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Stem Cell Strategies Get Compassionate Use in COVID-19

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The COVID-19 pandemic has inspired quests for treatments new and retooled. Mesenchymal stem cells (MSCs), already directed at an eclectic collection of conditions, are being reenvisioned as a weapon against the body-wide damage caused by the new infectious disease.

ClinicalTrials.gov currently lists more than 50 investigations of the use of stem cells for patients with COVID-19. All are variations on the mesenchymal theme, derived from bone marrow, Wharton jelly, fat, dental pulp, placenta, and surrounding blood vessels. At least 10 companies are exploring stem cell–based treatments, according to Paul Knoepfler, PhD, professor in the Department of Cell Biology and Human Anatomy at the UC Davis Health/School of Medicine, California.

Stem cell treatments for COVID-19 began to appear in March and April under the US Food and Drug Administration's (FDA's) expanded access designation during the crisis that began in New York City and that is now spreading around the country.

Although early media headlines highlighted hints of efficacy for stem cells, researchers say the first peer-reviewed reports won't appear for a few weeks. And at least one expert says simpler treatments might be safer.

Repurposing MSCs

The immediate goal of expanded access — popularly called compassionate use — is to save a patient's life. The FDA collects data on such patients, which can be used to catalyze a phase 1 clinical trial or even enable a start at phase 2 or 3 trials if safety has been shown for another indication. That's what happened with remestemcel-L, from Mesoblast Inc.

The MSCs, derived from bone marrow of healthy donors, are in advanced clinical trials for the treatment of graft-vs-host disease and chronic obstructive pulmonary disease (COPD). They display "a very clear mechanism of action that makes sense in treating patients who have moderate to severe ARDS [acute respiratory distress syndrome] from COVID," Fred Grossman, DO, chief medical officer at Mesoblast, told *Medscape Medical News*.

Their mesenchymal precursor cells hug blood vessels and secrete growth hormones. They naturally home in on the lungs, where they counter cytokine storms and facilitate healing, according to Grossman.

Through the expanded access pathway, clinicians used remestemcel-L to treat 12 COVID-19 patients who were on ventilators at Mt. Sinai Hospital in New York City. The patients received two infusions 5 days apart and were monitored for markers of inflammation as well as liver and kidney function. But a more visible benchmark was simply survival.

"Seventy-five percent (9) of the patients got off the ventilator and were ultimately discharged. Compare that to as high as 80% mortality of COVID patients on a ventilator in New York City at that time, and that's a pretty strong signal," Grossman said.

The FDA considered those results in approving the phase 3 trial, which is now enrolling 300 patients at 14 centers. Remestemcel-L leapfrogged over phase 1 and 2 because of its prior use in other settings, including treatment of COPD.

Other companies and groups are using the expanded access pathway to test stem cells in critically ill patients with COVID-19. For example, 24 patients with COVID-19 at the University of Miami Leonard V. Miller School of Medicine began receiving intravenous infusions of umbilical cord–derived MSCs on April 23. The cells were already in clinical trials for the treatment of type 1 diabetes and Alzheimer disease.

"Patients who die from COVID-19 have a median time of just 10 days between first symptoms and death. In severe cases, oxygen levels in the bloodstream drop, and the inability to breathe pushes patients towards their end very quickly. Any intervention that might prevent that trajectory would be highly desirable," said Camillo Ricordi, MD, director of the Diabetes Research Institute and Cell Transplant Center at the University of Miami, who is leading the clinical trial, in a news release.

Setting up a randomized, controlled clinical trial in these desperate times takes longer to plan than expanding access for a few patients, but it is happening.

In a clinical trial to assess allogeneic MSCs from dental pulp, which is ongoing at Renmin Hospital of Wuhan University, in China, 20 patients with COVID-19 received three injections of either MSCs or saline, with 3 days between each injection. The

study is triple blinded — patient, physician, and outcomes assessor do not know who received the cells and who received saline.

The study is tracking time to clinical improvement, lung CT findings, immune function, polymerase chain reaction test results, C-reactive protein levels, vital signs, and adverse effects.

Yet another MSC trial is assessing other outcomes. Pluristem Therapeutics announced a phase 2 trial in hot spots in the United States for COVID-19 patients with ARDS, following compassionate use for patients in Jerusalem at the end of March and at Holy Name Medical Center in New Jersey in mid-April. Primary endpoints for the phase 2 trial are number of ventilator-free days during the first 28 days and survival at weeks 8, 26, and 52. Secondary endpoints are duration of mechanical ventilation, number of ICU-free days, and number of hospitalization-free days.

Stem Cell Skepticism?

It's difficult to predict which therapeutic approaches are going to become part of the eventual arsenal against SARS-CoV-2. How will stem cells compete with other therapies? They might not in the long run.

"Given the recent study showing a benefit of steroids in some of the sickest COVID-19 patients, it's hard to imagine how infusing patients with stem cells will be better than that, given that steroids directly suppress inflammation," Knoepfler said.

Another hurdle: stem cells are far more complex than an antiviral agent or even an antibody cocktail.

"Cellular therapies have the added risk of being a living product, potentially with hundreds of millions or billions of cells, which, once infused, cannot be controlled. The biggest risk is likely to be making the cytokine storm worse or somehow overdoing suppressing immunity and making the patient less able to fight the infection. These immune-modulating approaches have to hit a sweet spot of not too much immunity or too little," Knoepfler said.

Like all the other potential COVID-19 treatments, time will tell.

Grossman is an employee of Mesoblast. Knoepfler has disclosed no relevant financial relationships.

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