Therapeutic Management of Patients With COVID-19

Executive Summary

Two main processes are thought to drive the pathogenesis of COVID-19. Early in the course of the infection, the disease is primarily driven by replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Later in the course of infection, the disease is driven by an exaggerated immune/inflammatory response to the virus that leads to tissue damage. Based on this understanding, it is anticipated that antiviral therapies would have the greatest effect early in the course of disease, while immunosuppressive/anti-inflammatory therapies are likely to be more beneficial in the later stages of COVID-19.

In the earliest stages of infection, before the host has mounted an effective immune response, anti-SARS-CoV-2 antibody-based therapies may have their greatest likelihood of having an effect. In this regard, although there are insufficient data from clinical trials to recommend either for or against the use of any specific therapy in this setting, preliminary data suggests that outpatients may benefit from receiving anti-SARS-CoV-2 monoclonal antibodies early in the course of infection. The Food and Drug Administration (FDA) has issued Emergency Use Authorizations (EUAs) for certain anti-SARS-CoV-2 monoclonal antibodies for the treatment of outpatients with mild to moderate COVID-19; please see Anti-SARS-CoV-2 Monoclonal Antibodies for more information.

Remdesivir, an antiviral agent, is currently the only drug that is approved by the FDA for the treatment of COVID-19. It is recommended for use in hospitalized patients who require supplemental oxygen. However, it is not routinely recommended for patients who require mechanical ventilation due to the lack of data showing benefit at this advanced stage of the disease.1-4

Dexamethasone, a corticosteroid, has been found to improve survival in hospitalized patients who require supplemental oxygen, with the greatest effect observed in patients who require mechanical ventilation. Therefore, the use of dexamethasone is strongly recommended in this setting.5-8

The COVID-19 Treatment Guidelines Panel (the Panel) continues to review the most recent clinical data to provide up-to-date treatment recommendations for clinicians who are caring for patients with COVID-19. Figure 1 summarizes the Panel’s recommendations for managing patients with varying severities of disease.
Figure 1. Pharmacologic Management of Patients with COVID-19 Based on Disease Severity
Doses and durations are listed in the footnote.

<table>
<thead>
<tr>
<th>DISEASE SEVERITY</th>
<th>PANEL’S RECOMMENDATIONS</th>
</tr>
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<tbody>
<tr>
<td>Not Hospitalized, Mild to Moderate COVID-19</td>
<td>There are insufficient data to recommend either for or against any specific antiviral or antibody therapy. SARS-CoV-2 neutralizing antibodies (bamlanivimab or casirivimab plus imdevimab) are available through EUAs for outpatients who are at high risk of disease progression. The Panel recommends against the use of dexamethasone or other corticosteroids (AI).</td>
</tr>
<tr>
<td>Hospitalized but Does Not Require Supplemental Oxygen</td>
<td>The Panel recommends against the use of dexamethasone (AI) or other corticosteroids (AI). There are insufficient data to recommend either for or against the routine use of remdesivir. For patients at high risk of disease progression, the use of remdesivir may be appropriate.</td>
</tr>
<tr>
<td>Hospitalized and Requires Supplemental Oxygen (But Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)</td>
<td>Use one of the following options: • Remdesivir (e.g., for patients who require minimal supplemental oxygen) (BI) • Dexamethasone plus remdesivir (e.g., for patients who require increasing amounts of supplemental oxygen) (BIII) • Dexamethasone (e.g., when combination therapy with remdesivir cannot be used or is not available) (BII)</td>
</tr>
<tr>
<td>Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation</td>
<td>Use one of the following options: • Dexamethasone (AI) • Dexamethasone plus remdesivir (BIII)</td>
</tr>
<tr>
<td>Hospitalized and Requires Invasive Mechanical Ventilation or ECMO</td>
<td>Dexamethasone (AI)</td>
</tr>
</tbody>
</table>

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIA = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

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a See the Anti-SARS-CoV-2 Monoclonal Antibodies section for more information on using bamlanivimab and casirivimab plus imdevimab in patients with mild to moderate COVID-19.
b Patients who are receiving corticosteroids for other indications should continue therapy for their underlying conditions as directed by their health care providers.
  The remdesivir dose is 200 mg IV for one dose, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge (unless the patient is in a health care setting that can provide acute care that is similar to inpatient hospital care). Treatment duration may be extended up to 10 days if there is no substantial clinical improvement by Day 5.
  For patients who are receiving remdesivir but progress to requiring oxygen through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO, remdesivir should be continued until the treatment course is completed.
  The dexamethasone dose is 6 mg IV or PO once daily for 10 days or until hospital discharge. If dexamethasone is not available, equivalent doses of other corticosteroids (e.g., prednisone, methylprednisolone, hydrocortisone) may be used. See the Corticosteroids section for more information.
  The combination of dexamethasone and remdesivir has not been studied in clinical trials.
  In the rare circumstances where corticosteroids cannot be used, baricitinib plus remdesivir can be used (BIIa). The FDA has issued an EUA for baricitinib use in combination with remdesivir. The dose for baricitinib is 4 mg PO once daily for 14 days or until hospital discharge.
  The combination of dexamethasone and remdesivir may be considered for patients who have recently been intubated (CIII). The Panel recommends against the use of remdesivir monotherapy in these patients.

Key: ECMO = extracorporeal membrane oxygenation; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

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Patients With Mild to Moderate COVID-19 Who Are Not Hospitalized

For definitions of the clinical severity categories for patients with COVID-19, please see Clinical Spectrum of SARS-CoV-2 Infection.

Recommendations

- There are insufficient data for the Panel to recommend either for or against the use of any specific antiviral or antibody therapy in these patients.
- SARS-CoV-2-neutralizing antibodies (bamlanivimab or casirivimab plus imdevimab) are available through EUAs for outpatients who have a high risk of disease progression. These EUAs do not authorize use in hospitalized patients.
- The Panel recommends against the use of dexamethasone or other corticosteroids (AIII). Patients who are receiving dexamethasone or another corticosteroid for other indications should continue therapy for their underlying conditions as directed by their health care provider.

Rationale for the Panel’s Assessment That There Are Insufficient Data to Recommend Either For or Against the Use of Specific Antibody Therapy

Preliminary data from two small randomized controlled trials (BLAZE-1 and R10933-10987-COV-2067) suggested that anti-SARS-CoV-2 monoclonal antibody products may reduce the number of visits to emergency departments or hospitalizations in outpatients with mild to moderate COVID-19 (see Anti-SARS-CoV-2 Monoclonal Antibodies: Selected Clinical Data).9,10 As a result of these studies, the FDA issued EUAs for two products—a single monoclonal antibody, bamlanivimab, and a combination of two antibodies, casirivimab plus imdevimab—for use in outpatients with a high risk of disease progression.10,11 However, these studies enrolled a relatively small number of participants, and most of these participants were aged <65 years. In addition, the low number of clinical events that occurred during these trials (hospitalizations or emergency department visits) make it difficult to draw definitive conclusions regarding the efficacy of these antibodies.

Because of these limitations, there are insufficient data for the Panel to recommend either for or against the use of these anti-SARS-CoV-2 monoclonal antibodies (bamlanivimab or casirivimab plus imdevimab) in nonhospitalized patients with mild to moderate COVID-19. Ongoing clinical trials will provide further evidence on the safety and efficacy of these agents. Health care providers are encouraged to discuss participation in anti-SARS-CoV-2 monoclonal antibody clinical trials with their patients, if any trials are available. Clinicians are encouraged to discuss the potential benefits and risks of using these products with high-risk patients who meet the EUA criteria for these antibodies.

Rationale for the Panel’s Assessment That There Are Insufficient Data to Recommend Either For or Against the Use of Specific Antiviral Therapies

Completed clinical trials evaluating the use of remdesivir for treating mild to moderate COVID-19 have been limited to hospitalized patients. An ongoing clinical trial is evaluating the use of remdesivir in outpatients with COVID-19; the results from this study will further inform the role of remdesivir in this setting.

Rationale for Recommending Against the Use of Dexamethasone or Other Corticosteroids

Dexamethasone was studied in hospitalized patients with COVID-19 and was found to reduce mortality in patients who required supplemental oxygen.5 Outpatients with mild to moderate COVID-19 were not included in this trial; therefore, the safety and efficacy of using corticosteroids in this population have not been studied. The Panel recommends against the use of corticosteroids in this population because
there are no clinical trial data to support their use (AIII). Moreover, the use of corticosteroids can lead to adverse events, such as hyperglycemia, neuropsychiatric symptoms, and superinfections. These events are more difficult to monitor in an outpatient setting. Outpatients who are receiving dexamethasone or another corticosteroid for other indications should continue therapy for their underlying conditions as directed by their health care provider. Please see Corticosteroids: Selected Clinical Data for additional information.

Patients Who Are Hospitalized With Moderate COVID-19 but Who Do Not Require Supplemental Oxygen

Recommendations

• The Panel recommends against the use of dexamethasone or other corticosteroids (AIIa). Patients who are receiving dexamethasone or another corticosteroid for other indications should continue therapy for their underlying conditions as directed by their health care provider.

• There are insufficient data to recommend either for or against the routine use of remdesivir in these patients. The use of remdesivir may be appropriate in patients who have a high risk of disease progression.

Rationale for Recommending Against the Use of Dexamethasone or Other Corticosteroids

In the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial, a multicenter, open-label trial in the United Kingdom, hospitalized patients with COVID-19 were randomized to receive either dexamethasone plus standard of care or standard of care alone (control arm). In the subgroup of participants who did not require supplemental oxygen at enrollment, no survival benefit was observed for dexamethasone: 17.8% of participants in the dexamethasone arm and 14% in the control arm died within 28 days of enrollment (rate ratio 1.19; 95% CI, 0.91–1.55). Please see Corticosteroids: Selected Clinical Data for additional information. Based on these data, the Panel recommends against the use of dexamethasone (AIIa) or other corticosteroids (AIII) for the treatment of COVID-19 in this subgroup, unless the patient has another indication for corticosteroid therapy.

Rationale for the Panel’s Assessment That There Are Insufficient Data to Recommend Either For or Against the Use of Remdesivir

The Adaptive COVID-19 Treatment Trial (ACTT-1) was a multinational randomized controlled trial that compared remdesivir to placebo in hospitalized patients with COVID-19. Remdesivir showed no significant benefit in patients with mild to moderate disease, which was defined as oxygen saturation >94% on room air or a respiratory rate <24 breaths/min without supplemental oxygen (rate ratio for recovery 1.29; 95% CI, 0.91–1.83); however, there were only 138 patients in this group. In a manufacturer-sponsored, open-label randomized trial of 596 patients with moderate COVID-19, patients who received 5 days of remdesivir had higher odds of having a better clinical status on Day 11 (based on distribution on a seven-point ordinal scale) than those who received standard of care (OR 1.65; 95% CI, 1.09–2.48; \( P = 0.02 \)). However, the difference between the groups was of uncertain clinical importance.

In the Solidarity trial, about 25% of hospitalized patients in the remdesivir and control arms did not require supplemental oxygen at study entry. The primary outcome of in-hospital mortality occurred in 2% of patients (11 of 661) in the remdesivir arm and 2.1% of patients (13 of 664) in the control arm (rate ratio 0.90; 99% CI, 0.31–2.58). The open-label design of this study makes it difficult to determine whether remdesivir affects recovery time as determined by duration of hospitalization, because patient discharge may have been delayed in order to complete remdesivir therapy. Please see Remdesivir:
Selected Clinical Data for additional information.

Because these three trials produced conflicting results regarding the benefits of remdesivir, the Panel finds the available data insufficient to recommend either for or against routine treatment with remdesivir for all hospitalized patients with moderate COVID-19. However, the Panel recognizes that there may be situations in which a clinician judges that remdesivir is an appropriate treatment for a hospitalized patient with moderate disease (e.g., a person who is at a particularly high risk for clinical deterioration).

For Hospitalized Patients With COVID-19 Who Require Supplemental Oxygen but Who Do Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or Extracorporeal Membrane Oxygenation

**Recommendations**

The Panel recommends one of the following options for these patients:

- **Remdesivir** (e.g., for patients who require minimal supplemental oxygen) (BIIa);
- **Dexamethasone plus remdesivir** (e.g., for patients who require increasing amounts of oxygen) (BIII); or
- **Dexamethasone** (e.g., when combination therapy with remdesivir cannot be used or is not available) (BI).

**Additional Considerations**

- If dexamethasone is not available, an alternative corticosteroid such as prednisone, methylprednisolone, or hydrocortisone can be used (BIII). See Corticosteroids for dosing recommendations.
- In the rare circumstances when corticosteroids cannot be used, baricitinib plus remdesivir can be used (BIIa). Baricitinib should not be used without remdesivir.

**Rationale for the Use of Remdesivir**

In ACTT-1, remdesivir was associated with improved time to recovery in the subgroup of participants (n = 435) who required oxygen supplementation but not high-flow oxygen, noninvasive ventilation, or mechanical ventilation (7 days for remdesivir vs. 9 days for placebo; recovery rate ratio 1.45; 95% CI, 1.18–1.79). A lower percentage of patients in the remdesivir arm than in the placebo arm progressed to requiring high-flow oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) among those who were not using these methods of oxygen delivery at baseline (17% vs. 24%). In a post hoc analysis of deaths by Day 29, remdesivir appeared to confer a substantial survival benefit in this subgroup (HR for death 0.30; 95% CI, 0.14–0.64).

The Solidarity trial was a large, multinational, open-label randomized controlled trial in which a 10-day course of remdesivir was compared to standard of care. This trial reported no difference in the rate of in-hospital deaths between patients who received remdesivir and those who received standard of care (rate ratio of death 0.95; 95% CI, 0.81–1.11 in the overall study population; rate ratio of death 0.86; 99% CI, 0.67–1.11 for patients who did not require mechanical ventilation at entry). There was no difference between patients who received remdesivir and those who received standard of care in the percentage of patients who progressed to invasive mechanical ventilation (11.9% vs. 11.5%) or in length of hospital stay. However, an open-label trial like Solidarity is less well-suited than a placebo-controlled trial to assess time to recovery. In Solidarity, because both clinicians and patients knew that remdesivir...
was being administered, it is possible that the hospital discharge could have been delayed in order to complete the 10-day course of therapy.

During ACTT-1, remdesivir hastened the time to recovery in patients who required minimal supplemental oxygen. Based on these results and data from other studies, the Panel recommends remdesivir (without dexamethasone) as a treatment option for patients in this group (BIIa). In these individuals, the hyperinflammatory state where corticosteroids might be considered most beneficial may not yet be present or fully developed. For more information, please see Remdesivir: Selected Clinical Data.

**Rationale for the Use of Remdesivir Plus Dexamethasone**

The safety and efficacy of using remdesivir plus dexamethasone for the treatment of COVID-19 have not been rigorously evaluated in clinical trials. Despite the lack of clinical trial data, there is a theoretical rationale for combining remdesivir and dexamethasone (see the discussion of clinical trial data for remdesivir above and the discussion for dexamethasone below). Patients with severe COVID-19 may develop a systemic inflammatory response that leads to multiple organ dysfunction syndrome. The potent anti-inflammatory effects of corticosteroids might prevent or mitigate these hyperinflammatory effects. Thus, the combination of an antiviral agent, such as remdesivir, with an anti-inflammatory agent, such as dexamethasone, may treat the viral infection and dampen the potentially injurious inflammatory response that is a consequence of the infection.

Based on these theoretical considerations, the Panel recommends the combination of dexamethasone plus remdesivir as a treatment option for patients in this group (e.g., in those who require increasing amounts of supplemental oxygen) (BIII).

**Rationale for the Use of Dexamethasone**

In the RECOVERY trial, treatment with dexamethasone conferred a survival benefit among participants who required supplemental oxygen at enrollment. In the dexamethasone group, 23.3% of participants died within 28 days of enrollment compared with 26.2% in the standard of care arm (rate ratio 0.82; 95% CI, 0.72–0.94). However, the amount of supplemental oxygen that participants were receiving and the proportions of participants who required oxygen delivery through a high-flow device or noninvasive ventilation were not reported. It is possible that the benefit of dexamethasone was greatest in those who required more respiratory support. It should be noted that <0.1% of patients in the RECOVERY trial received concomitant remdesivir. For more information, please see the Corticosteroids section.

However, some experts prefer not to use dexamethasone monotherapy in this group because of the theoretical concern that corticosteroids might slow viral clearance when they are administered without an antiviral drug. Corticosteroids have been associated with delayed viral clearance and/or worse clinical outcomes in patients with other viral respiratory infections. Some studies, but not all, have suggested that corticosteroids slow SARS-CoV-2 clearance, but the results to date are inconclusive.

**Rationale for the Use of Baricitinib Plus Remdesivir When Corticosteroids Cannot Be Administered**

In the ACTT-2 study, 1,033 hospitalized patients with COVID-19 were randomized to receive baricitinib (a Janus kinase inhibitor) plus remdesivir or placebo plus remdesivir. Among all participants, the median time to recovery was shorter with baricitinib plus remdesivir (7 days) than with remdesivir alone (8 days; rate ratio 1.16; 95% CI, 1.01–1.32; P = 0.03). New use of oxygen or mechanical ventilation was less likely with baricitinib plus remdesivir than with remdesivir alone, as were serious adverse events and new infections.
In a subgroup analysis of participants who required supplemental oxygen but who did not receive it through a high-flow device or invasive mechanical ventilation, the rate ratio for recovery was 1.17 (95% CI, 0.98–1.39). There was no statistically significant difference in mortality by Day 28 between the baricitinib and placebo arms in this subgroup (OR 0.4; 95% CI, 0.14–1.14) or in the overall population. Baseline corticosteroid use was an exclusion criterion, and the trial enrolled most participants prior to the public release of RECOVERY data.

Because dexamethasone has been shown to reduce mortality among patients who require supplemental oxygen, clinicians should prioritize the use of dexamethasone in this subgroup. The Panel therefore reserves baricitinib plus remdesivir for the rare circumstances in which corticosteroids are contraindicated (BIIa). It is unknown whether baricitinib would have an additive benefit or adverse effects when given in combination with corticosteroids. Therefore, the Panel recommends against using the combination of baricitinib, dexamethasone, and remdesivir, except in a clinical trial (BIII).

**For Hospitalized Patients With COVID-19 Who Require Delivery of Oxygen Through a High-Flow Device or Noninvasive Ventilation but Not Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation**

**Recommendations**

The Panel recommends one of the following options for these patients:

- **Dexamethasone** alone (AI); or
- A combination of **dexamethasone plus remdesivir** (BIII).

**Additional Considerations**

- The combination of dexamethasone and remdesivir has not been rigorously studied in clinical trials. Because there are theoretical reasons for combining these drugs, the Panel considers both dexamethasone alone and the combination of remdesivir and dexamethasone to be acceptable options for treating COVID-19 in this group of patients.
- The Panel recommends against the use of **remdesivir alone** because it is not clear whether remdesivir confers a clinical benefit in this group of patients (AIIa).
- For patients who initially received remdesivir monotherapy and progressed to requiring high-flow oxygen or noninvasive ventilation, dexamethasone should be initiated and remdesivir should be continued until the treatment course is completed.
- If dexamethasone is not available, equivalent doses of other corticosteroids such as prednisone, methylprednisolone, or hydrocortisone may be used (BIII). See Corticosteroids for more information.
- In the rare circumstances where corticosteroids cannot be used, baricitinib plus remdesivir can be used (BIIa). Baricitinib should not be used without remdesivir.

**Rationale for the Use of Dexamethasone**

In the RECOVERY study, treatment with dexamethasone conferred a survival benefit among participants who required supplemental oxygen without invasive mechanical ventilation at enrollment: 23.3% of the participants in the dexamethasone group died within 28 days of enrollment compared with 26.2% in the standard of care arm (rate ratio 0.82; 95% CI, 0.72–0.94).5
Rationale for the Use of Remdesivir Plus Dexamethasone

The combination of remdesivir and dexamethasone has not been rigorously studied in clinical trials; therefore, the safety and efficacy of this combination are unknown. The Panel recognizes that there are theoretical reasons to use the combination of remdesivir and dexamethasone, as described above. Based on these theoretical considerations, the Panel considers the combination of dexamethasone plus remdesivir a treatment option for patients in this group (e.g., in those who require delivery of oxygen through a high-flow device or noninvasive ventilation).

Rationale for Not Recommending Remdesivir Monotherapy

In ACTT-1, there was no observed difference in time to recovery between the remdesivir and placebo groups (recovery rate ratio 1.09; 95% CI, 0.76–1.57) in the subgroup of participants who required high-flow oxygen or noninvasive ventilation at enrollment (n = 193). A post hoc analysis did not show a survival benefit for remdesivir at Day 29.1 However, the trial was not powered to detect differences in outcomes within subgroups. The Panel does not recommend using remdesivir monotherapy in these patients because there is uncertainty regarding whether remdesivir alone confers a clinical benefit in this subgroup (AIIa). Dexamethasone or remdesivir plus dexamethasone are better treatment options for COVID-19 in this group of patients.

For patients who start remdesivir monotherapy and then progress to requiring oxygen delivery through a high-flow device or noninvasive ventilation, the Panel recommends initiating dexamethasone and continuing remdesivir until the treatment course is completed. Clinical trials that evaluated the use of remdesivir categorized patients based on their severity of illness at the start of treatment with remdesivir; therefore, patients may benefit from remdesivir even if their clinical course progresses to a severity of illness for which the benefits of remdesivir are less certain.

Rationale for the Use of Baricitinib Plus Remdesivir When Corticosteroids Are Contraindicated

During ACTT-2, the median time to recovery was shorter in the baricitinib plus remdesivir arm (7 days) than in the placebo plus remdesivir arm (8 days) in the overall study population (rate ratio 1.16; 95% CI, 1.01–1.32; P = 0.03). In a subgroup analysis of participants who required high-flow oxygen or noninvasive ventilation (n = 216), the median time to recovery was 10 days in the baricitinib plus remdesivir arm and 18 days in the remdesivir alone arm (rate ratio 1.51; 95% CI, 1.10–2.08). There was no statistically significant difference in mortality by Day 28 between the baricitinib and placebo arms (OR 0.65; 95% CI, 0.39–1.09) in the overall population.

Baseline corticosteroid use was an exclusion criterion, and the trial enrolled most participants prior to the public release of RECOVERY data. It is unknown whether baricitinib would have an additive benefit to treatment with corticosteroids, or whether baricitinib is safer or more efficacious than corticosteroids. Because dexamethasone has been shown to reduce mortality in patients with COVID-19 who required supplemental oxygen, clinicians should prioritize the use of dexamethasone over the use of baricitinib in this group of patients. The Panel therefore reserves baricitinib in combination with remdesivir for the rare circumstance in which corticosteroids are contraindicated for this subgroup (BIIa). It is also unknown whether baricitinib would have additive benefit or adverse effects when given in combination with corticosteroids. Therefore, the Panel recommends against the use of a combination of baricitinib, dexamethasone, and remdesivir, except in a clinical trial (BIII).
For Hospitalized Patients With COVID-19 Who Require Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation

Recommendations

• The Panel recommends the use of dexamethasone in hospitalized patients with COVID-19 who require invasive mechanical ventilation or ECMO (AI).

Additional Considerations

• If dexamethasone is not available, equivalent doses of alternative corticosteroids such as prednisone, methylprednisolone, or hydrocortisone may be used (BIII).

• For patients who initially received remdesivir monotherapy and progressed to requiring invasive mechanical ventilation or ECMO, dexamethasone should be initiated and remdesivir should be continued until the treatment course is completed.

• The Panel recommends against the use of remdesivir monotherapy (AIIa).

Rationale for the Use of Dexamethasone Monotherapy

As the disease progresses in patients with COVID-19, a systemic inflammatory response may lead to multiple organ dysfunction syndrome. The anti-inflammatory effects of corticosteroids mitigate the inflammatory response and have been associated with improved outcomes in people with COVID-19 and critical illness.

Dexamethasone reduces mortality in critically ill patients with COVID-19 according to a meta-analysis that aggregated seven randomized trials and included data on 1,703 critically ill patients. The largest trial in the meta-analysis was the RECOVERY trial, whose subgroup of mechanically ventilated patients was included. For details about the meta-analysis and the RECOVERY trial, see the Corticosteroids section. Because the benefits outweigh the potential harms, the Panel recommends the use of dexamethasone in hospitalized patients with COVID-19 who require invasive mechanical ventilation or ECMO (AI).

Considerations Related to the Use of Dexamethasone Plus Remdesivir Combination Therapy

Dexamethasone plus remdesivir combination therapy has not been evaluated in controlled studies; therefore, there is insufficient information to make a recommendation either for or against the use of this combination therapy. There is, however, a theoretical reason to administer dexamethasone plus remdesivir in patients who have recently been intubated. Antiviral therapy may prevent a steroid-related delay in viral clearance. This delay has been reported in the setting of other viral infections. Some studies have suggested that corticosteroids slow SARS-CoV-2 clearance, but the studies to date are not definitive. For example, an observational study in people with non-severe COVID-19 suggested that viral clearance was delayed in patients who received corticosteroids, whereas a more recent study in patients with moderate to severe COVID-19 found no relationship between the use of corticosteroids and the rate of viral clearance. Given the conflicting results from observational studies and the absence of clinical trial data, some Panel members would coadminister dexamethasone and remdesivir in patients who have recently been placed on mechanical ventilation until more conclusive evidence becomes available, based on their concerns about delayed viral clearance in patients who received corticosteroids. Other Panel members would not coadminister these drugs due to uncertainties about the benefit of using remdesivir in critically ill patients described below.
Rationale for Recommending Against the Use of Remdesivir Monotherapy

A clear benefit of remdesivir monotherapy has not been demonstrated in patients who require invasive mechanical ventilation or ECMO. During ACTT-1, remdesivir did not improve the recovery rate in this subgroup of participants (recovery rate ratio 0.98; 95% CI, 0.70–1.36), and, in a post hoc analysis of deaths by Day 29, remdesivir also did not improve survival in this subgroup (HR 1.13, 95% CI, 0.67–1.89). In the Solidarity trial, there was a trend toward increased mortality (rate ratio 1.27; 95% CI, 0.99–1.62) among patients who received mechanical ventilation and who were randomized to receive remdesivir rather than standard of care. Taken together, these results do not demonstrate a clear benefit of remdesivir in critically ill patients.

For patients who start remdesivir monotherapy and then progress to requiring invasive mechanical ventilation or ECMO, the Panel recommends initiating dexamethasone and continuing remdesivir until the treatment course is completed. Clinical trials that evaluated remdesivir categorized patients based on their severity of illness at the start of treatment with remdesivir; therefore, patients may benefit from receiving remdesivir even if their clinical course progresses to a severity of illness for which the benefits of remdesivir are less certain.

References


