Metformin

Last Updated: December 20, 2023

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.[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.[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 7c.

Recommendations

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of metformin for the treatment of COVID-19 in nonhospitalized patients.
- The Panel **recommends against** the use of **metformin** for the treatment of COVID-19 in hospitalized patients, except in a clinical trial **(BIII)**.
- Patients with COVID-19 who are receiving **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 using metformin in nonhospitalized patients with COVID-19. In these trials, the use of metformin did not reduce the risk of hospitalization or death in these patients. The Panel's recommendations are based on the results of these trials.

Other outpatient therapies (i.e., ritonavir-boosted nirmatrelvir [Paxlovid], remdesivir, molnupiravir) have been shown to be effective in preventing hospitalization or death in unvaccinated patients who are at high risk of disease progression.

Monitoring, Adverse Effects, and Drug-Drug Interactions

The most common adverse effects of metformin are nausea, vomiting, diarrhea, and headache. In rare cases, 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 estimated glomerular filtration rate of <30 mL/min/1.73m^2.

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 Pregnant People

Metformin is commonly used in pregnant people with type 2 diabetes mellitus. However, because clinical trials have not demonstrated a clear clinical benefit of using 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 Food and Drug Administration 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 clear 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)**.

Clinical Data

TOGETHER Trial

The TOGETHER trial was a placebo-controlled platform clinical trial that was conducted in Brazil.[8] The study enrolled nonhospitalized patients who had symptomatic SARS-CoV-2 infection for ≤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 >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 Trial

The COVID-OUT trial was a Phase 3, double-blind, placebo-controlled 2 x 3 factorial trial that evaluated the effectiveness of metformin, ivermectin, or fluvoxamine in patients with COVID-19.[9] Patients were randomized to receive metformin or placebo in 1 factor and ivermectin, fluvoxamine, or placebo in the other factor. 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 of <45 mL/min/1.73 m^2 were excluded. The metformin arm included those assigned to receive immediate-release oral metformin (titrated over several days to a final daily dose of 1,500 mg) alone or in combination with ivermectin or fluvoxamine. The control arm included those who received placebo with or without ivermectin or fluvoxamine.

The primary endpoint was a composite of development of hypoxemia (defined as oxygen saturation ≤93%, as measured by a home pulse oximeter), emergency department visit, hospitalization, or death by Day 14. While this study was underway, the Food and Drug Administration raised concerns about the accuracy of home pulse oximeters. Approximately 50% of the patients received a primary COVID-19 vaccine series. The analyses showed no benefit for any of the 3 investigational agents in preventing the primary endpoint. In addition, the use of these agents did not lower the severity of COVID-19 symptoms over 14 days. A prespecified secondary analysis determined that, over 14 days of follow-up, those who received metformin had a lower risk of an emergency department visit, hospitalization, or death than those who did not receive metformin (adjusted OR 0.58; 95% CI, 0.35–0.94). A key secondary endpoint in the analysis was a composite of hospitalization or death by Day 28. Eight of 596 patients (1.3%) who received metformin met this endpoint compared with 19 of 601 patients (3.2%) who did not receive

metformin.

A secondary endpoint in the COVID-OUT trial assessed the impact of metformin on the development of long COVID. Since there is no standardized definition for long COVID, the endpoint was based on whether the patient had been given this diagnosis by a health care provider during the 10 months of follow-up. The study reported lower rates of long COVID in the metformin arm than in the control arm.[10]

Although a secondary analysis of the COVID-OUT trial data demonstrated a benefit of metformin in patients with COVID-19, the results of the TOGETHER and COVID-OUT trials did not show a consistent benefit of metformin in these patients. Therefore, the Panel believes there is insufficient evidence to recommend either for or against the use of metformin for the treatment of COVID-19 in nonhospitalized patients. For more information on these trials, see Table 7c.

References

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