Infusion helps repair COVID-19 damage in severe cases

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Camillo Ricordi, M.D., director of the Diabetes Research Institute (DRI) and Cell Transplant Center at the University of Miami Miller School of Medicine Credit: University of Miami Health System

University of Miami Miller School of Medicine researchers led a unique and groundbreaking randomized controlled trial showing umbilical cord derived mesenchymal stem cell infusions safely reduce risk of death and quicken time to recovery for the severest COVID-19 patients, according to results published in *STEM CELLS Translational Medicine* in January 2021.

The study's senior author, Camillo Ricordi, M.D., director of the Diabetes Research Institute (DRI) and Cell Transplant Center at the University of Miami Miller School of Medicine, said treating COVID-19 with mesenchymal stem cells makes sense.

Results: Treatment group vs. control group

The paper describes findings from 24 patients hospitalized at University of Miami Tower or Jackson Memorial Hospital with COVID-19 who developed severe acute respiratory distress syndrome. Each received two infusions given days apart of either mesenchymal stem cells or placebo.

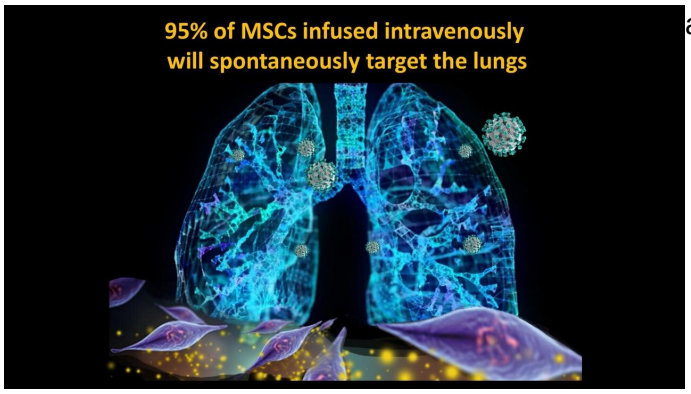
"It was a double-blind study. Doctors and patients didn't know what was infused," Dr. Ricordi said. "Two infusions of 100 million stem cells were delivered within three days, for a total of 200 million cells in each subject in the treatment group."

Researchers found the treatment was safe, with no infusion-related serious adverse events.

Patient survival at one month was 91% in the stem cell treated group versus 42% in the control group. Among patients younger than 85 years old, 100% of those treated with mesenchymal stem cells survived at one month.

Dr. Ricordi and colleagues also found time to recovery was faster among those in the treatment arm. More than half of patients treated with mesenchymal stem cell infusions recovered and went home from the hospital within two weeks after the last treatment. More than 80% of the treatment group recovered by day 30, versus less than 37% in the control group.

"The umbilical cord contains progenitor stem cells, or mesenchymal stem cells, that can be expanded and provide therapeutic doses for over 10,000 patients from a single umbilical cord. It's a unique resource of cells that are under investigation for their possible use in cell therapy applications, anytime you have to modulate immune response or inflammatory response," he said. "We've been studying them with our collaborators in China for more than 10 years in type 1 diabetes, and there are currently over 260 clinical studies listed in clinicaltrials.gov for treatment of other autoimmune diseases."



Umbilical cord-derived mesenchymal stem cells naturally migrate directly to the lung where they begin repair to COVID-19 damage. Credit: © Dr. Camillo Ricordi

Mesenchymal stem cells potential to restore normal immune response

Mesenchymal cells not only help correct immune and inflammatory responses that go awry, they also have antimicrobial activity and have been shown to promote tissue regeneration.

"Our results confirm the powerful anti-inflammatory, immunomodulatory effect of UC-MSC. These cells have clearly inhibited the 'cytokine storm', a hallmark of severe COVID-19," said Giacomo Lanzoni, Ph.D, lead author of the paper and assistant research professor at the Diabetes Research Institute. "The results are critically important not only for COVID-19 but also for other diseases characterized by aberrant and hyperinflammatory immune responses, such as autoimmune type 1 diabetes."

When given intravenously, mesenchymal stem cells migrate naturally to the lungs. That's where therapy is needed in COVID-19 patients with acute respiratory distress syndrome, a dangerous complication associated with severe inflammation and fluid buildup in the lungs.

"It seemed to me that these stem cells could be an ideal treatment option for severe COVID-19," said Dr. Ricordi, Stacy Joy Goodman Professor of Surgery, Distinguished Professor of Medicine, and professor of biomedical engineering, microbiology and immunology. "It requires only an intravenous (IV) infusion, like a blood transfusion. It's like smart bomb technology in the lung to restore normal immune response and reverse life-threatening complications."

Early success with mesenchymal stem cells

When the pandemic emerged, Dr. Ricordi asked collaborators in China if they had studied mesenchymal stem cell treatment in COVID-19 patients. In fact, they and Israeli researchers reported great success treating COVID-19 patients with the stem cells, in many cases with 100% of treated patients surviving and recovering faster than those without stem cell treatment.

But there was widespread skepticism about these initial results, because none of the studies had been randomized, where patients randomly received treatment or a control solution (placebo), to compare results in similar groups of patients.

"We approached the FDA and they approved our proposed randomized controlled trial in one week, and we started as quickly as possible," Dr. Ricordi said.

Dr. Ricordi worked with several key collaborators at the Miller School, the University of Miami Health System, Jackson Health System, and collaborated with others in the U.S. and internationally, including Arnold I. Caplan, Ph.D., of Case Western Reserve University, who first described mesenchymal stem cells.

Next steps

The next step is to study use of the stem cells in COVID-19 patients who have not yet become severely ill but are at risk of having to be intubated, to determine if the infusions prevent disease progression.

The findings have implications for studies in other diseases, too, according to Dr. Ricordi.

Hyper-immune and hyper-inflammatory responses in autoimmune diseases might share a common thread with why some COVID-19 patients transition

to severe forms of the disease and others don't.

"Autoimmunity is a big challenge for healthcare, as is COVID-19. Autoimmunity affects 20% of the American population and includes over 100 disease conditions, of which type 1 diabetes can be considered just the tip of the iceberg. What we are learning is that there may be a common thread and risk factors that can predispose to both an autoimmune disease or to a severe reaction following viral infections, such as SARS-CoV-2," he said.

The DRI Cell Transplant Center is planning to create a large repository of mesenchymal stem cells that are ready to use and can be distributed to hospitals and centers in North America, he said.

"These could be used not only for COVID-19 but also for clinical trials to treat autoimmune diseases, like type 1 diabetes," Dr. Ricordi said. "If we could infuse these cells at the onset of type 1 diabetes, we might be able to block progression of autoimmunity in newly diagnosed subjects, and progression of complications in patients affected by the disease long-term. We are planning such a trial specifically for diabetes nephropathy, a kidney disease that is one of the major causes of dialysis and kidney transplantation. We are also planning to do a study on umbilical cord mesenchymal stem cell transplantation in combination with pancreatic islets to see if you can modulate the immune response to an islet transplant locally."

Funding by The Cure Alliance made launching the initial trial possible, while a $3 million grant from North America's Building Trades Unions (NABTU) allowed Dr. Ricordi and colleagues to complete the clinical trial and expand research with mesenchymal stem cells.

"North America's Building Trades Unions (NABTU) has been a major supporter of the Diabetes Research Institute since 1984, when they started a campaign to fund, and build, our state-of-the-art research and treatment facility. NABTU has continued to support our work through the years, including our mesenchymal stem cell research that helped lead the way to this clinical trial," he said.

More information: *STEM CELLS Translational Medicine* (2021). dx.doi.org/10.1002/sctm.20-0472

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