Plitidepsin Could Treat COVID-19, Preclinical Data Suggest

Damian McNamara

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The antiviral agent plitidepsin (Aplidin) can block proliferation of the SARS-CoV-2 virus in different cell lines and in the lungs of mice, a new study shows.

The antiviral activity of plitidepsin was nearly 28-fold stronger than that of remdesivir against SARS-CoV-2 in the in vitro research. The researchers also note that the two agents act on different targets, so remdesivir plus plitidepsin, if approved for use, could provide an additive effect when given in combination.

"The potency of the inhibitor is quite amazing," senior author Adolfo Garcia-Sastre, PhD, told *Medscape Medical News*.

Given prophylactically, plitidepsin also reduced viral replication in the lungs of two different mice models by two orders of magnitude.

Plitidepsin works by inhibiting the eEF1A protein in the host, not the virus, which could be an advantage because it avoids problems associated with future viral resistance.

The study was published online January 25 in *Science*.

Early Data, Early Administration

The preclinical efficacy shown in this study and in a phase 1/2 clinical trial from the manufacturer suggest "that plitidepsin should be strongly considered for expanded clinical trials for the treatment of COVID-19," the researchers note.

Still, it's early days. "We have found a potent inhibitor of SARS-CoV-2 replication, but clinical trials are still needed to find whether it provides a benefit to patients," added Garcia-Sastre, director of the Global Health Emerging Pathogens Institute at Icahn School of Medicine at Mount Sinai in New York City.

Because plitidepsin is an antiviral agent, "it inhibits the replication of the virus and needs to be given during the active replication phase of COVID-19. Similar to remdesivir and all other antiviral drugs, the sooner it is given to you, the better chance it has of being effective," lead author Kris M. White, PhD, assistant professor of microbiology, Icahn School of Medicine at Mount Sinai, told *Medscape Medical News.*

A Paucity of Therapeutics

The investigators point out that current therapies for patients with COVID-19 include oxygen treatment, ventilation, remdesivir, and the steroid dexamethasone. They add that "remdesivir in particular has shown limited efficacy and dexamethasone is a steroid that does not directly inhibit viral replication.

"This leaves a continued need for the development or repurposing of antiviral drugs for the treatment of COVID-19," they note.

Given the need for effective therapeutics, they investigated the repurposing of existing agents. This led them to investigate the antiviral potential of plitidepsin against SARS-CoV-2. Plitidepsin was initially discovered in the sea squirt *Aplidium albicans.*

In both human cells and Vero e6 cells, or kidney cells derived from African green monkeys, the investigators demonstrated a cytostatic effect of plitidepsin. They added the antiviral at different time points over 24 hours. The agent significantly reduced genomic RNA content at 8 and 12 hours post infection in the Vero e6 cells and fell "just short of significance at the 24-hour time point," they note, similar to remdesivir.

"This laboratory study of plitidepsin showed that the drug hits one of the targets in animal cells that the SARS-CoV-2 virus needs to replicate. It cuts virus replication in vitro, though by 24 hours there was no statistically significant reduction in the amount of viral RNA," Robin Ferner, MD, told *Medscape Medical News* when asked to comment.

"It also reduced infection in mice if given before the virus," said Ferner, whose honorary posts include professor of clinical pharmacology at the University of Birmingham in the United Kingdom and associate professor at University College London.

Findings Further Validated in Mice

Garcia-Sastre and colleagues showed a nearly 2 log reduction in viral titers of SARS-CoV-2 in the lungs of mice treated with plitidepsin compared with others treated with a vehicle control.

"These experiments show that plitidepsin treatment can reduce the replication of SARS-CoV-2 by 2 orders of magnitude and reduce lung inflammation in vivo and has significant potential for clinical efficacy for the treatment of COVID-19," the researchers write.

Ferner raised a caveat regarding potential adverse effects. "The drug has been used experimentally to treat patients with multiple myeloma, but adverse effects are common and included raised liver enzymes" in a 2019 study, he said.

On a more positive note, plitidepsin "has cleared the first hurdles in the long steeplechase to show clinical efficacy in COVID-19. Most runners fall long before the end of the race," Ferner said.

Future Implications

Interestingly, dexamethasone is also commonly used to treat people with multiple myeloma. "This has led to plitidepsin already having an established safety profile with concurrent dexamethasone treatment and should allow for clinicians to treat with both drugs if warranted," the researchers note.

In the bigger picture, eEF1A inhibition might may be a good drug target for other human coronaviruses and unrelated viral pathogens. "This potential for broad-spectrum antiviral activity makes plitidepsin an intriguing candidate for further exploration as a treatment for viral infections with no clinically approved therapeutics," the researchers note.

"We would like to study the antiviral activity against other viruses in vitro and in animal models, while we hope our results will accelerate the execution of a phase 3 clinical trial," Garcia-Sastre said.

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Damian McNamara is a staff journalist based in Miami. He covers a wide range of medical specialties, including infectious diseases, gastroenterology and neurology. Follow Damian on Twitter: @MedReporter.

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