Clinical trial in COVID-19 patients tests anti-inflammatory drug

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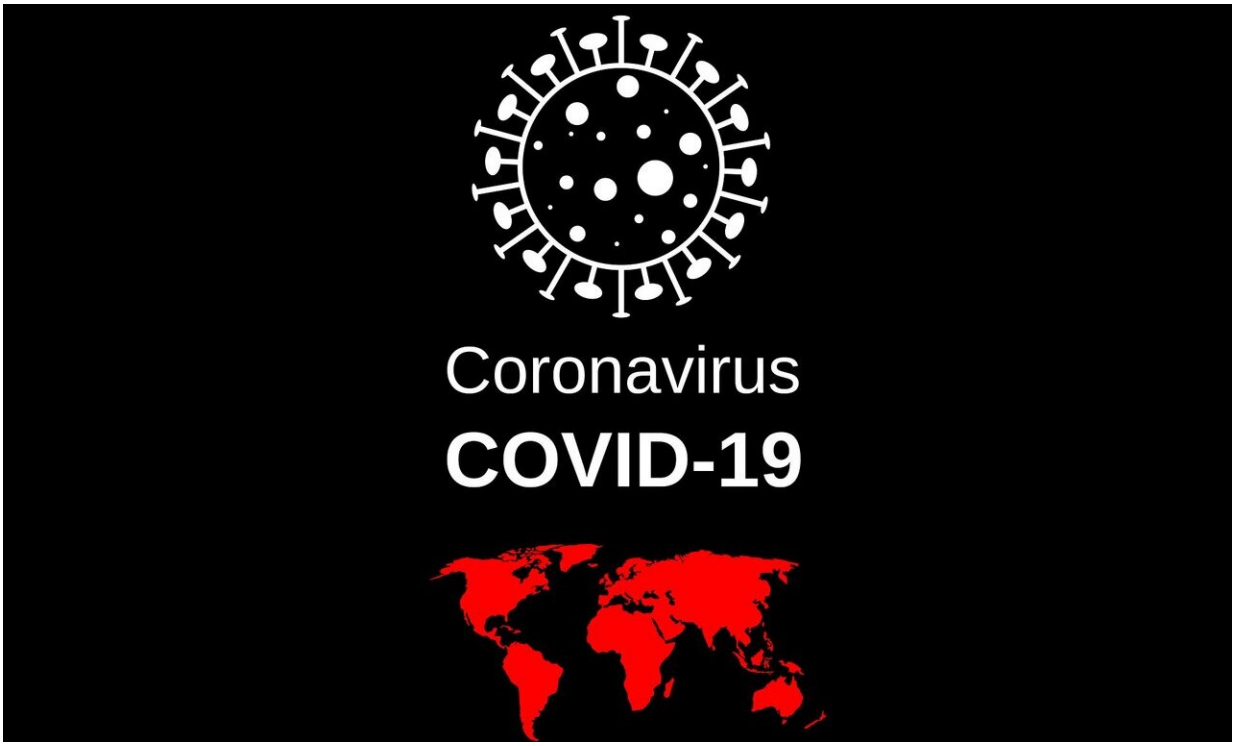

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An anti-inflammatory drug developed at Scripps Research 25 years ago is now being tested as a way to prevent acute respiratory distress in patients with COVID-19, the pandemic disease caused by the novel coronavirus.

The drug, a monoclonal antibody now owned by the pharmaceutical company Implicit Bioscience, is planned to be used in a small clinical trial taking place at four sites in Italy, Spain, Australia and Singapore.

The trial will assess whether the drug, known as IC14, can temper the immune system's response to coronavirus infection of the lungs, thus preventing dangerous levels of inflammation seen in patients with severe cases of the disease.

"Patients with severe COVID-19 often progress to acute respiratory distress, where inflammation results in lung damage and subsequent multiple organ failure," says Richard Ulevitch, Ph.D., a professor and former chairman of Immunology at Scripps Research, who originally developed the drug. "By dampening the innate immune system's response to the infection, IC14 may prevent patients from spiraling out of control and improve their chances for recovery."

The drug targets an immune system protein called CD14, that Ulevitch and Scripps Research colleagues first linked to innate immunity and inflammation in work started in the mid-1980s.

CD14 is a protein that helps immune cells recognize pathogens including bacteria, viruses or substances released from injured or dying cells that alarm the immune system to danger. CD14 has the unusual property of existing both on the surface of white blood cells and floating free in the blood and lung fluids. This dual existence allows CD14 to amplify the body's inflammatory responses in a variety of sites. While these immune responses can help fight infections, they also carry the risk of a dangerous overreaction, sometimes referred to as a "cytokine storm."

In patients with COVID-19, this out-of-control inflammation creates a vicious cycle in which the immune system floods the body with excessive levels of cytokines, which can lead to tissue damage and in

severe cases, multiple organ failure.

Ulevitch and colleagues developed the IC14 antibody to block the inflammatory signals that CD14 sends to immune system cells. In preclinical studies, the antibody showed promise in sepsis and the often-associated excessive inflammation leading to shock and multi-organ failure.

The drug was tested by a pharmaceutical company in a phase 1 clinical trial in 2004 and determined to be safe in patients. Collaborations with others, including Thomas Martin, MD, emeritus professor of Medicine at University of Washington, extended the work to clinical studies in humans with acute respiratory distress. While no follow up sepsis trials were conducted, IC14 was acquired by Implicit Bioscience in 2009 as a potential therapy to blunt the inflammation caused by the neurodegenerative disease amyotrophic lateral sclerosis (ALS). Implicit is currently conducting a phase 2 trial to evaluate the drug in patients with rapidly advancing ALS.

Soon after COVID-19 began spreading around the world earlier this year, Ulevitch contacted Martin, his former collaborator. They realized they were both thinking the very same thing: IC14, the monoclonal antibody they'd developed decades ago, might be effective at blocking the extreme inflammatory responses seen in COVID-19 patients. In fact, the same day Ulevitch contacted him, Martin had already reached out to Implicit to float the idea.

"It was really remarkable," Martin says. "We had both seen the reports about cytokine storms and knew that IC14 was a good candidate. It could potentially offer protection to the lungs, the most proximate danger of COVID-19, but also address the systemic response causing multiple organ failure."

Garry Redlich, CEO of Implicit Bioscience, informed Martin and Ulevitch that the company had several hundred doses of IC14 that could be used for a clinical trial in COVID-19. "We thought, 'here's this dreadful condition with no approved drug, and here we are with this outstanding data that says we can turn down all of the inflammatory parameters,'" says Redlich. "While we are committed to pursuing IC14 as an ALS therapy, deploying our inventory of the drug candidate to potentially help mitigate the COVID-19 crisis was clearly what needed to happen."

Working with Ulevitch and Martin, Implicit arranged for medical clinics in hard-hit areas of Italy to receive samples of the drugs for testing. Implicit is now collaborating with the clinics in Europe, Asia and Australia to test the drug in a dozen patients diagnosed with COVID-19 but have not yet progressed to severe respiratory symptoms that require ventilation.

The trial will test whether IC14 is safe in COVID-19 patients and whether it reduces the need for artificial ventilation and the risk of dying from the disease. If the results in initial trials are promising, Redlich says, Implicit will run additional trials to more rigorously test IC14 as a COVID-19 therapeutic.

Ulevitch is hopeful, yet he cautions that it's still not known if IC14 will help COVID-19 patients. What is crystal clear, however, is the value of having a bank of strong basic science during unpredictable times.

"This is a great example of how fundamental research done years ago at Scripps Research and extended by countless other scientists over the past three decades can lay the foundation for applications that you can't envision until a new situation arises," he says.

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