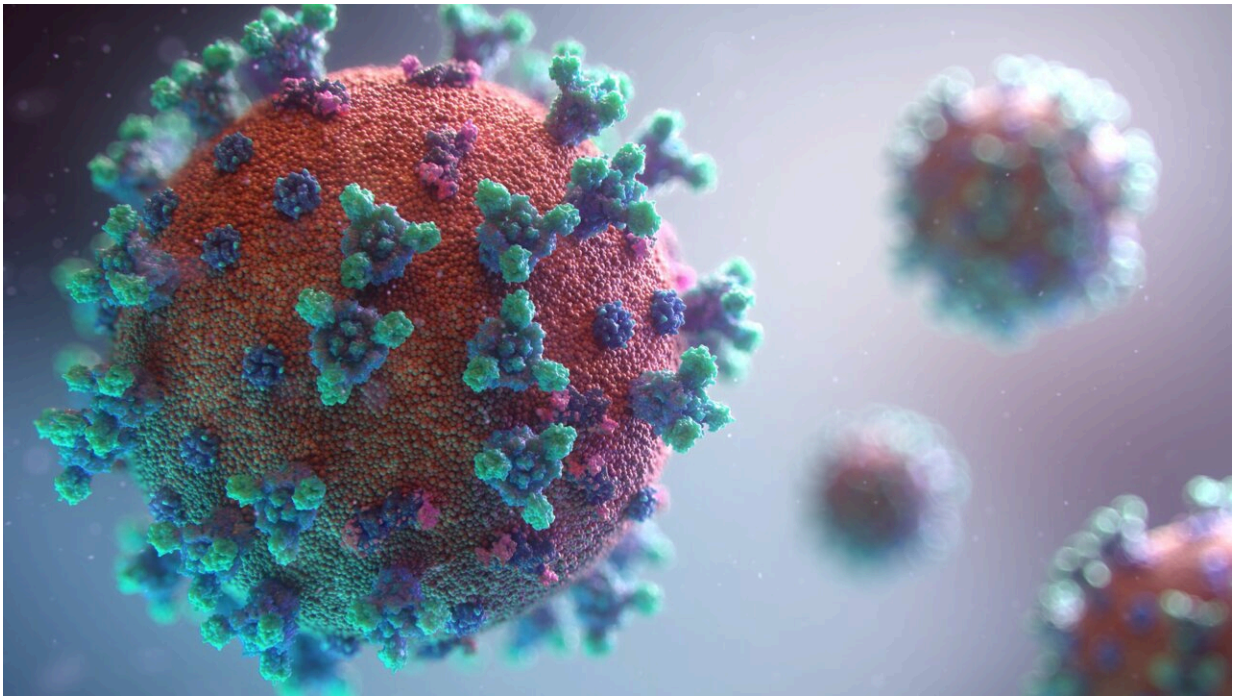
# Trial shows two investigational drugs are ineffective for treating severe COVID-19

April 11 2023



Credit: Unsplash/CC0 Public Domain

Despite the success of vaccines for preventing COVID-19, and of drugs for treating the disease, outcomes for severely ill patients admitted to the hospital remains poor. Identifying new therapies for severe COVID-19 remains a high priority and one in which Vanderbilt University Medical Center is taking a leading role.

A study published April 11 in the *Journal of the American Medical Association (JAMA)* evaluated two drugs that act on the renin-angiotensin system (RAS) as potential treatments for severe COVID-19. Severe acute respiratory syndrome coronavirus2 (SARS-CoV-2), the virus that causes COVID-19, enters pulmonary and myocardial cells through binding of its spike protein to the human angiotensin-converting enzyme 2 (ACE2). ACE2 is a vital enzyme that controls blood pressure and blood flow to multiple organs, including the lungs, heart and kidneys.

A prevailing hypothesis since early in the COVID-19 pandemic is that viral binding to ACE2 inhibits the conversion of angiotensin II (ANG II) to angiotensin 1-7 (ANG 1-7), thereby causing a pathological imbalance in the RAS, favoring the ANG II pathway, promoting inflammation, constriction of the blood vessels and thrombosis (blood clots). Thus, these RAS changes may be central to the development of severe clinical effects in the lungs and other organs.

VUMC led two blinded, placebo-controlled multicenter randomized clinical trials evaluating two investigational drugs aimed at regulating the RAS during SARS-CoV-2 infection. These two agents work in different ways to balance the Ang II to ANG (1-7) ratio. TRV-027 is a biased ligand acting on the angiotensin II receptor, while TXA-127 is synthetic angiotensin (1-7).

The trials demonstrated that neither drug was effective for treating severe COVID-19.

"The finding from these trials demonstrate that giving drugs that are designed to modulate the RAS in a way that would seem to counteract damage done by the virus are not helpful in very sick patients with COVID-19," said the study's first author, Wesley Self, MD, MPH, associate professor and vice chair of the Department of Emergency Medicine, Senior Vice President for Clinical Research and Deputy

Director, Vanderbilt Institute for Clinical and Translational Research.

"These results are disappointing in that we did not identify new drugs for patients suffering from COVID-19. But they are also important because we now understand that giving these drugs, which would seem very logical from a mechanistic perspective, should not be done," he said.

"We hypothesized increased levels of ANG II may be responsible for some of the changes in the human body due to COVID-19 infection," said Sean P. Collins, MD, MSci, professor of Emergency Medicine, study chair, and the paper's senior author.

"If there's too much ANG II, blood vessels in the lungs start to constrict, resulting in not enough blood flow to the lungs. This can lead to small blood clots in the lungs resulting in inflammation. We know that ANG II does that and that COVID-19 patients express some of those abnormalities. So, the logical thinking has been there's too much ANG II in COVID-19, and we need to counteract these levels. However, the results from these two trials do not support this idea," he said.

"We understand a lot better now that these simple fixes in this pathway aren't going to be effective," said Matthew S. Shotwell, Ph.D., the study's primary statistician and associate professor of Biostatistics. "We now are focusing on understanding why we saw the results we observed in these trials."

Self said that blood collected from the patients participating in the trial will now be analyzed to measure proteins to understand more about the process.

"The ACTIV-4 Host Tissue trial was created to rapidly assess therapies that could potentially alter the body's response to infection and support recovery," said Yves Rosenberg, MD, MPH, branch chief of the

Atherothrombosis and Coronary Artery Disease branch, located within the Division of Cardiovascular Sciences at the National Heart, Lung, and Blood Institute (NHLBI). "While these two drugs were not effective, we answered a pivotal question and are hopeful another agent being studied in ACTIV-4 Host Tissue may be beneficial."

**More information:** Wesley H. Self et al, Renin-Angiotensin System Modulation With Synthetic Angiotensin (1-7) and Angiotensin II Type 1 Receptor–Biased Ligand in Adults With COVID-19, *JAMA* (2023). DOI: 10.1001/jama.2023.3546

Provided by Vanderbilt University Medical Center