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The coronavirus disarms the foot soldiers of the immune system. Scientists theorize that boosting them could fight covid-19.

Several trials are underway giving patients immune proteins called interferons, either alone or in combination with other treatments, to see whether they speed recovery

By
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Researchers across the planet are racing to harness one of our immune system's front-line defenders as an early treatment for covid-19, the disease caused by coronavirus that has killed more than 800,000 people globally.

Until now, early-stage treatments have remained elusive. But an improved understanding how the virus disarms some of the body's immune fighters, called interferons, is creating excitement among scientists who theorize they might be able to counter that process and prevent infections from developing into severe disease. Interferons are immune proteins that normally interfere with a virus' life cycle — hence the name, interferon. In addition to their antiviral properties, they summon natural killer cells, "the best soldiers, as it were, of the innate immune system," Anthony S. Fauci, director of NIH's National Institute of Allergy and Infectious Diseases, said in an interview.

That system is both the body's whooping air-raid siren and its emergency responders rushing to the scene. The virus's ability to hamstring this system may be one of the keys to its success.

Now, several trials are underway in the United States and elsewhere to see whether giving interferon to coronavirus patients early on might prevent severe disease, or hasten recovery, if administered later.

Driving the trials are a spate of recent studies showing that interferons are weakest in the worst coronavirus cases. Scientists in France came to this conclusion after examining cells in the blood of 50 covid-19 patients who had spent 10 days in the hospital, as they wrote in a study published Aug. 7 in the journal Science.
"We found that the more severe the patients were, the less interferon type-1 they were producing," said Benjamin Terrier, a professor of internal medicine at the National

Reference Center for Rare Systemic Autoimmune Diseases in Paris's Cochin Hospital, referring to a subset of the proteins normally deployed against viruses.

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This spring, Benjamin tenOever, a microbiology professor at the Icahn School of Medicine at New York's Mount Sinai Hospital, and his colleagues came to similar conclusions after studying the virus in samples taken from humans, ferrets and infected cells grown in a lab. Interferons, as they reported in the journal Cell, were lacking in all of those.

"The virus is very actively repressing both the production of and the sequencing of interferons," meaning the process by which the body makes these proteins, tenOever said.

This weakening happens not only in patients' lungs but in their blood, according to new research by Bali Pulendran, an immune system expert at Stanford University School of Medicine, and his colleagues.

The team isolated immune cells from the blood of patients with severe covid-19, placed them in petri dishes and tried to provoke them with bacteria and viruses. Normally, such provocations would cause the immune cells to erupt in a shower of interferons and other defensive molecules.

But, as the scientists reported in a paper published Aug. 11 in Science, those cells in covid-19 patients were inert. It was as though the coronavirus, or a consequence of its infection, had snipped their fuses.

"After eight days or so, the type-1 interferon system is completely absent, and silenced, by the infection," Pulendran said.

Interferon's therapeutic possibility

Researchers caution that many questions remain unanswered about interferon's use in coronavirus patients. Past clinical studies that tested it to treat SARS and MERS showed little or no benefit.

But there are promising early signals. Preliminary results from a small randomized clinical trial, publicized in a news release in late July by the British company Synairgen, suggests that inhaled interferon reduced the odds of developing severe covid-19, compared with receiving a placebo. Experts cautioned that trial was small, just 101 patients, and the results were not yet published in a peer-reviewed study.
In France, investigators plan to test interferon if cases continue to rise. But they are currently too low to enroll enough patients in a clinical trial, Terrier said.

A large, NIH-sponsored clinical trial launched this month will test interferon as a drug injected in patients hospitalized with covid-19. Those patients will receive interferon beta-1a, a synthetic molecule identical to the protein our bodies make, every other day for the first week of their hospital stay.

The trial is recruiting about 1,000 patients from 100 hospitals around the world. The patients will be sick but not so ill as to require ventilators to breathe. That speaks to the goal of treating the disease before worsens.

“What you’re likely going to see, as more antivirals come along and then the monoclonal antibodies come along, will be a propensity to treating as early as you possibly can to prevent people from getting into the hospital,” Fauci said.

The patients in the study will also get remdesivir, an antiviral agent the FDA authorized in the spring. Researchers will compare their recovery against that of covid-19 patients who received remdesivir alone. “The purpose of it is to determine whether you get added value,” Fauci said. The trial is slated to run through November 2023.
Should interferon beta-1a prove useful, Fauci doubted there would be shortages because it is already widely used, for instance, to treat multiple sclerosis. Interferon drugs were also previously used as a standard treatment for hepatitis C, though newer, more effective therapies have largely replaced them.

Despite their potential, interferons may not be a panacea, scientists cautioned.
“In principle, you could think, why don’t we just give it to everybody who has a viral infection ever,” said Tufts University microbiologist Marta Gaglia. “But in reality, it has proven less effective than we would like.”

A critical factor may be getting the timing right. The new studies suggest interferon would be most helpful in the earliest stages of the disease, but that window may close before most people are hospitalized and doctors can treat them.

“Interferon also has a lot of side effects,” Gaglia pointed out. These include muscle aches, fever and other ailments associated with flu infections. “So we wouldn’t want to use it unless we think it’s going to be beneficial.”

She said she would like the NIH-sponsored trial to answer whether giving interferon to hospitalized patients is helpful, and what dosages yield the best results.
What’s more, pitting these virus fighters against coronavirus too late in the process could actually worsen symptoms, according to animal models cited in a recent review of interferon studies.

Missing interferon, severe symptoms
Scientists theorize that the virus’s ability to disarm interferons early on may explain other aspects of the disease, such as the out-of-control inflammation reaction that develops in some patients.

As the immune system mounts an inflammatory defense — but there is too little interferon to quickly contain the virus — the body’s response can spiral out of control, several scientists said. In some cases, this uncontrolled inflammation becomes deadly. Some experts also suggest that a person’s ability to mobilize interferons to wage a strong immune response at the start of the infection process may predict less severe disease.

“We know that individuals differ in their ability to mount an interferon response,” said pediatrician Petter Brodin, who studies the immune system at the Karolinska Institute in Sweden.

When otherwise healthy people fall ill, Brodin said, “it makes me wonder at least, do they have a genetic susceptibility, an underlying immunodeficiency that we haven’t picked up yet, which gives them this response, potentially because they failed to induce interferons?”

There’s preliminary evidence for this, such as a case study of four men under age 35, who had rare genetic variants associated with impaired interferon response, who were hospitalized in the Netherlands with severe covid-19.
Cause-and-effect is very difficult to determine in the human immune system. The Science papers used a variety of techniques to examine the virus, but they described only single points in time.

“You are getting more of a snapshot,” said Gaglia, who was not involved with these reports. What happens on the third day of an infection may not be what happens on the tenth. “And so you are trying then to make an inference of the sequence of events.”
Additional studies of the immune system can help unravel the stages of infection. Pulendran said his team is collecting blood samples at regular, frequent intervals “to map out the trajectory of this disease.” The race to understand and shore up our inner defenses continues.