Stem Cell Therapy for COVID-19 related ARDS (Acute Respiratory Distress Syndrome)

Acute respiratory distress syndrome or ARDS is a very serious complication for many patients suffering from COVID-19, and is believed to account for about 80% of the deaths in ventilated patients. There is no proven or FDA-approved treatment for it, other than oxygen therapy, including use of mechanical ventilation, and fluid management. Literature from previous studies with mesenchymal stromal stem cells (MSCs) support the idea that MSCs due to their anti-inflammatory activities may have the potential to improve management of COVID-19 related ARDS. Dr. Nimesh Desai, principal investigator of the study, explains the action of MSCs and the trial investigating the effectiveness of the stem cell therapy.

Full Transcript:

Priya Menon: Hello and welcome to CureTalks. This is University of Pennsylvania's Covid talk series. I'm Priya Menon and with me today is Patient Advocate Jack Aiello and we are talking about stem cell therapy for Covid-19 related Acute Respiratory Distress Syndrome or ARDS. With us is the principal investigator of the study. Dr. Nimesh Desai. Dr. Desai, welcome to CureTalks and thank you for joining us today. I know its a really busy time for you.

Dr. Nimesh Desai: Thank you for having me.

Priya Menon: Dr. Desai I'm going to start with a very basic question. So, can you talk about mesenchymal stromal cells and then go on to explain the mechanism of action under the conditions of Covid-19 ARDS.

Dr. Nimesh Desai: Oh sure. So, mesenchymal stromal cells which are also more commonly known these days is mesenchymal stem cells or Adult stem cells. So, they're from adult tissue that can basically differentiate into different types of cells. So, in humans these kind of cells are present in our bone marrow, in our fat actually adipose tissue, in the umbilical cord, in utero and even in amniotic fluid and these cells can be cultured or grown in a culture medium and then can actually differentiate into different things depending on what environment they're put into. So, there's studies that show that they can differentiate into bone cells, cartilage, muscles, nerves, skin and even heart muscle cells potentially. So, they are self-renewing, they can grow or be multiplied, and they can also differentiate into different things. Within the context of Covid-19, there is a different application for these stem cells that has been actually used in a slightly different context previously but is a potential way that we can decrease the damage that happens to the body from Covid-19. In particular Covid-19, in the most severe forms, causes a condition known as ARDS or Acute Respiratory Distress Syndrome. ARDS is an inflammatory process where what are called alveoli, little tiny sacs inside the lungs where the gas exchange happens, where the blood gets oxygen from the air and releases the CO2 back into the air and how we breathe. Where that happens is in these tiny little sacks, these elastics sacks that are inside the lung. With ARDS and Covid-19 being a cause of ARDS gas in this situation, these sacks become filled with fluid and the gas exchange doesn't happen properly anymore. And we think that's happening because of a very strong inflammatory reaction occurring because of the virus and this can actually cause the lungs to become really stiff and they can actually scar and even some permanent damage can happen to them. So, the Covid-19 virus we believe causes a very significant inflammatory response and this response leads to ARDS and ARDS then leads to lung failure which then can lead to death. One of the ways that we think we can mitigate the inflammatory processes is try and attack a cause. And in the Covid-19 virus, there's emerging evidence that what is happening in the human body is at the inflammatory response is getting charged up and we're actually having the release of all of these chemicals in the body called Cytokines, that cause sort of uncontrolled inflammation in the lung and that's called a Cytokine storm. And these are chemicals like interleukin-2, interleukin-6, TNF-alpha, they're

all chemicals. They're all things that the body secretes normally to try and work through an inflammatory process. But in this situation their release is not as controlled and it's causing this damage to the lung tissue. So, the idea is how do you decrease the lung tissue damage, the ARDS from the cytokine storm. And the concept behind using stem cells, mesenchymal stem cells in this scenario is that they actually can decrease the production of these pro-inflammatory cytokines. They can increase the production of anti-inflammatory cytokines since they can decrease the amount of inflation along. And they can also alter the kind of inflammatory cells that are in the lung to try and limit the damage. So, the idea is really that you're not attacking one particular part of the cytokine chain, but you're actually trying to reduce the entire cytokine storm with a single therapy.

Priya Menon: Okay, so can you also talk a little bit about some of the objectives of this trial and what we are looking for?

Dr. Nimesh Desai: So, the primary objective of this trial which is really designed to look at the sickest ARDS flicked Covid-19 patients, is to decrease mortality, to try and improve the survival of really severe critically ill Covid-19 ARDS patients. So, the primary endpoint is actually looking at mortality of 30 days. We do have some secondary endpoints as well looking at how many days people are off of the ventilator and the survival at other time points including 60 days and then even people's functional status, months and even a year after the initial treatment.

Priya Menon: So, you mentioned severe symptoms. So, how severe should the symptoms be?

Dr. Nimesh Desai: This trial, this therapy right now is being used in the absolute sickest ARDS Covid-19 patients. So, these are patients that meet the criteria for moderate to severe ARDS and includes a high oxygen requirement. Having to be on a ventilator, patients that are enrolled in this study are on ventilators and also having some biochemical evidence of a severe inflammatory process occurring.

Priya Menon: Okay. Jack over to you.

Jack Aiello: Sure, thank you and very nice to meet you over zoom Dr. Desai.

Dr. Nimesh Desai: Yeah, great meeting you.

Jack Aiello: I'm a myeloma patient. So, most of my questions are related to that and the very first one has to do with these pronounced mesenchymal which I'll call M-stem cells. They appear to be different than the blood-forming stem cells used for blood cancer patients. Assuming that's true, are they based on where you said they're located? Are they harvested differently? I mean we would go through something like apheresis or at worse bone marrow draw, and how are these MSC's obtained? Are they off the shelf for example?

Dr. Nimesh Desai: So, great question. So, they are off the shelf. So, this is a very different concept than some of the stem cell treatments that are used for some of the hematologic problems that stem cells are used to treat. So, these are not harvested from the patient. They are a cell line. They're derived from bone marrow, but that is done in commercial setting using pre-existing cell lines that are grown at the facility. So, it's a commercial product and there are obviously proprietary elements to process it. But it is primarily completely off the shelf product.

Jack Aiello: Do it need to be matched against the patient?

Dr. Nimesh Desai: No, we don't require any of that actually. So, essentially what happens is when we find an appropriate patient, we approach because in our trial the patients can't necessarily speak for themselves. We usually be talking to a family member to obtain the consent. Once the patient is enrolled in the trial, then the stem cells are ordered, and they can either be stored at our facility or they can be used. But they are commercial products that get thawed and then reconstituted and given to the patient. So, there isn't a complex need for a stem cell lab to take and isolate a particular cell, grow it for a few days or weeks and give

it back to the patient.

Jack Aiello: Cool. If this treatment is effective against ARDS, can it be scaled up so that practically it's affordable and implementable on a broad scale?

Dr. Nimesh Desai: So, it certainly cannot be scaled because again, it's not happening at that sort of individual patient level to retrieve bone marrow and then grow cells which is pretty complicated and you can imagine couldn't happen in a large group of patients simultaneously even at one hospital. Because of the constraints of what a stem cell lab could do. Because it's off-the-shelf, it theoretically can be scaled to actually be able to treat, literally thousands of patients, simultaneously. Because it doesn't require as much processing at the individual hospital level, I would assume costs are different but as a commercial product that becomes a kind of more complicated question.

Jack Aiello: When you said that it's meant to reduce the cytokine storm release syndrome, I was thinking back to a few days ago were out of London or England, they talked about getting dexamethasone do the same. And I was kind of curious since you mentioned DEX in the same issue. Did you ever thought as to whether those could ever be used in combination whether one might be more effective than the other? I know it's all really early, but I'm curious whether or not that caught your attention.

Dr. Nimesh Desai: Absolutely. So, it's an interesting area. We have looked at different types of steroids within the context of ARDS for years and have had very differentiating result. So, some trials been very positive, some of them very negative. We do think Covid-19 ARDS has elements that are generally similar to most ARDS, although there may be specific parts of the cytokine pathways that are a little bit different. So, this initial data on DEX, which is not fully published as of today, but looks very promising. I think that, these two therapies may be quite complementary in that regard. Being on steroids is not an exclusion for the trial. And totally we know that many of the trial patients that have been enrolled at the different centers across the US, may or may not have been on steroids simultaneously. So, I think that the data on dexamethasone again not having the final paper out yet looks very promising. Although, we have been down this road before a few times with therapies for Covid-19. So, I think one will have to really wait to see the final data, but assuming that there's even a decent signal that dexamethasone is helpful, I would imagine that we would start using it fairly routinely whether patients are eligible to enroll in this trial or not.

Jack Aiello: Can I understand more about the eligibility criteria? I think I read that and heard you say that only patients in the hospital can enroll. In fact, these are ones that have already symptoms of ARDS or have been at least intubated.

Dr. Nimesh Desai: Yeah, these are sick patients with ARDS. So, there's a pretty detailed criterion to get in, in terms of how bad your ARDS has to be. And there's a criteria system called the Berlin criteria for ARDS which is kind of a well-established way of grading how bad it is, particularly first trials like this so we can compare apples to apples and oranges and oranges so to speak. And so basically, what we're looking at is a ratio of the blood-oxygen level to the amount of oxygen that we're giving a patient and if that fulfills a certain ratio then we know it's moderate ARDS and if it is even worse than that and it's severe ARDS and if you have fulfilled those criteria, that's the main eligible criteria for the study other than you obviously will have to have a PCR that shows that you have Covid-19. And also, one other important element is what's called the C-reactive protein, which is a marker of inflammation in the body. So, in general ARDS destinations with Covid-19 have very high CRP. So, you have to have a high CRP to be in the trial as well.

Jack Aiello: Are there exclusion criteria such as other comorbidities or even advanced age or things like that?

Dr. Nimesh Desai: Right. So, age is not an exclusion criteria at all. If patients are in severe end-organ dysfunction already. So, they're in severe kidney failure, they're there in severe liver failure or they have bacterial infections that are severe in their lungs. Then these are patients we think probably wouldn't benefit from the stem cell therapy at that point. And so, they're not eligible. So, there are a few patient related

factors that would deem ineligibility, but generally speaking if you have a severe ARDS without having really severe end-organ dysfunction in your other organs, you should be eligible.

Jack Aiello: It's a one-time infusion of these MSCs?

Dr. Nimesh Desai: Two times, about three days apart, two singles.

Jack Aiello: And you mentioned the control group will be getting a placebo and patients are always nervous about placebos and kind of wonder if there is a standard of care for these types of patients? I'll ask that question first.

Dr. Nimesh Desai: Okay. Yes. So, the initial thing will be that the patients can receive all standard of care treatments for ARDS. Because we know this is such a rapidly evolving area. They can also receive any experimental approved emergency use treatment as well. So, Remdesivir for instance, is emergency use special approval from the FDA. So, a patient can receive emergency use special approval from FDA. So, a patient can receive emergency use Remdesivir and still be in the trial. Similarly, things like convalescent plasma and be in the trial as well or dexamethasone. But two different clinical trials at the same time, obviously because that would make it a very confusing thing to try and, so, any standard of care therapies patients are always eligible for and any emergency use type therapies that are not part of a clinical trial, patients would also be eligible for and still be in the study.

Jack Aiello: And if your primary objective is overall survival after 30 days, you'll be getting results very quickly, I presume.

Dr. Nimesh Desai: Right. So, the overall enrollment for the trial is about 300 patients. So, one about a hundred fifty randomized to each group. It's hard to know as Covid-19 kind of wines its way through different parts of the country, how quickly it will enroll but there isn't a long-lagged time between when we finish enrollment and when we will have some meaningful.

Jack Aiello: Dr. Desai, those are my questions. I really appreciate the information and I hope you're really successful.

Dr. Nimesh Desai: Thank you.

Priya Menon: Thank you. Dr. Desai, one last question. What are some of the risks associated with this trial?

Dr. Nimesh Desai: Good question. So, the stem cell use in ARDS patients has been done in multiple smaller studies, both about this product and other commercially available investigational stem cell products as well. So, their use in this group of patients is newer but there is still precedent for it already. What we've observed in general is, that because there is a little bit of fluid volume given when you infuse stem cells, it's not a large volume but it is volume which sometimes a little extra fluid when one already has a lot of fluid in their lungs could be potentially harmful. So, we try to make sure that the patients are really well optimized prior to the infusion. And again, it's not a large infusion. So, I think the risk of that is low, but it is something we watch for very carefully and the other one is having sensitivity type reactions to the either of the stem cells or the components that they're constituted in. And so, to try to prevent that we actually have a patient's medicine like Benadryl and a little bit of steroid beforehand, just so we don't get any inflammatory action while infusion is being given. But other than that, it's been shown to be fairly safe and well tolerated in patients with ARDS.

Jack Aiello: Can I ask one more question? Is there any chance that a patient's immune systems will wipe out these MSCs before they can do their thing?

Dr. Nimesh Desai: No, it doesn't happen like that. We don't expect the MSCs to carry on permanently within the body of the patient that they'll exert their effect and then eventually become absorbed by the

body. But from what we've seen in the early ARDS trials, small trials not done in Covid-19, but in other patients, there's been a fairly impressive change in the circulating levels of some of the inflammatory markers. So, I think the answer is, probably happens eventually but certainly doesn't happen immediately.

Jack Aiello: Thank you.

Priya Menon: Dr. Desai, thank you for your time and the great work. It was a pleasure to talk to you and Jack thanks for joining today. Acute Respiratory Distress Syndrome or the ARDS is a very serious complication for many patients suffering from Covid-19 and is believed to account for about 80 percent of the deaths in ventilated patients. Dr. Desai and team are working on mesenchymal stem cell therapy for the management of Covid-19 related ARDS. Stay tuned to Penns Covid talk series to learn more about breakthrough research happening at Penn. Thank you and stay safe.

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