Organizers also kept Recovery simple, allowing any NHS hospital to participate. Inspired by trials of heart-attack treatments that his Oxford colleague Richard Peto and others did in the 1980s, Landray says they radically cut down on the data health care workers need to collect, with only a few questions asked at enrollment and at just one later point: when the patient dies, is discharged, or 28 days after enrollment. Clinical trials have become excessively cumbersome in recent years, Landray argues.

Solidarity has a similarly straightforward design, but its more international nature has proved a challenge. The trial, designed to test four treatments—hydroxychloroquine, lopinavir/ritonavir, interferon beta plus lopinavir/ritonavir, and remdesivir—was announced on 20 March and enrolled its first patient in Norway 1 week later. But rolling out the trial in dozens of countries has meant getting approval from dozens of regulatory agencies and ethics boards as well. "That has taken a surprisingly long time in many jurisdictions, including in Europe," Røttingen says, and recruitment in Europe slowed over time as the epidemic subsided. "When countries were ready to sort of start, the epidemic was under control in many ways," he notes.

"The three Recovery trials are the best trials that have been performed to date."

Eric Topol, Scripps Research Translational Institute

A European trial called Discovery, coordinated by the French research institute INSERM and meant to join with Solidarity in testing the same drugs, also fell short. The goal was to enroll 3200 patients across the continent. The study almost met its goal of 800 participants in France, but it barely managed to recruit patients elsewhere. Although France funded its part of the trial, it expected partner countries to pick up their own tabs. "One of the issues was that not all the countries had funding," says Yazdan Yazdanpanah, head of infectious diseases at INSERM.

Meanwhile dozens of small trials competed for patients in countries, most of them focusing on the same drugs, such as hydroxychloroquine. "I don't understand why everyone was looking at the same thing," Yazdanpanah says. "I think we can do better." Susanne Herold, an expert on pulmonary infections at the University of Giessen, agrees. "There needs to be more coordination both within countries and across borders," she says.

Another problem has been the widespread use of treatments outside of randomized trials. Landray notes that tens of thousands of COVID-19 patients in the United States have been given convalescent plasma, for instance, but not alongside a group receiving a placebo. "We'll know what happened to those patients, but we won't know whether they would have been better off actually, if they hadn't got the convalescent plasma." Convincing clinicians that therapies still need to be tested can be difficult, Henao Restrepo says. "Some are convinced they know which drugs work."

She still has high expectations for the Solidarity trial. "The preparatory work is paying off," she says. Its recruitment has picked up as more countries, many with surging cases such as Iran, have joined. So far, 39 countries are participating and 60 more signing up. "One of the advantages of such a global trial is that you can follow the pandemic as it evolves," Røttingen says.

With recruitment running at about 500 patients per week now, Solidarity's two remaining treatment arms—it stopped the hydroxychloroquine and the lopinavir/ritonavir ones as results emerged—are likely to yield answers soon, raising the question of what drugs to test afterward. More repurposed drugs are being discussed, but increasingly the attention is turning to monoclonal antibodies targeting the virus.

Henao Restrepo thinks the international nature of Solidarity makes its results more generalizable and likely to be accepted. Herold expects that the Discovery trial contribute as well. Started in part to supplement Solidarity, it collects not only basic mortality data, but also information on viral levels and blood parameters. Those data can indicate not just which drugs are effective, but also how they work and at what stage of the disease.

The Recovery trial continues, with its team scrambling to publish full results. Some researchers have criticized its practice of releasing important results as press releases; so far, it has given details for only one of the three headline findings, on dexamethasone, in a preprint posted 6 days after the release. The Recovery team is still collecting trial data on the antibiotic azithromycin, an antibody called tocilizumab, and the antibody-rich plasma collected from recovered patients.

Results on those therapies are likely months away, Landray says. But he cautions he has been wrong before. On the morning of 4 June, he had predicted the first results from Recovery would likely come in early July. A few hours later, the chairperson of the trial's data monitoring committee called him to say there was enough patient data to declare a verdict on hydroxychloroquine. ■

COVID-19

Can interferons stop COVID-19 before it takes hold?

Biology of infection supports early treatment with body's own viral defenses

By **Meredith Wadman**

On 30 April, Valerie McCarthy's test result confirmed that her grinding fatigue and pummeling headaches were caused by the new coronavirus. She wasn't hospitalized, but the very next day, a nurse at Stanford University Medical Center gave the 52-year-old marathon runner an injection that contained either a placebo or a natural virus fighter: interferon.

McCarthy was Patient 16 in a clinical trial that, it's hoped, will help fill a huge void in treatments for COVID-19: Doctors have no drugs that, given early, have been proven to prevent infection or help beat back the virus before it takes hold. So far, the two scientifically validated treatments for COVID-19—remdesivir and dexamethasone—have only been shown to work in hospitalized patients with serious illness.

But a small flurry of recent papers suggests the novel coronavirus does some of its deadly work by disabling interferons, powerful proteins that are the body's own frontline defenders against viral invasion. If so, synthetic interferons given before or soon after infection may tame the virus before it causes serious disease—a welcome possibility that additional recent studies support.

Several interferons were approved decades ago by the U.S. Food and Drug Administration, their immune-boosting powers deployed against diseases including cancer and hepatitis. And in an early, unrandomized preventive trial in a hospital in China's Hubei province, none of 2415 medical workers who took daily interferon nose drops got the virus, according to a medRxiv preprint.

The Stanford trial is one of dozens now trying interferons against COVID-19, including in people who aren't sick but might have been exposed to the virus. First results from a controlled trial at the Univer-

sity of Southampton are expected by August.

"Every study in every species has shown that if you induce interferons before [a] virus comes in, the virus loses," says Andreas Wack, an immunologist at the Francis Crick Institute. "The earlier you can give it, the better, and the best thing you can do is to give it before the virus is there."

Timing is crucial, adds Miriam Merad, an immunologist at the Icahn School of Medicine at Mount Sinai. "It's going to be important to know when to give these drugs." If given too late in the course of infection, interferons might pour fuel on the out-of-control inflammation that is a hallmark of severe COVID-19, she and others say. "Interferons are strong antivirals," Merad says. "But they also activate immune cells and can cause immunopathology."

Interferons are molecular messengers that launch an immediate, intense local response when a virus invades a cell. They trigger production of myriad proteins that attack the virus at every stage of invasion and replication, and they alert uninfected neighboring cells to prepare their own defenses. Interferons also help recruit immune cells to the site of infection and activate them when they arrive.

But SARS-CoV-2, the virus that causes COVID-19, disables this defense by blocking the powerful interferons that lead it, says Benjamin tenOever, a virologist at Mount Sinai. He and his colleagues studied SARS-CoV-2 infection in a range of models: human lung and bronchial cells, ferrets, lung tissue from deceased COVID-19 patients, and blood from living ones. In virtually every system, "interferon is badly suppressed," tenOever says. As it shuts down interferons, his team reported in *Cell* in May, the virus also ramps up production of chemokines, a different set of messenger molecules that summon distant immune cells and trigger inflammation.

Findings from a team led by immunologist Benjamin Terrier of the Cochin Hospital in Paris and published as a preprint on medRxiv, echo tenOever's. Terrier's team also looked at blood from 50 COVID-19 patients, finding strikingly depressed interferon activity and elevated chemokines in those whose disease became severe and critical—but not in those who ended up with mild or moderate disease. Terrier posits that local viral replication, unchecked by interferons, gins up tissue-damaging inflammation, as do armies of immune cells summoned from afar. The result is the out-of-control inflammatory response that ends many lives (*Science*, April 24, p. 356).

But not everyone is persuaded that the virus itself is responsible for missing-in-action interferons. Are low interferons "the cause or the consequence of severe disease?" asks Jean-Laurent Casanova, an infectious disease geneticist at the Rockefeller University. Since 2015, he has found three inherited mutations that profoundly inhibit the interferon response, raising the possibility that genetic predisposition plays a role in some cases of severe COVID-19.

And some data challenge the notion that interferons are suppressed at all. One report, published in *Cell Host & Microbe* by Jianwei Wang of Peking Union Medical College and colleagues last month, found strong expression of numerous interferon-stimulated genes (ISG's)—often used as a marker for interferon activity—in the lung fluid of eight COVID-19 patients. Similarly, in unpublished data, John Tsang, a systems immunologist at the U.S. National Institute of Allergy and Infectious Diseases, found robust ISG expression in immune cells in the blood of 35 severely ill COVID-19 patients.

All the same, at least five studies since April have found that interferon treatment or pretreatment has a protective effect in cells and in mice infected with SARS-CoV-2. These studies parallel earlier ones that found beneficial effects of early interferon administration in mice infected with the new coronavirus' cousins, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome. The data support giving interferons as a treatment for COVID-19, especially early in infection, advocates say.

But plenty of caveats remain. For starters, when given as drugs, the powerful type I interferons can have awful side effects, as patients who have taken them for months on end for cancer and other diseases know. Side effects include flulike symptoms, headache, vomiting, and depression. But COVID-19 treatment does not require continuous dosing for months, and one trial in chronic hepatitis showed that a synthetic type III interferon had fewer side effects than a type I interferon. (Type I interferons have receptors on every cell in the body, but type III do not.)

McCarthy's trial was of a type III interferon. She was warned of "headaches and fatigue," but was not dissuaded. "I thought: 'I'm already tired … that's OK,'" she says.

Two papers published in *Science* last month suggested type III interferons might be harmful if given late in infection. In one paper, Wack's group reported that in mice, naturally occurring type III interferon disrupted the lung repair crucial to recovery from influenza; in the other, a team led by immunologist Ivan Zanoni of Boston Children's Hospital reported similar findings in mice—and also found type III interferons in the lung fluid of severely ill COVID-19 patients. "The take home message for the clinical people," says Zanoni, is: "If you want to give type III interferons as antivirals, give them early."

Eleanor Fish, an immunologist at the University of Toronto who is launching, with colleagues, two preventive interferon trials, says data already point to interferons' safety. She and colleagues published an uncontrolled study of 77 hospitalized patients in Wuhan, China, in *Frontiers in Immunology*. They reported that patients given a type I interferon (with or without an antiviral medicine) had lower levels of a key inflammatory biomarker than other patients—and also cleared the virus 7 days sooner. Similar promising findings emerged from uncontrolled studies that Fish published years ago, examining the effects of the drugs in patients hospitalized with SARS and Ebola. "This notion of [interferons being] harmful later, I just want to throw it out the window," Fish says.

Even as scientists debate the underlying biology, they are keenly aware that only controlled clinical trials will answer their questions. As for McCarthy, 8 weeks after first testing negative for the virus, she struggles to slowly run 3 kilometers. She still doesn't know whether she received placebo or an interferon. Like everyone else, she'll have to wait for the trial's results. ■

Valerie McCarthy received an injection that contained either placebo or an interferon.

PHOTO: STEVE FISCH

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