The COVID-19 Treatment Guidelines Panel's Statement on the Use of Anti-SARS-CoV-2 Monoclonal Antibodies or Remdesivir for the Treatment of COVID-19 in Nonhospitalized Patients When Omicron Is the Predominant Circulating Variant

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The Omicron (B.1.1.529) variant of concern (VOC) has become the dominant variant in many parts of the United States.[1] **The Omicron variant, which includes numerous mutations in the spike protein, is predicted to have markedly reduced susceptibility to several anti-SARS-CoV-2 monoclonal antibodies (mAbs), especially bamlanivimab plus etesevimab and casirivimab plus imdevimab. Sotrovimab appears to retain activity against the Omicron variant.**

With the rapid rise in the prevalence of the Omicron VOC, it is anticipated there will be a limited supply of therapeutic agents that are active against the variant (e.g., the anti-SARS-CoV-2 mAb sotrovimab and small molecule antiviral agents, once they become available) for patients who are at high risk of progression to severe COVID-19 and who might benefit from these therapies.

Intravenous (IV) remdesivir is approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 in hospitalized adult and pediatric patients (aged ≥12 years and weighing ≥40 kg). Remdesivir has also been studied in nonhospitalized patients with mild to moderate COVID-19. Results from the PINETREE trial showed that 3 consecutive days of IV remdesivir resulted in a significant reduction in hospitalizations and deaths compared to placebo.[2] Remdesivir is expected to be active against the Omicron VOC.

This statement provides guidance on the use of anti-SARS-CoV-2 mAbs or remdesivir when the Omicron VOC is the predominant circulating variant. Ritonavir-boosted nirmatrelvir and molnupiravir, 2 new oral antiviral therapies, have just received Emergency Use Authorizations for use in nonhospitalized patients at high risk of progression to severe COVID-19 (see the FDA EUAs for recommendations). The COVID-19 Treatment Guidelines Panel (the Panel) will provide further recommendations as soon as more treatment options become available for this patient population.

Recommendations

When the Omicron variant represents the majority (e.g., >80%) of infections in a region, it is expected that bamlanivimab plus etesevimab and casirivimab plus imdevimab will not be active for treatment or post-exposure prophylaxis (PEP) of COVID-19.

In this setting, the Panel recommends using 1 of the following options to treat nonhospitalized patients with mild to moderate COVID-19 who are at high risk of clinical progression:

- **Sotrovimab** 500 mg IV as a single infusion **(AIIa)** administered as soon as possible and within 10 days of symptom onset; *or*
- **Remdesivir** 200 mg IV on Day 1, then 100 mg once daily on Days 2 and 3 **(BIIa)** initiated as soon as possible and within 7 days of symptom onset.
  - Because remdesivir requires IV infusion for 3 consecutive days, logistical constraints may make it difficult to administer the drug in some settings.

- Remdesivir should be administered in a setting where management of severe hypersensitivity reactions, such as anaphylaxis, is possible. Patients should be monitored during the infusion and observed for at least 1 hour after the infusion.
- Remdesivir is currently FDA-approved for hospitalized individuals; however, use of the drug for outpatient treatment would be an off-label indication.

If neither sotrovimab nor remdesivir are feasible to use, and the Delta VOC still represents a significant, but not dominant proportion (e.g., ≥20%) of infections in the region:

- Patients could be offered bamlanivimab plus etesevimab or casirivimab plus imdevimab with the understanding that treatment would be ineffective if they are infected with the Omicron variant.
- Consider the use of bamlanivimab plus etesevimab or casirivimab plus imdevimab for PEP on a case-by-case basis with the understanding that the drugs may be ineffective if the person has been exposed to the Omicron variant.

Rationale

The data that support the EUA for sotrovimab are from the Phase 3 COMET-ICE trial, which included outpatients with mild to moderate COVID-19 who were at high risk for progression to severe COVID-19 and within 5 days of symptom onset. The primary endpoint was the proportion of participants who were hospitalized for ≥24 hours or who died from any cause by Day 29. Endpoint events occurred in 3 of 291 participants (1%) in the sotrovimab arm and 21 of 292 participants (7%) in the placebo arm ($P = 0.002$), resulting in a 6% absolute reduction and an 85% relative reduction (95% CI, 44–96) in hospitalizations or death associated with sotrovimab.[3,4] In vitro studies indicate sotrovimab remains active against the Omicron variant.[5]

Data supporting the clinical benefit of early outpatient treatment with remdesivir emerged from PINETREE, a randomized placebo-controlled trial in nonhospitalized patients with COVID-19 who were at high risk of clinical progression and within 7 days of symptom onset. The primary outcome was the proportion of participants who were hospitalized for ≥24 hours (defined as ≥24 hours of acute care) or who died from any cause by Day 28. Participants were randomized to receive 3 days of IV remdesivir or placebo as outpatients. At treatment initiation, the median duration of symptoms was 5 days. By Day 28, there was a significant decrease in hospitalizations and/or death among those who received remdesivir: the primary endpoint occurred in 2 of 279 (0.7%) remdesivir recipients versus 15 of 283 (5.3%) placebo recipients, resulting in a 4.6% absolute reduction and an 87% relative reduction in hospitalizations and/or death for remdesivir (HR 0.13; 95% CI, 0.03–0.59; $P = 0.008$).[2]

References

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