

## Are Mesenchymal Stem Cells a Promising Treatment for COVID-19?

As the first clinical data become available on treating coronavirus patients with the cells, scientists are equivocal about the rationale for the intervention.



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A recent pilot study in China in which seven COVID-19 patients received intravenous infusions of donor mesenchymal stem cells—multipotent cells thought to have immunomodulatory capacities—indicates that the intervention was safe, and that the approach may [improve patient outcomes](#). While all seven patients recovered, scientists are mixed in their opinions on the logic behind the approach and how well it truly performed.

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On Sunday (April 5) the US Food and Drug Administration [approved](#) mesenchymal stem cell (MSC) treatments for use in the very sickest COVID-19 patients under what's known as expanded access compassionate use.

“The rationale for [the China] study is not clear [and] the results are . . . inconclusive in terms of how effective it is,” says developmental biologist and stem cell researcher [Christine Mummery](#) of Leiden University, who has no conflicts of interest to declare. “One should view it with a certain amount of healthy skepticism.”

Regenerative medicine researcher [Ashok Shetty](#) of Texas A&M University College of Medicine disagrees. The results of the study in China “demonstrate that intravenous infusion of MSCs is a safe and effective approach for treating patients with COVID-19 pneumonia, including elderly patients displaying severe pneumonia,” he writes in an email to *The Scientist*. “However, studies in a larger cohort of patients are needed to validate these benefits.” Shetty was not involved with the study and says he does “not have any conflicts of interest with companies providing MSCs for therapy,” but has previously received project funding from CellTex—a company [involved in MSC-based therapies](#) for unrelated work on Alzheimer's disease.

COVID-19, the disease caused by the novel SARS-CoV-2 coronavirus, can have vastly different outcomes—some infected individuals are symptom-free, others have a mild, flu-like illness, a smaller number of patients become critically ill with severe pneumonia, and some die. Global deaths currently stand at over 92,000.

### Cytokine release syndrome

For the sickest patients, there appears to be a [frequently observed](#) pathology—an uncontrolled ramping up of the immune response, of the sort observed in sepsis, known as cytokine release syndrome or, more colloquially, as a cytokine storm.

Cytokines are small proteins released by immune cells that orchestrate the attack-and-destroy mode of the host's immune system when faced with a foreign invader. But if levels of these proteins surge wildly, and the immune system goes into overdrive, the patient's own tissues and organs can be damaged—often fatally.

The rationale for the Chinese pilot study was that MSCs may help to combat a cytokine storm. MSCs are multipotent cells found in various locations in the body including bone marrow, placenta, and umbilical cord that are reported to have immunomodulatory abilities. Indeed, on the basis of this ability, MSCs isolated from donors and expanded in culture are infused into patients as experimental treatments for a number of different diseases. For example, there are trials underway examining the use of MSCs for acute respiratory distress syndrome (ARDS)—build up of fluid on the lungs that results in severe oxygen deprivation. ARDS is a common manifestation of cytokine storms, and the cause of death in many COVID-19 patients.

But the evidence for effective immune response modulation “is not that strong,” says Mummery. “Many of [the trials] have turned out not to be significant in terms of clinical outcome.” There’s also a great deal of variability in terms of the source tissue of the MSCs and therefore the type or types of cells that are being injected, she says. As for the mechanism of action isn’t clear. As to whether they work, she says, “you have believers and disbelievers.”

### See “[Call to Stop Using the Term ‘Mesenchymal Stem Cell’](#)”

An expert in cytokine storms, [Randy Cron](#) of the University of Alabama at Birmingham points out that there are other drugs in trials for tackling cytokine storms that are already available, including tocilizumab, which was recently [approved](#) in China and the US for the treatment of severe COVID-19 cases. MSCs, which are more “experimental,” he says, therefore “wouldn’t be the first thing that comes to my mind [for COVID-19 treatment],” “if it works, it works.” Cron has links to certain pharmaceutical companies that manufacture drugs for treating cytokine storms.

In Japan, MSCs have been [approved](#) to treat another form of cytokine storm called graft-versus-host disease, and pending such approval in the US. There are also a number of [clinical trials](#) starting to test the benefits of MSCs for treating COVID-19.

“There’s a lot of circumstantial evidence that suggests [MSCs] should work . . . in this realm,” says [Martin Grumet](#), stem cell researcher at Rutgers University and the chief scientific officer of CytoStormRx, a company developing technologies for MSC therapies. Grumet, who did not participate in the Chinese study, adds that the data look promising.

## The clinical results of MSCs for COVID-19

In the Chinese study, which was reported in [Aging and Disease](#) last month, seven COVID-19 patients—one critically ill, four severely ill and two with milder symptoms—were given intravenous infusions of MSCs and, in all cases, the patients recovered with some being discharged from the hospital by the end of the 14-day observation period. In contrast, of the three patients in the placebo control group, all of whom had severe disease, one died, one developed ARDS, and one achieved a stable condition.

The two patients with the worst outcomes (death and ARDS), were about 10 years older than the oldest subjects in the test group, points out [Daniel O’Toole](#) of the National University of Ireland who was not involved in the research. “It’s very well established that the mortality rate [of COVID-19 patients] is probably more connected to age than anything,” he says, indicating this may have skewed the results. O’Toole has no conflicts of interest to declare.

In addition to these seven patients, a 65-year-old female COVID-19 patient received MSC therapy in a separate case study reported in a paper submitted to the preprint site [ChinaXiv](#) at the end of February. Her condition also improved, but, says Cron, “the patient, at least by many of the lab markers, was getting better . . . before the mesenchymal stem cell [treatment].” So the result is “not compelling,” he says.

“We understand that it is only a small number of cases,” says [Kunlin Jin](#) of the University of North Texas Health Science Center who is an author of the *Aging and Disease* paper. But from the results, he says, “we can see that MSCs are a very promising approach for treatment of COVID-19 patients.”

Stem cell biologist [Paul Knoepfler](#) of the University of California, Davis, writes in an email to *The Scientist* that he “not convinced at all.” The disease is so variable and the study numbers so small that, “they don’t have the power from a few patients to say anything about efficacy.” They don’t even really show that the approach is safe, he adds. Because MSCs are thought to suppress immunity, “there are also risks . . . that MSCs could weaken the overall immune response to the novel coronavirus,” he adds. Knoepfler has no conflicts of interest to declare.

“It’s a great relief that [following] injection of MSCs into these patients, they didn’t suddenly all die,” says Mummert. But she agrees with Knoepfler that it’s too early to determine safety. While MSCs are generally considered safe and well tolerated by patients, “we don’t know in this particular group of patients what the safety record is.”

Doctors are likely to get more data on safety and efficacy soon. Lin tells *The Scientist* that his team now has unpublished data from a further 24 MSC-treated patients—all of whom, he claims, have improved. And the FDA’s recent approval of the treatment (for extreme cases and trials) together with the recruitment of COVID-19 patients to existing MSC trials for ARDS around the world, mean data will likely come in fast. “Unfortunately,” says O’Toole “my suspicion is there will be large numbers coming soon, because there probably won’t be anything else in the ICUs except for COVID-19 ARDS patients.”

**Z. Leng et al., “Transplantation of ACE2<sup>-</sup> mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia,” *Aging and Disease*, 11:216–28, 2020.**

**B. Liang et al., “Clinical remission of a critically ill COVID-19 patient treated by human umbilical cord mesenchymal stem cells,” *ChinaXiv*, 202002.00084, 2020.**

### Keywords:

cell therapy, coronavirus, COVID-19, cytokine release syndrome, cytokine storms, disease & medicine, mesenchymal stem cells, pneumonia, SARS-CoV-2, stem cell, stem cell therapies