverse events** | | | |
| 5-d course vs. placebo/standard care | 1 RCT (391): 1 RCT good quality (9) | Remdesivir (5-d course) may slightly increase any adverse events compared with standard care (9) | Low |
| 10-d course vs. placebo/standard care | 3 RCTs (1674): 3 RCTs good quality (6, 9, 10) | Remdesivir (10-d course) may not reduce any adverse events compared with placebo/standard care (6, 9, 10) | Low |
| 5-d vs. 10-d course | 2 RCTs (781): 1 RCT fair quality (4); 1 RCT good quality (9) | Remdesivir 5-d course may modestly reduce any adverse events compared with a 10-d course (4, 9) | Low |

COVID-19 = coronavirus disease 2019; ECMO = extracorporeal membrane oxygenation; NA = not applicable; RCT = randomized controlled trial.

* Good quality: methodologically sound study with low risk of bias. Fair quality: methodologically questionable study with moderate risk of bias. Poor quality: methodologically flawed study with a high risk of bias.

† Insufficient certainty of evidence: confidence is inadequate to assess the likelihood of benefit (benefit minus harm) of an intervention or its effect on a health outcome. Low certainty of evidence: confidence in the effect is limited because the true effect may be substantially different from the estimated effect. Moderate certainty of evidence: confidence in the effect is moderate because the true effect is likely close to the estimated effect, but there is a sizable possibility that it is substantially different. High certainty of evidence: confidence that the true effect is close to the estimated effect.

‡ Invasive ventilation is administering supplemental oxygen with positive pressure to the lungs via an endotracheal or tracheostomy tube. Non-invasive ventilation is administering supplemental oxygen with positive pressure to the lungs to deliver a fixed amount of oxygen, independent of the patient's breathing pattern [e.g. continuous positive airway pressure (CPAP), bi-level positive airway pressure (BIPAP), or high-flow oxygen]. Supplemental oxygen is administering oxygen without positive pressure to the lungs [e.g. low-flow nasal cannula, simple face mask].

§ The certainty of evidence was not assessed for this comparison determined from a subgroup analysis.

|| Recovery was defined as discharge from the hospital or hospitalization for infection control purposes only in 1 RCT (6) and as discharge from the hospital or hospitalized but not requiring supplemental oxygen or ongoing medical care in 3 RCTs (9, 10).

¶ Remdesivir (5-d and 10-d courses) may not decrease the percentage of persons hospitalized between days 11 and 14 (2, 11).

** *Severe adverse events* reported in studies included in the evidence review (4, 6, 9, 10) were acute coronary syndrome, acute kidney injury, acute respiratory distress syndrome, acute respiratory failure, increased aminotransferase levels, atrial fibrillation, bronchitis, cardiac arrest, cardiopulmonary failure, increased D-dimer level, deep venous thrombosis, diabetic

ketoacidosis, dyspnea, endotracheal intubation, decreased glomerular filtration rate, hemorrhage of the lower digestive tract, hypotension, hypoxia, ileus, lung abscess, mechanical ventilation, multiple organ dysfunction syndrome, respiratory distress, respiratory failure, pneumothorax, pulmonary embolism, pulmonary failure, recurrence of COVID-19, septic shock, sepsis, shock, tachycardia, thrombocytopenia, and viral pneumonia. *Any adverse events* reported in the studies included in the evidence review (4, 6, 9, 10) were acute kidney injury, acute respiratory failure, increased alanine aminotransferase level, anemia, increased aspartate aminotransferase level, increased blood glucose level, increased blood lipid levels, increased blood urea nitrogen level, constipation, hyperlipidemia, hypoalbuminemia, hypokalemia, hypotension, insomnia, nausea, increased neutrophil count, rash, respiratory failure, increased serum potassium level, reduced serum sodium level, thrombocytopenia, increased total bilirubin level, vomiting, and increased leukocyte count. 1 study included in the review stated that remdesivir did not reduce the frequency of nausea, vomiting, and increase in liver enzymes or creatinine (8) and any adverse events were not identified in 1 study included in the evidence review (5).

††Clinical improvement was defined as a 2-point reduction in patients' admission status on a 6-point ordinal scale (1 = live discharge to 6 = death) or live discharge from the hospital (whichever came first) in 1 study (10) and as an improvement of at least 2 points from baseline on a 7-point ordinal scale (1 = death to 7 = discharged from hospital) in 2 studies (4, 9).

*Table 4.* Thresholds for Determining Magnitude of Effect*

| Outcome | Little/No Effect | Small Effect† | Modest Effect‡ | Large Effect§ |
|---|---|---|---|---|
| **Critical outcomes** | | | | |
| All-cause mortality, *%* | <1 | 1 to 2.9 | 3 to 4.9 | ≥5 |
| Recovery, *%* | <2 | 2 to 4.9 | 5 to 9.9 | ≥10 |
| Length of stay, *d* | <1 | ≥1 to 2 | >2 to <3 | ≥3 |
| Severe adverse event, *%* | <1 | 1 to 4.9 | 5 to 9.9 | ≥10 |
| **Important outcomes** | | | | |
| Time to recovery, *d* | <1 | ≥1 to 2 | >2 to <3 | ≥3 |
| Clinical improvement, *%* | <2 | 2 to 4.9 | 5 to 9.9 | ≥10 |
| Time to clinical improvement, *d* | <1 | ≥1 to 2 | >2 to <3 | ≥3 |
| Invasive ventilation or ECMO, *%* | <1 | 1 to 4.9 | 5 to 9.9 | ≥10 |
| Any adverse event, *%* | <2 | 2 to 4.9 | 5 to 19.9 | ≥20 |

ECMO = extracorporeal membrane oxygenation.
* Measured as absolute risk difference (when not otherwise specified).
† Described as "slight increase or decrease."
‡ Described as "modest increase or decrease."
§ Described as "large increase or decrease."

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*Appendix Table.* Updated Estimates: Use of Remdesivir as Treatment for Patients With COVID-19*

| Outcome | Study Design (Patients, *n*) | Evidence | Certainty of Evidence† |
|---|---|---|---|
| **All-cause mortality** | | | |
| 5-d course vs. placebo/standard care (FU: 11-24 d) | 2 RCT (473) | Remdesivir 5-d course, 0% (0/191), vs. standard care, 2% (4/200); ARD, −2.0% (CI, −4.2% to 0.2%) (9)<br><br>Remdesivir 5-d course, 14.7% (5/34), vs. standard care, 8.3% (3/36); ARD, 6.4% (CI, −8.6% to 21.3%) [Per Protocol Day] (8) | Low |
| 10-d course vs. placebo/standard care (FU: 11–29 d) | 4 RCTs (7142) | Remdesivir 10-d course, 10.6% (384/3635), vs. placebo/standard care, 11.2% (394/3507); pooled ARD, −0.8% (CI, −2.2% to 0.7%) (5, 6, 9, 10)<br><br>*Note: The effect of remdesivir (10-d course vs. placebo/standard care) by baseline respiratory support requirements**‡:*<br>• *In patients not requiring supplemental oxygen: remdesivir 10-d course, 1.7% (16/929), vs. placebo/standard care, 2.2% (20/927); pooled ARD, −0.5% (CI, −0.2% to 0.8%) (5, 6, 9)*<br>• ***In patients receiving supplemental oxygen who did not need mechanical ventilation/ECMO: remdesivir 10-d course, 9.7% (212/2189), vs. placebo/standard care, 12.1% (251/2082); pooled ARD, −2.3% (CI, −4.2% to −0.4%) (5, 6, 10)***<br>• *In patients receiving mechanical ventilation (high-flow, non-invasive, invasive)/ECMO: remdesivir 10-d course, 30.6% (156/509), vs. placebo/standard care, 24.8% (123/495); pooled ARD, 4.9% (CI, −0.6% to 10.3%)(5, 6, 10)*<br><br>*Note: The effect of remdesivir (10-d course vs. placebo) by symptom duration**:*<br>• *≤10 d of symptoms: remdesivir, 11% (8/71), vs. placebo, 15% (7/47); ARD, −3.6% (CI, −16.2% to 8.9%)(10)*<br>• *>10 d of symptoms: remdesivir, 14% (12/84), vs. placebo, 10%; ARD, 4.6% (CI, −8.2% to 17.4%)(10)* | Moderate |
| 5-d vs. 10-d course (FU: 11–14 d) | 2 RCTs (781) | 5-d course, 8.0% (16/200), vs. 10-d course, 10.7% (21/197); ARD, −2.7% (CI, −8.4% to 3.1%) (4)<br><br>5-d course, 0% (0/191), vs. 10-d course, 1.0% (2/193); ARD, −1.0% (CI, −2.8% to 0.7%) (9)<br><br>*Note: Among patients receiving invasive ventilation/ECMO‡ at day 5 (4):*<br>• *Remdesivir 5-d course, 40% (10/25), vs. remdesivir 10-d course, 17% (7/41); ARD, 23.0% (CI, 0.5% to 4.5%) (insufficient certainty of evidence)*<br>• *Note: Among patients who were receiving noninvasive positive-pressure ventilation or high- or low-flow oxygen or who were breathing ambient air at 5 d, treatment beyond 5 d did not reduce mortality.* | Low |
| **Recovery§** | | | |

| | | | |
|---|---|---|---|
| 5-d course vs. placebo/standard care (FU: 28 d) | 1 RCT (391) | **Proportion of patients recovered with remdesivir 5-d course, 91.6% (175/191), vs. standard care, 85% (170/200); ARD, 6.6% (CI, 0.3% to 12.9%) (9)** | Low |
| 10-d course vs. placebo/standard care (FU: 28–29 d) | 3 RCTs (1682) | **Proportion of patients recovered with remdesivir 10-d course, 77.3% (683/884), vs. placebo/standard care, 71.6% (571/798); pooled ARD, 6.5% (CI, 2.4% to 10.7%) (6, 9, 10)** | Moderate |
| 5-d vs. 10-d course (FU: 11–14 d) | 2 RCTs (781) | Proportion of patients recovered with remdesivir 5-d course, 64.5% (129/200), vs. 10-d course, 53.8% (106/197); baseline-adjusted ARD, 6.3% (CI, −2.8% to 15.4%) (4)<br><br>Proportion of patients recovered with remdesivir 5-d course, 73.8% (141/191), vs. 10-d course, 68.4% (132/193); ARD, 5.4% (CI, −3.6% to 14.5%) (9) | Low |
| **Hospital length of stay**‖ | | | |
| 5-d course vs. placebo/standard care | NA | No evidence | NA |
| 10-d course vs. placebo/standard care (FU: 28–29 d) | 2 RCTs (1299) | 10-d course, median 12 d (IQR, 6 to 28 d), vs. placebo, median 17 d (IQR, 8 to 28 d); MD, −5 d (CI, −7.7 to −2.3 d) (6)<br><br>Remdesivir 10-d course, median 25 d (IQR, 16 to 38 d), vs. placebo, median 24 d (IQR, 18 to 36 d); MD, 0 d (IQR, −4.0 to 4.0 d) (10) | Low |
| 5-d vs. 10-d course | NA | No evidence | NA |
| **Serious adverse events**¶ | | | |
| 5-d course vs. placebo/standard care (FU: 11 d) | 1 RCT (391) | Remdesivir 5-d course, 4.7% (9/191), vs. standard care, 9.0% (18/200); ARD, −4.3% (CI, −9.3% to 0.7%) (9) | Low |
| 10-d course vs. placebo/standard care (FU: 11–29 d) | 3 RCTs (1674) | **Remdesivir 10-d course, 19.2% (169/880), vs. placebo/standard care, 25.3% (201/794); pooled ARD, −6.3% (CI, −10.2% to −2.4%) (6, 9, 10)** | Moderate |
| 5-d vs. 10-d course (FU: 11–14 d) | 2 RCTs (781) | **Remdesivir 5-d course, 21.0% (42/200), vs. 10-d course, 34.5% (68/197); ARD, −13.5% (CI, −22.2% to −4.8%) (4)**<br><br>Remdesivir 5-d course, 4.7% (9/191), vs. 10-d course, 5.2% (10/193); ARD, −0.5% (CI, −4.8% to 3.9%) (9)<br><br>*Note: The effect of remdesivir 5-d course vs. 10-d course by baseline respiratory support‡, among patients with radiologic evidence of pneumonia**:*<br>• *In patients with reduced oxygen levels who did not require invasive ventilation at study entry, there was a large reduction in severe adverse events with a 5-d course vs. a 10-d course (13.5%) (4).*<br>• *In patients without reduced oxygen levels on room air at study entry, there was little to no difference in severe adverse events (0.5% decrease) between a 5-d course vs. a 10-d course (9).* | Low |

**Time to recovery**§

| | | | |
|---|---|---|---|
| 5-d course vs. placebo/standard care (FU: 11 d) | 1 RCT (391) | Remdesivir 5-d course, median 6 d (IQR, 5 to 10 d), vs. standard care, median 7 d (IQR, 4 to 15 d); HR, 1.18 (CI, 0.96 to 1.45) (9) | Low |
| 10-d course vs. placebo/standard care (FU: 29 d) | 2 RCTs (1455) | Remdesivir 10-d course, median 8 d (IQR, 4 to 13 d), vs. standard care, median 7 d (IQR, 4 to 15 d); HR, 1.11 (CI, 0.90 to 1.37) (9) | Insufficient |
| | | **Remdesivir 10-d course, median 10 d (IQR, 9 to 11 d), vs. placebo, median 15 d (IQR, 13 to 18 d); *P* < 0.001; Rate ratio, 1.29 (CI, 1.12 to 1.49) (6)**<br><br>*Note: The effect of remdesivir (10-d course) by symptom duration* (6)*:*<br>• *≤9 d (median) of symptoms: HR, 1.32 (CI, 1.09 to 1.61)*<br>• *>9 d (median) of symptoms: HR, 1.29 (CI, 1.04 to 1.59)*<br><br>*Note: The effect of remdesivir (10-d course) by baseline respiratory support requirements‡ (6):*<br>• *Patients receiving invasive ventilation/ECMO at study entry (HR, 0.98 [CI, 0.70 to 1.36])*<br>• *Patients receiving high-flow oxygen or noninvasive ventilation at study entry (HR, 1.09 [CI, 0.76 to 1.57])*<br>• *Patients receiving oxygen at study entry (HR, 1.45 [CI, 1.18 to 1.79])*<br>• *Patients not receiving oxygen at study entry (HR, 1.29 [CI, 0.91 to 1.83])* | Low |
| 5-d vs. 10-d course (FU: 11–14 d) | 2 RCTs (781) | Remdesivir 5-d course, median 10 d (IQR, 6 to 18 d), vs. remdesivir 10-d course, median 11 d (IQR, 7 d to not able to estimate); *P* NS; HR, 0.81 (CI, 0.64 to 1.04) (4)<br><br>Remdesivir 5-d course, median 6 d (IQR, 5 to 10 d), vs. remdesivir 10-d course, median 8 d (IQR, 4 to 13 d); HR NR (9) | Low |

**Clinical improvement**††

| | | | |
|---|---|---|---|
| 5-d course vs. placebo/standard care (FU: 28 d) | 1 RCT (391) | Remdesivir 5-d course, 89.5% (171/191), vs. standard care, 83% (166/200); ARD, 6.5% (CI, −0.3% to 13.3%) (9) | Low |
| 10-d course vs. placebo/standard care (FU: 28 d) | 2 RCTs (629) | Remdesivir 10-d course, 65.2% (103/158), vs. placebo, 57.7% (45/78); ARD, 7.5% (CI, −5.7% to 20.7%) (10)<br><br>**Remdesivir 10-d course, 90.2% (174/193), vs. standard care, 83% (166/200); ARD, 7.2% (CI, 0.5% to 13.8%) (9)** | Low |
| 5-d vs. 10-d course (FU: 11–14 d) | 2 RCTs (781) | Remdesivir 5-d course, 64.5% (129/200), vs. remdesivir 10-d course, 54.3% (107/197); baseline-adjusted ARD, 6.5% (CI, −2.8% to 15.7%) (4)<br><br>Remdesivir 5-d course, 70.2% (134/191), vs. remdesivir 10-d course, 65.3% (126/193); ARD, 4.9% (CI, −4.5% to 14.2%) (9) | Low |

**Time to clinical improvement**††

| | | | |
|---|---|---|---|
| 5-d course vs. placebo/standard care | NA | No evidence | NA |
| 10-d course vs. placebo/standard care (FU: 28 d) | 1 RCT (237) | Remdesivir 5-d course, median 21 d (IQR, 13 to 28 d), vs. placebo, median 23 d (IQR, 18 to 36 d); HR, 1.23 (CI, 0.87 to 1.75) (10)<br><br>*Note: The effect of remdesivir (10-d course) by symptom duration** (10):*<br>• *≤10 d of symptoms: remdesivir, median 18 d (IQR, 12 to 28 d), vs. placebo, median 23 d (IQR, 15 to 28 d); HR, 1.52 (CI, 0.95 to 2.43)*<br>• *>10 d of symptoms: remdesivir 23 d vs. placebo 24 d; HR, 1.07 (CI, 0.63 to 1.83)* | Low |
| 5-d vs. 10-d course | NA | No evidence | NA |
| **Invasive ventilation/ECMO‡** | | | |
| 5-d course vs. placebo/standard care (FU: 11-24 d) | 2 RCT (473) | At Follow-Up (Invasive Ventilation/ECMO)‡ : Remdesivir 5-d course, 0% (0/191), vs. standard care, 2.0% (4/200); ARD, −2.0% (CI, −4.2% to 0.2%) (9)<br><br>New Need (Invasive Ventilation)‡ : Remdesivir 5-d course, 11.8% (4/34), vs. standard care, 5.6% (2/36); ARD 6.2% (-7.0% to 19.4%) (8) | Low<br><br>Insufficient |
| 10-d course vs. placebo/standard care (FU: 11–29 d) | 3 RCTs (1686)<br><br>1 RCT (4964) | **At Follow-Up (Invasive Ventilation/ECMO) ‡ : Remdesivir 10-d course, 11.3% (100/887), vs. placebo/standard care, 16.5% (132/799); pooled ARD, −4.8% (CI, −8.0% to −1.5%) (6, 9, 10)**<br><br>New Need (Non-Invasive or Invasive Ventilation/ECMO)‡ : Remdesivir 10-d course, 11.9% (295/2489), vs. placebo/standard care, 11.5% (284/2475); ARD, 0.4% (CI, −1.4% to 2.2%) (5) | Low<br><br>Moderate |
| 5-d vs. 10-d course (FU: 11–14 d) | 2 RCTs (781) | **Remdesivir 5-d course, 8.0% (16/200), vs. remdesivir 10-d course, 16.8% (33/197); ARD, −8.8% (CI, −15.2% to −2.3%) (4)**<br><br>Remdesivir 5-d course, 0% (0/191), vs. remdesivir 10-d course, 0.5% (1/193); ARD, −0.5% (CI, −1.9% to 0.9%) (9)<br><br>*Note: The effect of remdesivir 5-d course vs. 10-d course by baseline oxygen requirements among patients with radiologic evidence of pneumonia who did not require invasive ventilation at study entry**‡:*<br>• In patients with reduced oxygen levels not requiring invasive ventilation at study entry, there was a modest reduction in the proportion of patients on invasive ventilation/ECMO at follow-up with a 5-d course vs. a 10-d course (8.8%) (4).<br>• In patients without reduced oxygen levels on room air at study entry, there was little to no difference in the proportion of patients on invasive ventilation/ECMO at follow-up between a 5-d course vs. a 10-d course (0.5% reduction) (9). | Low |
| **Any adverse events** | | | |
| 5-d course vs. placebo/standard care (FU: 11 d) | 1 RCT (391) | Remdesivir 5-d course, 51.3% (98/191), vs. standard care, 46.5% (93/200); ARD, 4.8% (CI, −5.1% to 14.7%) (9) | Low |
| 10-d course vs. placebo/standard care (FU: 11–29 d) | 3 RCTs (1674) | 10-d course, 59.1% (520/880), vs. placebo/standard care, 58.7% (466/794); pooled ARD, −0.3% (CI, −5.0% to 4.4%) (6, 9, 10) | Low |

| | | | |
|---|---|---|---|
| 5-d vs. 10-d course (FU: 11–14 d) | 2 RCTs (781) | Remdesivir 5-d course, 70.5% (141/200), vs. remdesivir 10-d course, 73.6% (145/197); ARD, −3.1% (CI, −11.9% to 5.7%) (4)<br><br>Remdesivir 5-d course, 51.3% (98/191), vs. remdesivir 10-d course, 58.5% (113/193); ARD, −7.2% (CI, −17.2% to 2.7%) (9) | Low |

ARD = absolute risk difference; CI = confidence interval; COVID-19 = coronavirus disease 2019; d= days; ECMO = extracorporeal membrane oxygenation; FU = follow-up; HR = hazard ratio; IQR = interquartile range; MD = mean difference; NA = not applicable; RCT = randomized controlled trial; RR = relative risk.

* Statistically significant findings are in boldface.

† Insufficient certainty of evidence: confidence is inadequate to assess the likelihood of benefit (benefit minus harm) of an intervention or its effect on a health outcome. Low certainty of evidence: confidence in the effect is limited because the true effect may be substantially different from the estimated effect. Moderate certainty of evidence: confidence in the effect is moderate because the true effect is likely close to the estimated effect, but there is a sizable possibility that it is substantially different. High certainty of evidence: confidence that the true effect is close to the estimated effect.

‡ Invasive ventilation is administering supplemental oxygen with positive pressure to the lungs via an endotracheal or tracheostomy tube. Non-invasive ventilation is administering supplemental oxygen with positive pressure to the lungs to deliver a fixed amount of oxygen, independent of the patient's breathing pattern [e.g. continuous positive airway pressure (CPAP), bi-level positive airway pressure (BIPAP), or high-flow oxygen]. Supplemental oxygen is administering oxygen without positive pressure to the lungs [e.g. low-flow nasal cannula, simple face mask].

§ Recovery was defined as discharge from the hospital or hospitalization for infection control purposes only in 1 RCT (6) and as discharge from the hospital or hospitalized but not requiring supplemental oxygen or ongoing medical care in 3 RCTs (4, 9, 10).

|| Remdesivir (5-d course and 10-d course) may not decrease the percentage of persons hospitalized between days 11 and 14 (4).

¶ *Severe adverse events* reported in studies included in the evidence review (4, 6, 9, 10) were acute coronary syndrome, acute kidney injury, acute respiratory distress syndrome, acute respiratory failure, increased aminotransferase levels, atrial fibrillation, bronchitis, cardiac arrest, cardiopulmonary failure, increased D-dimer level, deep venous thrombosis, diabetic ketoacidosis, dyspnea, endotracheal intubation, decreased glomerular filtration rate, hemorrhage of the lower digestive tract, hypotension, hypoxia, ileus, lung abscess, mechanical ventilation, multiple organ dysfunction syndrome, respiratory distress, respiratory failure, pneumothorax, pulmonary embolism, pulmonary failure, recurrence of COVID-19, septic shock, sepsis, shock, tachycardia, thrombocytopenia, and viral pneumonia. *Any adverse events* reported in studies included in the evidence review(4, 6, 9, 10) were acute kidney injury, acute respiratory failure, increased alanine aminotransferase level, anemia, increased aspartate aminotransferase level, increased blood glucose level, increased blood lipid levels, increased blood urea nitrogen level, constipation, hyperlipidemia, hypoalbuminemia, hypokalemia, hypotension, insomnia, nausea, increased neutrophil count, rash, respiratory failure, increased serum potassium level, reduced serum sodium level, thrombocytopenia, increased total bilirubin level, vomiting, and increased leukocyte count. 1 study included in the review stated that remdesivir did not reduce the frequency of nausea, vomiting, and increase in liver enzymes or creatinine (8) and any adverse events were not identified in 1 study included in the evidence review (5).

** The certainty of evidence was not assessed for this comparison determined from a subgroup analysis.

†† Clinical improvement was defined as a 2-point reduction in patients' admission status on a 6-point ordinal scale (1 = live discharge to 6 = death) or live discharge from the hospital (whichever came first) in 1 study (10)(8) and as an improvement of at least 2 points from baseline on a 7-point ordinal scale (1 = death to 7 = discharged from hospital) in 2 studies (4, 9).

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