ILLUSTRATION BY ERICK M. RAMOS

THE LONG WAIT FOR A LONG-COVID THERAPY

After a slow start, researchers are ramping up the search for long-COVID treatments.

By Heidi Ledford

Bhasha Mewar has had it with doctors. Over the past two years, Mewar has spent nearly all of her life savings seeing heart and respiratory specialists, haematologists, urologists, dermatologists and more, in a desperate bid to tame her long-COVID symptoms. She has taken a slew of drugs: beta blockers to calm her racing heart, steroid inhalers to ease her laboured breathing and an antimalarial drug prescribed to her for reasons she never fully understood.

And when Mewar — a curator at an art museum in Ahmedabad, India, who has been sick since what was probably a bout of COVID-19 in March 2020 — would visit her lung doctor twice a month, he always told her the same thing: you need to exercise. "I can't even walk to the bathroom," she would reply.

It's an unwelcome odyssey undertaken by millions of people living with long COVID, a complex and sometimes debilitating syndrome that can linger for months or years after an acute SARS-CoV-2 infection. There is no proven treatment, leaving physicians

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and people with the condition to play whack-a-mole with its many symptoms. And sometimes, people with the syndrome turn to untested, self-prescribed therapies. Although at least 26 randomized clinical trials of long-COVID therapies are under way (see 'Trials take off'), many are too small or lack the necessary control groups to give clear results. "If you look at long COVID at this moment in time, I'd paint a slightly 'Wild West' and desperate picture really," says immunologist Danny Altmann at Imperial College London.

Even so, researchers are narrowing in on the pathology that underlies long COVID. In the next year, key trials could yield results for drugs that target the immune system, blood clots or lurking fragments of the coronavirus itself. "I'm still optimistic," Altmann says. "The right stuff is going on, and there's a fair amount of funding out there. Something is going to give."

Complex condition

A key barrier to developing long-COVID treatments has been uncertainty about the condition's root cause. Over the past two years, a number of hypotheses have emerged as frontrunners, and researchers hope that insight into which ones are correct could help them to develop therapies. Evidence is mounting that lingering SARS-CoV-2 – or fragments of it – continues to cause trouble by stimulating the immune system. There are also signs that the infection generates antibodies that mistakenly attack the body's own proteins, causing damage long after the initial illness. Researchers have found hints that COVID-19 could cause microscopic blood clots that block oxygen flow to tissues. It is also possible that a SARS-CoV-2 infection can wreak long-term havoc on gut microorganisms.

These hypotheses are not mutually exclusive: many researchers think that long COVID can have multiple causes. Each idea suggests a route to relief. Antiviral drugs might vanquish persistent reservoirs of SARS-CoV-2. Drugs that suppress the immune system could quench a misguided immune response. Powerful anti-coagulants could dissolve micro-clots.

Although evidence is gradually accumulating in support of each of these possibilities, their links to long COVID are still tenuous enough to give some investigators pause before launching clinical trials. "The hypotheses are getting a bit stronger," says Altmann. "But they're not cast iron."

This uncertainty could dissuade researchers from launching trials, says epidemiologist Martin Landray, at the University of Oxford, UK. If long COVID has a number of causes, a promising treatment could be ruled ineffective in a clinical trial simply because it was given to the wrong group.

Plus, there is no shortlist of key symptoms to help to enrol participants or sort them into subgroups. More than 200 symptoms have been associated with the syndrome[1], and many – such as fatigue and brain fog, two of the most common and debilitating – are hard to measure objectively, and can wax and wane. "I've had a whole list of symptoms; half of them I've forgotten," says Mewar, who keeps a library of photographs of the medicines she has tried, to keep track of her treatments amid the brain fog that permeates her memory. "They would come and go, here a week, and then gone."

All of this complicates clinical-trial design, says Landray, an architect of RECOVERY, a large UK trial of treatments for acute COVID-19. That trial took just four months to find that low doses of the steroid dexamethasone reduced deaths from severe COVID-19 by one-third. Landray has received requests from people with long COVID and their families to engineer a similar effort to address long COVID. "I haven't gotten involved in this space," he says. "The science hasn't seemed sufficiently mature."

A trickle of trials

But some researchers have pushed ahead. Several trials try to tame errant immune responses. Some of these rely on familiar drugs, such as colchicine, an anti-inflammatory drug that treats gout and is often prescribed to people with long COVID. Other trials are using drugs that have shown some success in treating severe acute COVID-19, including steroids and other immunosuppressants, such as sirolimus, which is used to prevent organ rejection after a transplant. Small trials and anecdotal reports suggest that antihistamines show some promise, and they provide "a Band-Aid solution", says Hannah Davis, who has long COVID and lives in New York City. Davis is a co-founder of the Patient-Led Research Collaborative, a research and advocacy group. "But it would be good to confirm that it's helping."

Rheumatologist James Andrews at the University of Washington in Seattle is investigating a new approach to taming inflammation in people with long COVID: an experimental drug called RSLV-132. The drug, made by Resolve Therapeutics in St Petersburg, Florida, is designed to remove RNA circulating in the blood, where it is thought to promote inflammation, says Andrews. The company has tested its drug in small trials for other conditions and has found some success in reducing fatigue in people with Sjögren's syndrome, an autoimmune disorder.

> "IT'S TAKEN A WHILE TO GET TO A POSITION WHERE THE COMPANIES ARE READY TO START INVESTING."

Other approaches aim to manage symptoms, such as extreme fatigue, muscle weakness and memory and concentration difficulties. Roger McIntyre, who studies psychiatry and pharmacology at the University of Toronto, Canada, is enrolling participants in a trial of vortioxetine, an antidepressant that has been shown to boost cognition, to find out whether it alleviates the brain fog associated with long COVID.

Another set of trials aims to tackle COVID-19's lingering impact on the cardiovascular system. Some studies have found evidence of inflammation in the lining of blood vessels and suggest that, in some people, this could trigger the formation of microclots that then clog the lung's tiniest vessels, the capillaries[2]. Cardiologist Rae Duncan, at Newcastle upon Tyne Hospitals NHS Foundation Trust, UK, and her colleagues are planning to launch a clinical trial to test a cocktail of drugs targeting this clotting process. Duncan says when she presented her clinical-trial plans to a panel of people with long COVID and their advocates, two of them became emotional: "They said, 'This is the trial we've been waiting for.'"

Duncan does not yet want to disclose which drugs have been chosen, out of fear that people with long COVID will try to buy them on the Internet and treat themselves. "These are individuals who are very sick at the minute and who are understandably desperate for treatment," she says. "These drugs do increase your risk of bleeding and need to be administered and monitored very carefully."

Already, some people with long COVID have been taking treatment into their own hands. Some have taken a combination of anticoagulant drugs to replicate a triple-drug therapy that was tested in a small trial of 24 people with long COVID. That trial did not include a control group and has not yet been published in a peer-reviewed journal[3]. Others, says Davis, have been traveling to clinics that will perform apheresis, a procedure that filters the blood with the aim of removing clots or proteins that can promote inflammation. These people have paid thousands of dollars for the unproven procedure, often after spending months on a waiting list, she says.

Future hopes

Some of the most logical candidate drugs for long COVID are still not being tested in trials. Several antivirals are used against acute COVID-19. Some researchers think these drugs could ease the symptoms of long COVID, too – particularly as evidence grows that a lingering SARS-CoV-2 reservoir could trigger the condition.

Two antivirals were approved by the US

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Food and Drug Administration at the end of last year – molnupiravir (Lagevrio), made by Merck in Rahway, New Jersey, and Ridgeback Biotherapeutics in Miami, Florida; and a combination consisting of nirmatrelvir and ritonavir (Paxlovid), made by Pfizer in New York City. Another drug, remdesivir (Veklury), made by Gilead Sciences in Foster City, California, has been used to treat COVID-19 since the early days of the pandemic.

But there are still no registered studies directly looking at whether these antivirals – which are expensive and in relatively short supply compared with generic drugs – could ease long-COVID symptoms.

An indirect assessment of Lagevrio and Paxlovid's impacts on long COVID could come later this year: both companies say researchers will continue to follow clinical-trial participants for six months after treatment. Gilead is exploring collaborations to test remdesivir in people with long COVID. As data pile up on how common and long-lasting long COVID can be, pharmaceutical companies might be persuaded to launch more studies, says David Strain, who specializes in medicine for older adults, at the University of Exeter, UK. On 1 June, the UK Office for National Statistics announced that 1.4 million people in the United Kingdom reported lingering symptoms three months after acute infection. About 380,000 people had been experiencing symptoms for at least two years.

Soon after those numbers were released, a pharmaceutical company agreed to sponsor a trial of an antiviral drug that Strain had proposed be tested; he will not say which, because the deal has not yet been finalized. "It's taken a while to get to a position where the companies are ready to start investing," he says. "The drugs are expensive."

Each of these trials could help researchers to better understand the causes of long COVID, as well as how to treat it – as long as trials include detailed analyses of markers associated with the condition, such as autoantibodies, says immunologist Akiko Iwasaki, at Yale University in New Haven, Connecticut. "This is an opportunity to learn more about the disease, as opposed to just finding a cure," she says.

But to do that properly, researchers need to conduct large-scale, well-designed trials, Iwasaki adds, and those can be difficult for individual investigators to set up. "We can't just have one site doing one thing, and another site doing something else," she says. "We need a coordinated effort."

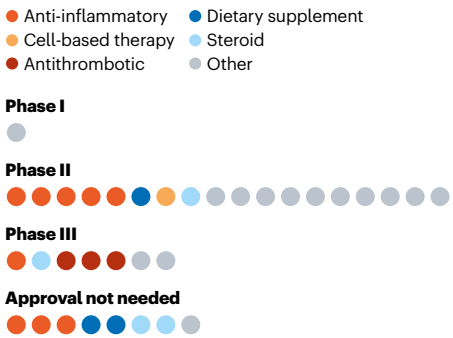
Although the United States and United Kingdom have dedicated large sums of money to long-COVID research, relatively little of that has gone to finding treatments, says Altmann. "I feel like there hasn't been the kind of will from the top that we need," he says.

Some larger trials are getting ready to begin, but have yet to start enrolling participants. In the United States, a large study called RECOVER has thus far focused mostly on characterizing long COVID, rather than testing potential treatments. But earlier this year, the US$1.15-billion effort, led by the US National Institutes of Health, put out a call for proposals for trials that would test interventions for treatment or prevention.

And in the United Kingdom, a trial called STIMULATE-ICP, announced last July, began enrolling participants this summer. The trial will test several medicines against long COVID: first-round candidates are the anti-inflammatory colchicine; two antihistamines, called famotidine and loratadine; and an anticlotting drug, called rivaroxaban. Strain, who has long COVID, is eager to conduct further proof-of-concept trials of other agents, which could be added to a later phase of the trial. These include immune-suppressing drugs and COVID-19 vaccines: one study found that two doses of an mRNA or adenoviral-vector vaccine was associated with a 9% reduction in the odds of long COVID in people who were infected with SARS-CoV-2 before vaccination[4].

TRIALS TAKE OFF

At least 26 randomized trials are under way to test therapies for long COVID. Many candidates target symptoms such as inflammation or clots. Some, such as the antidepressant fluvoxamine, act on different symptoms. Some researchers are repurposing drugs already approved for other conditions.



SOURCE: AIRFINITY

Patchwork treatments

Until results from trials such as these are in, physicians and people with long COVID will continue to experiment with combinations of pharmaceuticals and rehabilitation therapies. Much of the treatment that Kathy Raven, an infectious-disease genomicist at the University of Cambridge, UK, has received at her long-COVID clinic consists of management techniques – such as setting alarms to help her to remember to take her medicine after the brain fog sets in, and guidance on pacing herself to avoid too much activity. Raven has recently learnt that she'll be discharged from the clinic, with no significant change to her condition: "They've said there's nothing more they can offer me."

Other physicians are applying their previous experience treating conditions similar to long COVID. In Dhaka, rehabilitation specialist Taslim Uddin, at the Bangabandhu Sheikh Mujib Medical University, treats people with long-term muscle weakness after chikungunya, a viral illness carried by mosquitoes. The treatments are painstakingly tailored to each individual, and involve rehabilitating debilitated muscles without worsening their function – a condition called post-exertional malaise. Most people with long COVID whom he has treated respond well to similar therapy, he says, but there are some who remain seriously ill despite it.

In the absence of a solid evidence base, some physicians worry about potential harm from long-COVID treatments. Shinichiro Morioka, deputy director of the Disease Control and Prevention Center at the National Center for Global Health and Medicine in Tokyo, says that some doctors are using epipharyngeal abrasive therapy, in which the throat is scraped with cotton swabs soaked in zinc chloride. The aim is to decrease inflammation at a key site of coronavirus infection, he says. Some physicians say they have achieved promising results in small trials with no control group[5]. "But I do not think this is evidence-based, and it is invasive for patients," says Morioka. "We need to run randomized controlled trials." At the moment, he does not know of any randomized controlled trials for this or any other long-COVID treatment in Japan.

Like Mewar, some people with long COVID have encountered doctors who push them to simply exercise more. And some physicians are still advocating for a controversial form of therapy, called graded exercise therapy, says Duncan. But graded exercise therapy, which establishes a baseline of tolerable exercise and aims to increase it by incremental amounts, has been found to worsen symptoms for some people with post-viral illnesses, such as chronic fatigue syndrome and myalgic encephalomyelitis. "Graded exercise therapy should not be offered," says Duncan.

For now, Mewar has decided to stop putting her faith in doctors or trying to follow the scientific literature herself. After two years with long COVID, her symptoms have begun to ease, but she knows from experience that they will resurge with fresh vigour if she exerts herself.

She takes a concoction of vitamins, crafted on the basis of online accounts from others with long COVID, and is exploring traditional Indian medicines for her symptoms. "I stopped trying to explain to people what this is," she says. "I just try to take care of my own health."

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