Therapeutic Management of Hospitalized Adults With COVID-19

Last Updated: July 8, 2021

Figure 2. Therapeutic Management of Hospitalized Adults With COVID-19 Based on Disease Severity

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or other **corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients who are at high risk of disease progression, the use of remdesivir may be appropriate.
Hospitalized and Requires Supplemental Oxygen	Use one of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone**[d] **plus remdesivir**[b,c] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)** • **Dexamethasone**[d] (when combination therapy with remdesivir cannot be used or is not available) **(BI)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	Use one of the following options: • **Dexamethasone**[d] **(AI)** • **Dexamethasone**[d] **plus remdesivir**[b,c] **(BIII)** For patients who were recently hospitalized[e] with rapidly increasing oxygen needs and systemic inflammation: • Add either **baricitinib**[f,g] **(BIIa)** or **tocilizumab**[f,h] **(BIIa)** to one of the two options above
Hospitalized and Requires IMV or ECMO	For most patients: • **Dexamethasone**[d,i] **(AI)** For patients who are within 24 hours of admission to the ICU: • **Dexamethasone**[d,i] **plus tocilizumab**[f,h] **(BIIa)**

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

[a] 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.
[b] The dose for remdesivir 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 to up to 10 days if there is no substantial clinical improvement by Day 5.
[c] For patients who are receiving remdesivir but progress to requiring oxygen through a high-flow device, noninvasive ventilation, IMV, or ECMO, remdesivir should be continued until the treatment course is completed.
[d] The dose for dexamethasone 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.
[e] For example, within 3 days of hospital admission. See the Interleukin-6 Inhibitors section for more information.
[f] As there are no studies that directly compare using baricitinib and tocilizumab as treatments for COVID-19, the Panel has insufficient evidence to recommend one drug over the other. Treatment decisions should be based on local guidance, drug availability, and patient comorbidities.
[g] The dose for baricitinib is 4 mg PO once daily for 14 days or until hospital discharge (refer to Table 4c for dose modifications for patients with renal impairment). Baricitinib should be used in combination with steroids (with or without remdesivir). The combination of baricitinib plus tocilizumab has not been studied, and the Panel **recommends against** the use of this combination, except in a clinical trial **(AIII)**.
[h] The dose for tocilizumab is 8 mg/kg of actual body weight (up to 800 mg) administered as a single IV dose. The combination of tocilizumab plus baricitinib has not been studied, and the use of this combination should be avoided outside of a clinical trial. See the Interleukin-6 Inhibitors section for more information.
[i] The combination of **dexamethasone plus 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; ICU = intensive care unit; IMV = invasive mechanical ventilation; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally

Patients Who Do Not Require Supplemental Oxygen

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)** for the treatment of COVID-19. 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 is insufficient evidence 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 RECOVERY, 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).[1] 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 Table 4a 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 Is Insufficient Evidence to Recommend Either for or Against the Use of Remdesivir

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.[2]

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 arms was of uncertain clinical importance.[3]

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 (control arm). 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 11 of 661 patients (2%) in the remdesivir arm and in 13 of 664 patients (2.1%) in the control arm (rate ratio 0.90; 99% CI, 0.31–2.58).[4] 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 Table 2a for additional information.

Because these trials produced conflicting results regarding the benefits of remdesivir, the Panel finds the available evidence 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., in cases where a person is at a particularly high risk for clinical deterioration).

Patients 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** (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.
- There is insufficient evidence to determine which patients in this group would benefit from adding baricitinib or tocilizumab to dexamethasone treatment. Some Panel members would add baricitinib or tocilizumab to a patient's dexamethasone treatment in cases where the patient has rapidly increasing oxygen needs and increased markers of inflammation but does not yet require high-flow oxygen or noninvasive ventilation.
- As there are no studies that directly compare using baricitinib and tocilizumab as treatments for COVID-19, the Panel has insufficient evidence to recommend one drug over the other. Treatment decisions should be made based on local guidance, drug availability, and patient comorbidities.

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).[2]

The Solidarity 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 for death in the overall study population 0.95; 95% CI, 0.81–1.11; rate ratio for death in patients who did not require mechanical ventilation at entry 0.86; 99% CI, 0.67–1.11). 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.[4] However, an open-label trial like Solidarity is less well-suited to assess time to recovery than a placebo-controlled trial. In Solidarity, because both clinicians and patients knew that remdesivir was being administered, it is possible that hospital discharge was delayed in order to complete the 10-day course of therapy.

Based on the results of ACTT-1, the Panel recommends **remdesivir** (without dexamethasone) as a treatment option for certain patients who require supplemental oxygen (e.g., those who require minimal supplemental oxygen) **(BIIa)**. In these individuals, the hyperinflammatory state where corticosteroids might be most beneficial may not yet be present or fully developed. For more information, please see Table 2a.

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. However, the data on clinical outcomes for patients who received this combination are currently limited.[5]

Based on the theoretical benefits of combining antiviral and anti-inflammatory effects, the Panel recommends the combination of **dexamethasone plus remdesivir** as a treatment option for patients in this group (e.g., those who require increasing amounts of supplemental oxygen) **(BIII)**.

Rationale for the Use of Dexamethasone

In RECOVERY, 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).[1] 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 RECOVERY received concomitant remdesivir. For more information, please see the Corticosteroids section.

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.[6-8] Some studies have suggested that corticosteroids slow SARS-CoV-2 clearance, but the results to date are inconclusive.[9-13]

Rationale for the Panel's Assessment That There Is Insufficient Evidence to Determine Which Patients Would Benefit from Dexamethasone Plus Baricitinib or Tocilizumab

In COV-BARRIER (a multinational, randomized, placebo-controlled trial), 1,525 hospitalized patients with COVID-19 who had evidence of pneumonia, an elevation in one or more inflammatory markers, and an estimated glomerular filtration rate >30 mL/min/1.73 m^2 were randomized 1:1 to receive oral baricitinib 4 mg or placebo.[3] The baricitinib dose was adjusted for patients with renal impairment. There was no significant difference between the study arms in the primary endpoint of the trial, which was the proportion of patients who progressed to requiring high-flow oxygen, noninvasive ventilation, or invasive mechanical ventilation or who died by Day 28. In the subgroup of patients who required supplemental oxygen but who did not receive it through a high-flow device or mechanical ventilation (n = 962), the addition of baricitinib resulted in a lower mortality compared to those who received placebo (HR 0.72; 95% CI, 0.45–1.16; *P* = 0.11); however, this difference was not statistically significant.

Early trials that evaluated the use of tocilizumab in patients who were hospitalized with COVID-19 did not show a treatment effect for tocilizumab. These trials included a high proportion of patients who were receiving conventional oxygen therapy; however, many of these trials were underpowered, and only a small proportion of patients were also receiving corticosteroids.[14-18] Although RECOVERY reported a mortality benefit for tocilizumab, the study did not identify a particular subgroup of hospitalized patients on conventional oxygen therapy who benefited most from receiving the drug.[19] Among 21,550 participants who were randomized into the RECOVERY platform trial, only 4,116 of the participants (19%) underwent a second randomization into the tocilizumab intervention arm, suggesting that the study results are generalizable only to a restricted subset of hospitalized patients. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram for RECOVERY suggests that patients with clinical evidence of progressive COVID-19 were preferentially selected for the tocilizumab study.

The Panel recognizes that there may be some hospitalized patients who are receiving conventional oxygen therapy who may have progressive hypoxemia associated with significant systemic inflammation. The addition of baricitinib or tocilizumab to their standard treatment may provide a modest benefit. Nevertheless, there is insufficient evidence to clearly characterize the subgroups within this patient population who would benefit from receiving these interventions. As there are no studies that directly compare using baricitinib and tocilizumab as treatments for COVID-19, the Panel has insufficient evidence to recommend one drug over the other. Treatment decisions should be made based on local guidance, drug availability, and patient comorbidities.

Patients 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*
  - **Dexamethasone plus remdesivir (BIII)**.

- For recently hospitalized patients (i.e., those who are within 3 days of hospital admission) who have rapidly increasing oxygen needs, require high-flow oxygen or noninvasive ventilation, and have increased markers of inflammation, add **baricitinib (BIIa)** or **tocilizumab (BIIa)** (drugs are listed alphabetically) to one of the two options above.

- The Panel **recommends against** the use of **baricitinib** in combination with **tocilizumab** for the treatment of COVID-19, except in a clinical trial **(AIII)**. Because both baricitinib and tocilizumab are potent immunosuppressants, there is the potential for an additive risk of infection.

Additional Considerations

- Immunosuppressive therapy (e.g., dexamethasone with or without baricitinib or tocilizumab) may increase the risk of opportunistic infections or reactivation of latent infections; however, randomized trials have not demonstrated an increase in the frequency of infections.
- Prophylactic treatment with ivermectin should be considered for patients who are from areas where strongyloidiasis is endemic.

Using Corticosteroids

- 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, add dexamethasone and complete the treatment course of remdesivir.
- 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.

Using Baricitinib and Tocilizumab

- Baricitinib or tocilizumab should only be given in combination with dexamethasone or another corticosteroid at an equivalent dose. Some clinicians may choose to assess a patient's clinical response to dexamethasone before deciding whether adding baricitinib or tocilizumab is necessary.
- Studies that directly compare using baricitinib and tocilizumab as treatments for COVID-19 are not available. Therefore, the Panel has insufficient evidence to recommend one drug over the other. Treatment decisions should be made based on local guidance, drug availability, and patient comorbidities.
- Although some patients in REMAP-CAP and RECOVERY received a second dose of tocilizumab at the discretion of their treating physicians, there is insufficient evidence to determine which patients, if any, would benefit from an additional dose of the drug.

Rationale for the Use of Dexamethasone

In RECOVERY, 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).[1]

Rationale for the Use of Remdesivir Plus Dexamethasone

The combination of remdesivir plus 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 this combination, 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.

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.[2] 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 Recommending the Use of Baricitinib Plus Dexamethasone in Certain Hospitalized Patients

In COV-BARRIER, 1,525 hospitalized patients with COVID-19 were randomized 1:1 to receive oral baricitinib 4 mg or placebo in addition to the local standard of care for up to 14 days (or until hospital discharge).[3]

There was no difference in the primary endpoint of progression to high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or death by Day 28 between the baricitinib arm (27.8% of patients) and the placebo arm (30.5% of patients; OR 0.85; 95% CI, 0.67–1.08; *P* = 0.18). All-cause mortality by Day 28 was 8.1% of patients in the baricitinib arm and 13.1% in the placebo arm, resulting in a 38.2% reduction in mortality (HR 0.57; 95% CI, 0.41–0.78; nominal *P* = 0.002). Across all the prespecified baseline disease severity subgroups, mortality estimates were numerically lower among those who received baricitinib than among those who received placebo. The difference in mortality was most pronounced in the subgroup of 370 patients who were receiving high-flow oxygen or noninvasive ventilation at baseline (17.5% of patients died in the baricitinib arm vs. 29.4% in the placebo arm; HR 0.52; 95% CI, 0.33–0.80; nominal *P* = 0.007). The occurrence of adverse events, serious adverse events, serious infections, and venous thromboembolic events was comparable in the baricitinib and placebo arms.

ACTT-2 demonstrated that baricitinib used in combination with remdesivir improved time to recovery in hospitalized patients with COVID-19. The effect was most pronounced in patients who were receiving high-flow oxygen or noninvasive ventilation. Although people who were receiving corticosteroids were excluded from ACTT-2, the results of the study support the idea that baricitinib may have a clinical benefit among patients with severe COVID-19 who are not able to receive corticosteroids.[20]

Rationale for Recommending the Combination Use of Tocilizumab and Dexamethasone in Certain Hospitalized Patients

REMAP-CAP and RECOVERY, the two largest randomized controlled tocilizumab trials to date, have both reported a mortality benefit for tocilizumab among patients with rapid respiratory decompensation who require oxygen delivery through a high-flow device or noninvasive ventilation.[19,21] Corticosteroids were given to a majority of patients in both studies. In REMAP-CAP, a narrowly defined population of patients who were admitted to an intensive care unit (ICU) with severe to critical COVID-19 and who were exhibiting rapid respiratory decompensation were randomized to receive open-label tocilizumab or usual care alone. Compared to usual care, the use of tocilizumab reduced in-hospital mortality (28% vs. 36%) and, over 21 days of follow-up, increased the median number of days free of respiratory and cardiovascular organ support (10 days vs. 0 days; OR 1.64; 95% CI, 1.25–2.14). Enrollment occurred within 24 hours of ICU admission and within a median of 1.2 days of hospitalization (IQR 0.8–2.8 days), suggesting that the benefit of tocilizumab occurs specifically in patients who are experiencing rapid respiratory decompensation. In REMAP-CAP, the evidence for therapeutic benefit was strongest among recipients who had recently started receiving oxygen through a high-flow device or noninvasive ventilation; however, the lack of subgroup analyses by oxygen requirement is a notable limitation of this study.

RECOVERY also suggested a mortality benefit for tocilizumab plus dexamethasone in patients who specifically required noninvasive ventilation or high-flow oxygen. In this study, a subset of participants with hypoxemia and C-reactive protein levels ≥75 mg/L

were offered enrollment into a second randomization to receive tocilizumab or usual care. Tocilizumab reduced all-cause mortality in these patients; by Day 28, 29% of participants in the tocilizumab arm had died compared to 33% in the usual care arm (rate ratio 0.86; 95% CI, 0.77–0.96).

The Panel **recommends against** using tocilizumab without concomitant corticosteroids, as multiple trials have reported that the clinical benefit of tocilizumab is seen among patients who are receiving tocilizumab plus a corticosteroid (see Table 4c).

Rationale for Recommending Against Using the Combination of Baricitinib and Tocilizumab

The Panel **recommends against** the use of the combination of baricitinib and tocilizumab for the treatment of COVID-19, except in a clinical trial **(AIII)** because there is insufficient evidence for the use of this combination. Given that both baricitinib and tocilizumab are potent immunosuppressants, there is the potential for an additive risk of infection.

Patients 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)**.
- The Panel recommends the use of **dexamethasone plus tocilizumab** for patients who are within 24 hours of admission to the ICU **(BIIa)**.

Additional Considerations

- If dexamethasone is not available, equivalent doses of alternative corticosteroids (e.g., **prednisone, methylprednisolone, 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)**.
- Tocilizumab should be given only in combination with dexamethasone (or another corticosteroid at an equivalent dose).
- Although some patients in the REMAP-CAP and RECOVERY trials received a second dose of tocilizumab at the discretion of their treating physicians, there is insufficient evidence to determine which patients, if any, would benefit from an additional dose of the drug.
- The combination of dexamethasone and tocilizumab may increase the risk of opportunistic infections or reactivation of latent infections. Prophylactic treatment with ivermectin should be considered for patients who are from areas where strongyloidiasis is endemic.

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 the use of corticosteroids has 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.[22] The largest trial in the meta-analysis was the RECOVERY trial, whose subgroup of mechanically ventilated patients was included.[1] 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 to 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.[6,7]

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,[23] 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.[13] 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 **(CIII)** 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.

Rationale for Recommending the Use of Tocilizumab Plus Dexamethasone in Patients Within 24 Hours of Admission to the Intensive Care Unit

The REMAP-CAP and RECOVERY studies, the two largest randomized controlled tocilizumab trials to date, have both reported a mortality benefit for tocilizumab among patients who experienced rapid respiratory decompensation and were recently admitted to the ICU, including those who required invasive mechanical ventilation.[19,21] REMAP-CAP enrolled patients within 24 hours of admission to the ICU. Prior trials that enrolled patients later in the ICU course and/or who received oxygen support >24 hours after ICU admission have failed to show consistent clinical benefits for tocilizumab (see Table 4c). Thus, it is unclear whether there is a clinical benefit for tocilizumab in patients who received invasive mechanical ventilation >24 hours after ICU admission. Findings from RECOVERY suggest a clinical benefit for tocilizumab plus corticosteroids among patients with rapid clinical progression who received invasive mechanical ventilation. See the section above for additional details on the clinical trial data and rationale for using tocilizumab in this situation.

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 did not improve survival among participants in this subgroup (HR 1.13; 95% CI, 0.67–1.89).[2] In the Solidarity trial, there was a trend toward increased mortality among patients who received mechanical ventilation and who were randomized to receive remdesivir rather than standard of care (rate ratio 1.27; 95% CI, 0.99–1.62).[4] 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 +