Metformin has been identified as a potential COVID-19 therapeutic agent because of its possible action against the proteins that are involved in translation, its antiviral activity in vitro, and its anti-inflammatory and antithrombotic activities.\textsuperscript{1-4} Data from observational studies have suggested that patients who were receiving metformin as treatment for diabetes at the time of their COVID-19 diagnosis had a lower risk of progressing to severe COVID-19.\textsuperscript{5-7} Randomized controlled trials have provided insight into the role of metformin in treating nonhospitalized patients with COVID-19. These trials are described below and in Table 7e.

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) \textbf{recommends against} the use of \textbf{metformin} for the treatment of COVID-19 in nonhospitalized patients (BIIa) and hospitalized patients (BIII), except in a clinical trial.
- Patients with COVID-19 who are receiving \textbf{metformin} for an underlying condition should continue this therapy as directed by their health care provider (AIII).

Rationale

Two randomized controlled trials (the TOGETHER and COVID-OUT trials) assessed the efficacy of metformin in nonhospitalized patients with COVID-19. Neither trial demonstrated a benefit of metformin in reducing the risk of hospitalization or death in patients with COVID-19. The Panel’s recommendations are based on the results of these trials.

Other outpatient therapies (e.g., ritonavir-boosted nirmatrelvir [Paxlovid], remdesivir, anti-SARS-CoV-2 monoclonal antibodies) have been shown to be highly effective in preventing hospitalization or death in unvaccinated patients who are at high risk of disease progression.

Clinical Data

The TOGETHER trial was a placebo-controlled platform clinical trial that was conducted in Brazil.\textsuperscript{8} The study enrolled nonhospitalized individuals who had symptomatic SARS-CoV-2 infection for \(\leq 7\) days, no history of COVID-19 vaccination, and an increased risk of progressing to severe disease. Patients were randomized to receive extended-release metformin 750 mg (\(n = 215\)) or placebo (\(n = 203\)) twice daily for 10 days.

The primary endpoint was a composite of retention in an emergency setting for \(\geq 6\) hours or hospitalization within 28 days of randomization. Secondary endpoints included viral clearance at Days 3 and 7, clinical improvement at Day 28, time to hospitalization or death, and the occurrence of adverse events. The study was stopped by the data and safety monitoring board for futility, as there was a low probability of demonstrating a difference between the study arms. Overall, there was no difference between the arms in the number of adverse events; however, the proportion of patients who experienced Grade 3 events was higher in the metformin arm (9.8%) than in the placebo arm (4.4%).

COVID-OUT was a Phase 3, double-blind, placebo-controlled 2 \(\times\) 3 factorial trial that evaluated the effectiveness of metformin, ivermectin, and fluvoxamine in patients with COVID-19.\textsuperscript{9} Patients were randomized to receive metformin or placebo in 1 factor, and ivermectin, fluvoxamine, or placebo in
The study enrolled nonhospitalized adults within 3 days of a confirmed diagnosis of COVID-19 and ≤7 days from symptom onset. Patients were aged 30 to 85 years and overweight. Those with stage 4 or 5 chronic kidney disease or an estimated glomerular filtration rate (eGFR) of <45 mL/min/1.73 m² were excluded. The metformin arm included those assigned to receive immediate-release oral (PO) metformin (titrated over several days to a final daily dose of 1,500 mg) alone or in combination with ivermectin (390–470 µg/kg PO per day for 3 days) or fluvoxamine (50 mg PO twice daily for 14 days). The control arm included those who received placebo with or without ivermectin or fluvoxamine.

The primary endpoint was a composite of hypoxemia (measured by a home pulse oximeter) or health care utilization for COVID-19 (defined as an emergency department [ED] visit, hospitalization, or death) by Day 14. It is notable that after the study had begun, the Food and Drug Administration (FDA) raised concerns about the accuracy of home pulse oximeters. Approximately 50% of the patients enrolled in this study had received a primary COVID-19 vaccine series. The analyses showed no benefit for any of the 3 investigational agents in preventing the primary endpoint. There were also no benefits seen for these agents in preventing the secondary endpoints, except in the metformin arm, where the risk of the pre-specified secondary endpoint of an ED visit, hospitalization, or death was lower than in the control arm (adjusted OR 0.58; 95% CI, 0.35–0.94). The analyses of the secondary endpoints were not adjusted for multiple comparisons.

For more information on these trials, see Table 7c.

Monitoring, Adverse Effects, and Drug-Drug Interactions

The most common adverse effects of metformin are nausea, vomiting, diarrhea, and headache. Rarely, lactic acidosis may occur. The risk factors associated with lactic acidosis include older age, impaired renal or hepatic function, the use of iodinated contrast dye, cardiac dysfunction, metabolic disturbances, and excessive alcohol consumption. Metformin is not recommended for patients with an eGFR of <30 mL/min/1.73 m².

Metformin is a substrate of the human organic cation transporters OCT1 and OCT2. Drugs that inhibit these transporters may increase the systemic exposure of metformin and increase the risk of metformin-related adverse effects.

Considerations in Pregnancy

Metformin is commonly used in pregnant people. However, because clinical trials have not demonstrated a clinical benefit of metformin in nonpregnant adults with COVID-19, there is no justification for administering it to pregnant people to treat COVID-19 outside of a clinical trial.

Considerations in Children

Although metformin is approved by the FDA for the treatment of type 2 diabetes mellitus in children aged >10 years, clinical trials that have evaluated its use for the treatment of COVID-19 have not included people aged <18 years. Given the lack of evidence of efficacy in adults, the Panel recommends against the use of metformin for the treatment of COVID-19 in pediatric patients, except in a clinical trial (AIII).

References


