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Covid 19 Convalescent Plasma Study

Convalescent plasma therapy involves the transfusion of plasma collected from a donor who has recovered from Covid-19 to a patient with an active infection. Two recent studies have shown that convalescent plasma therapy can be used in treating critically-ill covid-19 patients. Penn's recently launched two part study will investigate how convalescent plasma therapy works in moderately and severely ill patients. We are talking to Principal Investigator of the study Dr. Katharine Bar to understand the nuances of the study.

Full Transcript:

Priya Menon: Hello and welcome to Cure talks. And this is University of Pennsylvania's Covid talk Series where we discuss latest trials and studies on Covid, that PENN is part of. I'm Priya Menon and with me today is patient advocate Cynthia Chmielewski. We are talking about the Convalescent Plasma Study with the principal investigator Dr. Katharine Bar. Dr. Bar welcome to Cure talks and thank you for being here today.

Dr. Katharine Bar: Thank you for having me.

Priya Menon: Dr. Bar let's just start with the very simple question. Can you describe the theory behind the Convalescent Plasma and what we are trying to achieve with this trial?

Dr. Katharine Bar: Yeah, so good place to start. So, the theory behind Convalescent Plasma or the biological plausibility is actually quite old for many infectious diseases. For a long period of time people have used plasma as the carrier of antibodies as a treatment. So, for infections as old as the flu and other types of viruses before we had specific targets or antiviral medications. We had been thinking that people who were previously infected and made an effective immune response, we could take plasma from those individuals, take the hopefully effective and well-formed antibodies from those individuals and give them to another person, who was suffering from an acute disease. So, this is actually been going on for a long time. There are data in other infections. They're not overwhelmingly positive but the Convalescent Plasma has been used since and shown some benefit. And then the next step of that process, for other infections is that people will take out the antibodies either making monoclonal antibodies or other antibody formulations and that is considered standard of care for several different infections.

So, for Covid-19, we're kind of in the same situation. We have a new virus where we haven't had enough time to study it and develop a full range of specific antiviral drugs nor pull out the best kinds of antibodies and make antibody-based therapies. And so, we're going to the primary source and that is, people who have recovered from Covid and have detectable antibodies in their plasma and using those plasmas to treat acutely infected individuals. So, that's the basic premise of the trial. So, here at PENN, the blood bank led by Dr. Don Siegel, Nicole Aqui and Andrew Fesnak have been collecting plasma from individuals who had Covid disease, tested positive during their acute infection, recovered and then were at least 28 days or full month symptom-free days. Afterwards, they went in and donated blood. And so, from those individuals we've collected plasma, we've tested that plasma with an antibody test to make sure that there are at least some level of antibodies against Covid and then those people's plasma has been stored in the blood bank. So, that's one component of the operation.

The clinical trials that we are running for patients in the hospital, there are two of them but the basic premises, we take people who are acutely ill and sick in the hospital with Covid. And we give them plasma from one or two of these donors who have donated Convalescent Plasma. The plasma is matched to their blood type. And again, it's just been screened to show it has at least some level of antibodies and we give

that to people in the hospital, we monitor them to see if it helps. Now, there have been a couple reports to date of this sort of Convalescent Plasma strategy. So, there are several small trials out of China where they gave Convalescent Plasma to somewhere between 5 and 10 participatory patients each. And these are not randomized controlled trials. They're just more observational of what happened. And what those trials suggested was that it was safe, there weren't a lot of bad reactions to the plasma and at least some of those people seem to get better, either be it their breathing improved, they'll potentially leave the hospital.

There is a large study that was recently published by the Mayo Clinic for an expanded access program, where they looked at thousands of individuals around the United States who received Convalescent Plasma and they don't have data about how well the Convalescent Plasma affected their disease course. But it was shown to be safe with a very low level of adverse events or bad reactions or bad clinical events that happened around the plasma. So, where we are at PENN and the goal of these trials is to test this little more rigorously in a scientific manner. So, we have two trials. The first is looking at our sickest patients those who are intubated and mechanically ventilated, who can't breathe on their own. And so we're going to follow those individuals after they get two units of plasma and ask whether this plasma improves their condition. We're going to compare the results clinically to a different trial conducted by the NIH and which one arm we're Placebo recipients. So, they basically were similarly sick with Covid but didn't receive any intervention. So, it's not a perfect randomized control trial. But at least it's a group of match participants that we can compare and say how did the clinical outcomes differ in this group that got plasma versus this similar group who did not get Plasma.

Our second trial is for individuals who are a little less sick. So, you have to be hospitalized and have pneumonia and have difficulty breathing with your Covid, but you don't have to be in the Intensive Care Unit, on a mechanical ventilator. That's an 80% trial where half of the people will get plasma and half won't. And we'll compare the standard of care plus plasma to see the outcomes, are they any different than standard of care alone? And so hopefully with these trials we can take this atmosphere where we have optimism and we think that plasma could help but we can have a little bit more rigorous understanding of whether it actually is safe and efficacious for patients who are quite sick in the hospital with Covid.

Priya Menon: This is very interesting. My next question was actually on the eligibility as to who can donate plasma, but I think that you've already answered saying that somebody who was recovered from Covid-19 is eligible.

Dr. Katharine Bar: Yeah. So right now, for this protocol we are required to have people who had an actual diagnostic test. So, while they were sick, if they went and got one of the nasal swabs and were shown to have the virus. So, if you have that while you were ill and then you've recovered then you are eligible to donate plasma for this study. If you just suspected that you were, let's say you had a contact who was diagnosed, and you had very similar symptoms or you had a disease course that sounds a lot like Covid, but you didn't have the opportunity to get tested. There are still clinical trials here at PENN that you can volunteer for, contribute to the scientific effort in great ways. But per the FDA guidance right now, we are not allowed to use those individual's plasma as a part of this therapeutic program.

Priya Menon: Okay. So, I would like a little bit more detail about as to how this plasma donation is done. Like is it like you match blood for example.

Dr. Katharine Bar: Yes. So, we use compatible blood types. It's similar to blood cell products, except what we have in the plasma is that antibody reaction to whatever types of cells you have. So, basically, we have to make sure whatever blood people receive, the antibodies in the donor plasma aren't going to react to their cells. So, it's similar. If I'm A type blood, I can receive A type plasma. O type blood can receive O type plasma. It's a similar concept.

Priya Menon: That's clear. With that I'm going to handle it to Cindy for her questions.

Cynthia Chmielewski: Thank you. Dr. Bar for explaining lots of this. I want to talk a little bit more about the target population. You explained that there's going to be two trials going on one for the severely ill and one

less severe. In both of those populations if you used to have the Convalescent Plasma, does that exclude you from any other of the treatments like gazetteer or any of the other promising therapies.

Dr. Katharine Bar: That's a really good question because we're kind of in this gray zone right now where there's lots of new and evolving, maybe promising therapies but we don't know which one is better. So, it's hard for patients and patient's families to decide which trials they should participate in. Because this is a phase 1 study and we're really trying to determine what the safety and the advocacy are, we can't enroll a person who's getting this therapeutic trial getting this experimental therapy in another phase 1 study. So, a patient who agrees that this Convalescent Plasma is something that they'd like to participate in. They are excluded from most other Covid therapeutic trials. But that doesn't mean they can't be allowed the other experimental therapies. So, for instance, Remdesivir is now available from an expanded used program where the government is providing certain hospitals with the certain amount of the drug. So, if that drug is available, and it's honestly, it's not a sure thing how much of that drug is going to be available for which patients or for which hospitals. But if the drug is available, the patient who is getting plasma is still able to receive that drug. If there is a different trial that is not about Covid then that would be fine. But in order for us to fully distinguish what the safety signal is from this plasma, we can't have multiple experimental trials at the same time. Otherwise, we won't be able to tell if something happened is that because of the plasma or is that because of the other experimental therapy that we're giving you.

Cynthia Chmielewski: Okay, but you are still able to give other therapies that are not experimental?

Dr. Katharine Bar: Right. So, that's kind of the gray zone because everything is experimental for the most part. We have a little data about Remdesivir. So, Remdesivir is now considered sort of, one of the standards of care medicines. We have some data about hydroxychloroquine, etc. And so, some people have been giving that as a part of routine clinical care. Anything that your medical team thinks is appropriate for your medical care can be used. It's just the experimental clinical trials that you're limited from.

Cynthia Chmielewski: Okay. And a little bit more about the target population and the eligibility criteria. Any groups of people excluded from this trial?

Dr. Katharine Bar: Yeah. We're trying to make this the pretty broad trial. So, for a first trial it's called PENN's CCP 1 or PENN's Covid-19 Convalescent Plasma 1. This is for our sickest patient, for critically ill patients who have mechanical ventilation. So, the only exclusion criteria are that you need to be on a ventilator, you need to have a recent test showing that somewhere in your respiratory tract, there's a virus. So, we want to make sure that we're actually treating Covid and not another issue. We need to make sure we have the right blood type available for the plasma and then we want the study team and a medical team to think that Covid-19 is actually driving a major part of the disease process. There are a lot of very sick patients with Covid who maybe can get over the Covid but they're dealing with all the other problems that happen from very sick patients in the hospital. So, we don't want to give plasma to an individual where we don't think it has any chance of helping. So, we're trying to give it to people who we think the active virus replication is causing the problem. So, those are really the exclusion criteria. But for instance, if your kidneys aren't working well or if your liver is inflamed, those are all fine.

Cynthia Chmielewski: This is a trial that you have to be offered or could someone asked to be part of the trial.

Dr. Katharine Bar: Yeah. So, what I should mention that this second trial, it's very similar criteria, except you don't have to be on a ventilator. You just have to be hospitalized, have evidence of pneumonia and have the Covid test be positive and have your team think that Covid is driving disease. Yeah. So, these studies are only currently being offered at our PENN hospitals. So, at the hospital of the University of Pennsylvania and at Penn Presbyterian because that's where our blood bank has a relationship. So, we look for all eligible patients within the hospital system and try to enroll those individuals. If a specific patient or a patient family has an interest in plasma that at times they brought it to our attention that the family is interested, but we're trying to sort of get as many people who we think would be good candidates enrolled as possible. So, if people were to request it and be hospitalized in our system, that would be great.

Cynthia Chmielewski: Now, let's talk a little bit about the plasma donor. What's the donation process? Is it just a blood draw or is it apheresis? I know when I got my stem cell transplant. I had to be on an apheresis machine to get my plasma cells out. So, what is the process?

Dr. Katharine Bar: It's similar to what you went through. It's not exactly the same process but it's the same sort of machine. So, what we do with the plasma donation process is you have a couple of large IVs placed in your arm and instead of taking the whole blood donation, the blood gets processed through the machine and your cells get returned to you and they just take some of the plasma. So, it's like you said it's an apheresis machine and they're taking the plasma and a plasmapheresis process and giving you back your cells, your red cells etc. So, it doesn't make people quite as anemic as a regular blood donation would.

Cynthia Chmielewski: And how long does that process usually is?

Dr. Katharine Bar: I think it's about one or two hours.

Cynthia Chmielewski: Okay, and do they get enough donations for several patients, or is it a one-to-one donation?

Dr. Katharine Bar: That's a good question. So, what we're doing right now, I think that the plasma team has got about 50 or 60 donors so far and each donor gives about two units if they can get that amount. Each unit is about a cup of blood so that's about two cups of plasma and we actually end up giving each recipient two cups of blood. But we oftentimes don't give the same one person's two units to the same recipient. So, in order to try to mix and match some of the antibody levels we've tried if we can. Because we have flexibility with the blood type to give plasma from two donors to each recipient. Sometimes for the more rare blood types, where we aren't able to do that, but that's been our goal.

Cynthia Chmielewski: So, the recipient gets two doses of the plasma at the same time or is there a time between it?

Dr. Katharine Bar: Yeah, so each unit of plasma goes in over about 30 minutes to an hour and then we break for an hour to monitor and make sure there's no infusion reactions or issues and then we give the second unit. So, it's within the first few hours. If the participant has any reasons that they need to slow the infusion, they're welcome to do that. But most people tolerate the infusion within just a few hours.

Cynthia Chmielewski: Okay, great. And I know you had said earlier that the donor had to have a positive Covid-19 test. Do you test for antibodies also prior to the donation? Is it just yes, no, or is there like titer's testing that they have to have a certain level of antibodies?

Dr. Katharine Bar: That's such a good question. I think that's really the heart of the matter. So, for clinical trials, we have to use FDA-approved to sort of, a certain high level of clinical grade assay in order to make any clinical decisions. So, because we're relatively early in this disease process, we don't have a lot of great antibody tests that are validated for this sort of thing. And we don't actually know what the type of antibodies or the amount of antibodies is that's needed to be an effective therapy. So, for this trial all we are doing is a qualitative test, where we show by an Elisa assay that there are Covid antibodies. So, it's more of a yes or no. What we're going to do at the back end of this study is, we're going to follow those antibody levels. Both, in the donor before we give the donor plasma to the recipients and the recipient at baseline before they get any plasma and then over time after the recipient gets the plasma. So, we have a good sense in a much more sort of thorough way, what the quality and the quantity of those antibodies are. And we'll be able to correlate that a little bit with the clinical outcome. And so that's more sort of translational research level information. But it will hopefully help us understand in this therapeutic scenario, what types or amounts of antibody are needed to improve. What types of patients if you have a patient who's been sick for a long time and they actually have high levels of antibodies. Could they be helped by an antibody transfusion or not. If you have someone with very low-level antibodies. Are they more likely to be helped by a certain type of antibody? So, there's lots of questions that will give us answers about whether Convalescent Plasma is effective. But also help us move into the next line of therapy where people make monoclonal antibodies or

maybe a mixture of antibodies that could be used in a more directed way for the next round of therapy against Covid.

Cynthia Chmielewski: Okay, and then thats kind of looking into the future there.

Dr. Katharine Bar: Yeah. That's a great question. You hit the nail on the head. That's what we all would really love to be able to just choose the most effective high type of antibodies and give those directly to these patients. We just don't know yet what those are. And it's kind of a limited resource because there aren't that many people who were diagnosed with Covid and are now recovered, who are coming in to donate. So, we're having a good response and there's lots of people. But there are an infinite number of people who had Covid, have the test and are now feeling great and want to come in and donate.

Cynthia Chmielewski: And they have to come to your facility?

Dr. Katharine Bar: Yes, they can come to the PENN blood bank and if anyone's interested, you can Google Search the PENN Covid volunteers or plasma. There is a donor registry that you can sign up to donate plasma, if you're interested or volunteer for various other studies.

Cynthia Chmielewski: Can you donate more than once.

Dr. Katharine Bar: I believe so. I believe you can up to twice for the plasma antibodies. But all that information would be available on the website as well.

Cynthia Chmielewski: Okay, and how long can that Plasma be kept in? Is it like frozen in liquid nitrogen?

Dr. Katharine Bar: Yeah. So, when people donate their plasma is frozen and it can be kept for quite a while when it's frozen. And then we don't thaw it until we have a matched donor that we think is appropriate and then once that bag of plasma is thawed, it can actually be kept in refrigeration for a couple days. But we generally use it once we thaw it.

Cynthia Chmielewski: Okay, great. And besides I guess, on your informed consent form. There's always the risk and benefits. Besides not working what other risks do you think are associated with receiving the Convalescent Plasma?

Dr. Katharine Bar: Yeah, that's a good question. So, fortunately plasma is given all the time during routine medical care, so it's actually a fairly safe clinical procedure. We do it for lots of different situations. Most often if people have bleeding problems or if they've lost a lot of blood. But we have a good understanding of how safe this is. So, the specific risks are that people could have an allergic reaction. If you've ever had an allergic reaction to blood products before, you're more at risk for that. So, we would make sure we asked about that and determined your risk for that. It's only two cups, but actually two cups of volume is potentially a lot of volume for some very sick patients. So there's the possibility of sort of a volume overload situation that the clinical team would need to monitor and either, encourage urination or dialysis or something to keep the volume status even. And then there's very low level, sort of theoretical risks that we don't know if they're real or not. But given Covid's level of uncertainty that we have about Covid that we usually mention. So, we know that with Covid there's an increased risk of blood clots, blood clots in the leg, blood clots in the lung, even strokes and heart attacks. And so most Covid patients, they're being very closely monitored for that and they're anti-coagulated to prevent that. Now, its been shown if people get lots and lots of blood products then you can increase their risk for clots. So, in theory plasma may contribute to that but it's probably a nominal increase in the risk of clotting and it's something we're already very aware of and trying to prevent in our Covid population anyway.

Cynthia Chmielewski: In the future, right now, it's kind of a one-to-one donation like one bag or maybe they're getting plasma from two different people. But in the future, is there any idea of maybe making a pulled plasma donation, kind of like IVIG where you might have a number of different people's antibodies in one infusion.

Dr. Katharine Bar: Yeah, and that's the way a lot of these antibody related products have been delivered for other infections is through an IVIG type of formulation. I think what will happen with Covid is, there are a lot of groups right now pursuing monoclonal antibodies. So, these are specific antibodies they pulled out of people who had Covid and they're basically searching for the ones that are the most potent neutralizers and are the most effective. I think these will be sort of developed as products and there will either be a single monoclonal or a mixture of these monoclonals that could be used as a therapy. These same sort of things could be used as a preventive strategy also. So, there is a huge amount of scientific effort into identifying and characterizing these monoclonals. And I think we're going to see Phase 1 clinical trials in the not-too-distant future. Testing these antibodies for both preventions, as sort of a passive immunization like a passive vaccine process and as therapy if it looks like these antibodies are effective in the sort of Convalescent Plasma type mode. So, I think that's probably the next step.

Cynthia Chmielewski: Great.

Dr. Katharine Bar: That takes away some of the issues with blood transfusion and volume and what not. It Just directly gives the antibodies.

Cynthia Chmielewski: And one kind of last question, I guess because you're on the line and I get to ask you this question. What if you had your crystal ball and for people like me who have multiple myeloma who have a hard time producing intact antibodies anyway. What would a Convalescent Plasma look like for us. Would it be something we would want to consider or is that something that maybe I won't be able to make those antibodies?

Dr. Katharine Bar: Yeah. So, for people with any sort of immunodeficiency, where their immune responses are a little bit weakened. You might be a perfect person to consider a monoclonal antibody as a preventive therapy as opposed to just vaccinations. So, hopefully we'll develop a good vaccine that we can give to almost everybody. And that basically is a part of the virus that your own immune system responds to you by making good antibodies and good T-Cell responses. But for some people who are maybe a little immunocompromised and aren't able to mount that good active vaccination response, this sort of passive vaccination concept where we just give you good antibodies, through delivery of a long act long-lasting antibody, monoclonal antibody, that might be a good pathway to protect people like you who want to go, I mean, hopefully we're able to get out and walk around and do things in public again. And for people who may not be able to have the highest or the best vaccine responses, a monoclonal antibody product might be a good sort of surrogate for that.

Cynthia Chmielewski: That sounds promising to me. I would really like to get out my house someday. Well, thank you so much. Priya, do you have any other questions.

Priya Menon: No. Dr. Bar, thank you so much for your time. I think it was a real great pleasure to talk to you and learn about the study. And Cindy thanks for joining today. Stay tuned to PENN's Covid talk series to learn more about breakthrough Covid research happening at PENN. Thank you everybody and stay safe.

Dr. Katharine Bar: Thank you.

Cynthia Chmielewski: Thank you. That was great. I learned a lot.