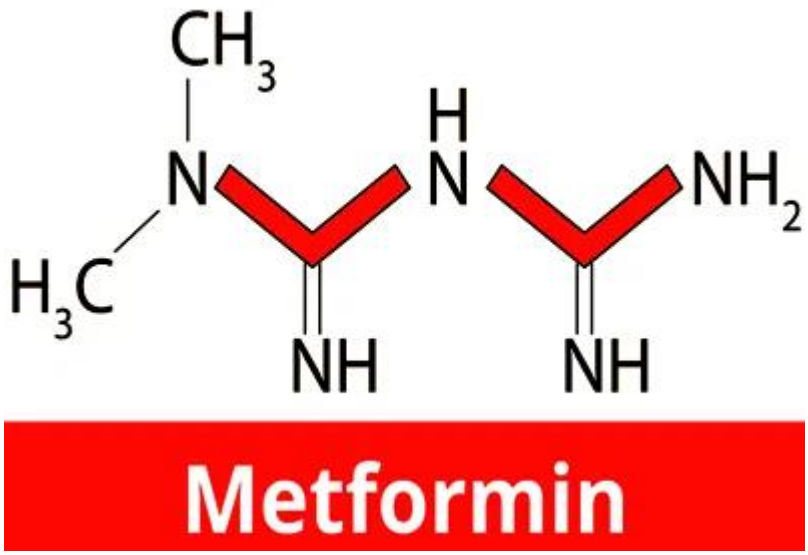
Infection with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) can lead to a new disease called long-COVID-19 or post-acute COVID-19 syndrome (PACS). Long/post-COVID syndrome represents a heterogeneous nosological entity, despite similar or overlapping symptoms between patients, and clear diagnostic criteria are yet to be established. The spectrum of long COVID symptoms is diverse, ranging from a single symptom to extensive multiorgan involvement, and from mild to chronically debilitating. These two randomized, placebo-controlled studies by American authors investigated whether outpatient treatment with metformin, ivermectin, or fluvoxamine reduces viral load in patients infected with SARS-CoV-2, whether metformin, ivermectin, or fluvoxamine can prevent severe forms of COVID-19 within the first two weeks after infection, and whether outpatient treatment with metformin, ivermectin, or fluvoxamine shortly after infection can reduce the risk of long COVID syndrome development during a long-term follow-up.

Metformin has an antiviral activity against RNA viruses, including SARS-CoV-2, and pleiotropic effects and actions important for COVID-19 pathophysiology. Interestingly, metformin was found to block the senescence of dopaminergic (DA) neurons infected with SARS-CoV-2 by reducing lysosomal senescence-associated β-galactosidase (SA-β-gal) activity, down-regulating the genes involved in the senescence pathway, and reducing viral RNA in DA neurons
https://discovermednews.com/changes-in-dopaminergic-neurons-linked-to-sars-cov-2/



The first study

This randomized, placebo-controlled, quadruple-blind, phase 3 trial (COVID-OUT) had two objectives: to evaluate whether metformin, ivermectin, or fluvoxamine can prevent severe forms of COVID-19 within the first two weeks after infection, and to investigate whether outpatient treatment with metformin, ivermectin, or fluvoxamine shortly after infection can reduce the risk of long COVID syndrome development during a long-term follow-up.

The study was conducted at six locations in the United States and included 1126 participants, 56% women, and 44% men. The SARS-CoV-2 infection was confirmed by a positive polymerase chain reaction (PCR) or antigen test within three days of symptom onset. On days 180, 210, 240, 270, and 300 after enrollment, participants were asked if they had been diagnosed with long COVID. On day 180, 1126 individuals completed at least one survey for long COVID.

Women who were pregnant or lactating were not assigned to fluvoxamine or ivermectin, but they were randomly assigned to receive metformin or a placebo. The authors noted that a substantial body of scientific literature supports the safety of metformin during pregnancy and lactation. However, there is less safety data for fluvoxamine or ivermectin.

COVID-19 vaccination was not a criterion for exclusion. Before enrollment, 55% of 1126 participants received the first COVID-19 vaccine, including 5% who received an initial 2021 monovalent booster.

Metformin was administered to 564 participants, and a placebo to 562. Metformin dose was titrated over six days: 500 mg on day one, 500 mg twice daily on days two to five, followed by 500 mg in the morning and 1000 mg in the evening on days 6 to 14. Ivermectin was administered to 361 individuals and a placebo to 378. The dose of ivermectin was 390 to 470 µg/kg per day for three days (median 430 µg/kg per day). Fluvoxamine was administered to 297 individuals and a placebo to 298. The dose of fluvoxamine was 50 mg on day one, followed by 50 mg twice daily until day 14. The study drugs were all taken orally in tablet form.

Results

By day 300, 8.3% of 1126 participants were diagnosed with long COVID (11% of women and 5% of men). The mean incidence of long COVID was 7.9% during the Alpha variant-dominant period, 8·3% during the Delta variant-dominant period, and 8·4% during the Omicron variant-dominant period.

By day 14 of metformin treatment, metformin reduced the risk of emergency department visits, hospitalizations, and death due to COVID-19 by 42.3% compared to a placebo. Also, by day 28, participants treated with metformin were less likely to be hospitalized than those who received a placebo. Ivermectin and fluvoxamine had no significant effect on severe COVID-19 outcomes by day 14.

By day 300, the cumulative incidence of long COVID syndrome was 6.3% in the group treated with metformin and 10.4% in those who received a placebo. Early outpatient treatment with metformin decreased the incidence of long COVID syndrome by approximately 41%, with an absolute reduction of 4.1%, compared to a placebo.

Importantly, when metformin treatment started less than four days after the onset of COVID-19 symptoms, the effect on reducing the risk of long COVID syndrome development was potentially greater than when treatment started four days or more after the onset of COVID-19 symptoms.

Ivermectin and fluvoxamine had no significant effect on the incidence of long COVID syndrome. By day 300, the cumulative incidence of long COVID was 7.7% in participants

who received ivermectin, 8.1% in individuals who received a placebo, 10.1% in participants who received fluvoxamine, and 7.5% in those who received a placebo.

The authors stated that they would not recommend starting metformin therapy without a multiple-day dose titration. In this trial, the dose was titrated over six days. Safety concerns for metformin have focused on the risk of lactic acidosis, but the authors noted that the risk of hypoglycemia is low. Several large studies and Cochrane reviews have shown no increased risk of lactic acidosis in people receiving metformin compared to controls. Metformin has also been shown to be safe for children and for women who are pregnant or lactating.

This article was published in The Lancet Infectious Diseases.

Journal Reference

Bramante CT et al. Outpatient treatment of COVID-19 and incidence of post-COVID-19 condition over 10 months (COVID-OUT): a multicentre, randomized, quadruple-blind, parallel-group, phase 3 trial. Lancet Infect Dis 2023, Published Online June 8, 2023. (Open Access) https://doi.org/10.1016/S1473-3099(23)00299-2

The second study

In this randomized, placebo-controlled double-blind trial, the authors evaluated the effects of metformin, fluvoxamine, and ivermectin on viral load in outpatients infected with SARS-CoV-2. Viral load was quantified using rtPCR for SARS-CoV-2.

The trial included 999 participants who self-collected anterior nasal swabs on day one (n = 945), day five (n = 871), and day ten (n = 775).

The results demonstrated that the mean viral load of SARS-CoV-2 was 3.6-fold lower in the group treated with metformin than in the placebo group. Viral rebound, defined as a higher viral load on day 10 than on day 5, was less frequent with metformin (3.28%) than with placebo. The effect of metformin was consistent across subgroups and increased over time.

In contrast, neither ivermectin nor fluvoxamine demonstrated any beneficial effect over placebo.

This article was published in Clinical Infectious Diseases.

Journal Reference

Bramante CT, Beckman KB, Mehta T, Karger AB, Odde DJ, Tignanelli CJ, et al. Favorable Antiviral Effect of Metformin on Severe Acute Respiratory Syndrome Coronavirus 2 Viral Load in a Randomized, Placebo-Controlled Clinical Trial of COVID-2019, Clinical Infectious Diseases, 2024; 79: 354-363. https://doi.org/10.1093/cid/ciae159

Conclusion

Two randomized, placebo-controlled trials showed that metformin reduced SARS-CoV-2 viral load and decreased the incidence of long COVID syndrome. The authors of the first study emphasized that this trial did not prove whether metformin would be effective in preventing long COVID if treatment started during COVID-19 hospitalization, or as a treatment for people who were diagnosed with long COVID.

They also stated that prospective and interventional studies should assess the incidence of long COVID in vaccinated individuals or those previously infected with SARS-CoV-2 for all therapeutic approaches.