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Analyzing the Available Treatments for Adrenoleukodystrophy

Dr. Doghramji:
Even though there isn't a cure for the rare genetic disorder adrenoleukodystrophy, or ALD for short, we do fortunately have access to treatment options that have proven to be effective for some of our younger patients living with ALD, and what those treatment options are and how we can select the best one for our patients will be the focus of today's discussion. Welcome to Clinician's Roundtble on ReachMD. I'm Dr. Paul Doghramji, and here with me today is Dr. Maria Escolar, the Director of the Program for the Study of Neurodevelopment in Rare Disorders and Professor of Pediatrics at the University of Pittsburgh School of Medicine. Thanks for joining us today, Dr. Escolar.

Dr. Escolar:
You're welcome.

Dr. Doghramji:
So, Dr. Escolar, to get started, can you give us a brief overview of what adrenoleukodystrophy actually is?

Dr. Escolar:
Sure. So, adrenoleukodystrophy is an inherited condition that can affect the neurologic system. They have a mutation in a gene that, causes them to have difficulty with the metabolism of a protein, and so they accumulate, something that we call very long chain fatty acids, and unfortunately with accumulation, they develop toxicity in the cells that produce myelin, so the cells that are surrounding the nerves both in the brain and spinal cord and peripheral nerve. There are different types of disease; one is the cerebral form. If you have the cerebral form, you are going to develop disease as an infant as or as a child or a juvenile, and you will have brain deteriorations, so neurodegeneration. There's a different type of ALD that we call adrenomyeloneuropathy, abbreviated AMN, that occurs in adults, and this only affects the spinal cord and the peripheral nerves, although there is a percentage, about 20 percent, of men that can develop the cerebral disease as adults. So, it's a condition that is unfortunately fatal, it can progress, and in children it progresses very quickly, and children die after they've lost their vision, their hearing, their ability to move, and their ability to eat, so it's a pretty aggressive and sad condition.

Dr. Doghramji:
And now that we have that base knowledge to go off of, could you share some updates on the treatment options that are available for ALD?

Dr. Escolar:
Yes, let's start with the more historical approach. Their initial treatment that was used was with Lorenzo's oil, which is a type of diet that is trying to bypass these metabolisms so that you don't accumulate very long chain fatty acids. That has been used over the years, but it's a very difficult diet to have, and it doesn't seem to be very effective. There is also bone marrow transplantation, in which you would provide chemotherapy and open space in the bone marrow so that you can then receive cells from a donor, and this has been shown to stabilize the disease. In the past it was sometimes difficult to find a match, so a donor that would match that you could give to the patient very quickly because once the disease starts progressing, it's very difficult to stop it. So, sometimes when you're trying to get a bone marrow from a donor, that can take anywhere from three to six months, and so we needed something where you could find a donor match faster, and in the late 90s, early 2000s, patients started getting transplanted with unrelated umbilical cord blood, which is blood that is collected from the placenta after a baby's born, and so this blood gets processed and banked, and the US now have banks with millions of these cord bloods, so it's very easy to find a donor. So, these days when a patient gets diagnosed with ALD, usually because we want to do this very quickly, you find a match, which is usually umbilical cord blood, or sometimes you can match it with a sibling and

then use bone marrow, and if you are able to do it early, and that's a very key point – it has to be done early – you can prevent the deterioration of the disease. However, if the patient is already showing changes in the brain MRI and any symptoms, then it's much more difficult to stop it completely, and so you may be able to stabilize it and have some degree of motor disability, or you may not be able to stabilize it, and the child can continue to progress and maybe live a little bit longer but still be very affected. The last approach that has been looked at but is still being evaluated in clinical trials is using gene therapy, and this is using something that we call lentiviral approach, which is a viral vector that is able to infect the cells and produce cells that now have this protein that they were missing, and so the approach to this is you still need chemotherapy, but what you do is you harvest the bone marrow of the patient. Then, in a lab, you transect it with this lentiviral vector, and then you put it back into the patient, and now you have these high levels of this protein, and that's the way you then try to stop the disease from progression. This is a relatively new treatment, and they're still doing trials collecting information, but the preliminary results seem to be very positive. The other thing that happened, which has been very important for the field of adrenoleukodystrophy, is that there is newborn screening in some states. So, when you identify a baby, you can now monitor them. The family, they come here to hear about the disease, what to look for, and the doctors can then monitor them, for example, with MRIs or some behavioral testing, and you make people aware of what are those initial symptoms, and that way the kids can get picked up very, very early, and then you can treat them and prevent the disease from progressing.Another advantage of newborn screening is that sometimes you not only identify the baby, but you can identify other family members that maybe are still asymptomatic but may be older, like cousins that, when they were born, there was no newborn screening, but now because you have a baby that you have identified, you may be able to then test other family members and diagnose the disease early.

Dr. Doghramji:
So, Dr. Escolar, with that being said, how do you go about deciding which treatment option is best for your patients? And as a follow-up, if we look at stem cell transplantation, what symptoms does a patient need to present with in order to suggest that this is the right treatment option for them?

Dr. Escolar:
So, right now the only option that we have is hematopoietic stem cell transplant because the lentiviral therapy is still in clinical trials. So, if you are in that center that is able to do the lentiviral therapy through the trial, that's a great option. Otherwise, their other option is to just provide them with either umbilical cord blood or bone marrow transplant. You choose one of the two depending if you have a good donor source that is available right away. Once you decide to do the transplant, it's because you have found that there are symptoms, signs, or changes in the brain MRI. If you pick up the patient through newborn screening, you will have to track them over time by looking at these MRIs and doing the neurobehavioral testing, and the moment you see a problem, that's when you refer them. On the other hand, if the patient comes to you because they are symptomatic, you have to assess if the patient is too advanced and will actually not benefit from this transplant or if the patient is still able to tolerate a transplant without, let's say, inducing progression of the disease, which is what happens if you're too advanced.

Dr. Doghramji:
And looking at both of these treatments then, Dr. Escolar what are the benefits and even some of the drawbacks that patients can expect?

Dr. Escolar:
With the hematopoietic stem cell transplant, which is bone marrow and umbilical cord blood, there's still a chance of dying from infection, and so when you do these transplants, you have to immune suppress the patient. They can then develop infections that sometimes are very difficult to treat, so there's still a five percent mortality. You can also develop something called graft-versus-host disease where you reject the transplant. These type of complications are not seen as much in the other lentiviral vector approach, so it seems to be a slightly safer treatment, but I would say that the pros and cons of these two therapies is in one, we have 20 years of experience. The other one is a new therapy, and we don't know how this therapy would behave long term, if we are going to continue to have the same effects or not. So, there's a lot more unknowns in the lentiviral therapy than the hematopoietic stem cell transplant, but the hematopoietic stem cell transplant has more mortality, and you can have graft-versus-host disease, while with lentiviral vector you wouldn't develop this because it is your own bone marrow that is being put back now with the transfused vector.

Dr. Doghramji:
So, for those just tuning in, this is Clinician's Roundtable on ReachMD. I'm Dr. Paul Doghramji, and today I'm speaking with Dr. Maria Escolar about the available treatment options for a rare yet fatal genetic disease called adrenoleukodystrophy, or ALD. So, Dr. Escolar, you've given us a really great understanding of the two treatment options available for ALD, but now I'd like to focus specifically on stem cell transplantation for a moment because I'm sure a lot of us are wondering if this technology has improved over time and, even more importantly, if it's safe. So, can you speak of those two points, Dr. Escolar?

Dr. Escolar:

I started working with trans centers 20 years ago, and I have seen the changes have been actually quite drastic because they were using much more toxic regimens in the past. So, the patients that I saw with adrenoleukodystrophy that were treated, let's say, 15, 18 years ago the chemotherapy was quite strong and patients really deteriorated many times because the chemo can actually be neurotoxic, too. They can develop graft-versus-host disease, and they can develop infection. I would say during the last eight years, they have improved with their regimens, and they're using a reduced toxicity type of conditioning that is a lot less harsh on their organs. They really do pretty well in terms of the toxicity part. However, because of the immune suppression, they are still at risk of developing viral infections. So, the mortality rate that in the past was close to 40 percent now is more like 5 to 10 percent, and in the best centers, it's really 5 percent. So, we have seen a huge change in how transplant was given before and now the outcomes are much better these days than in the past.

Dr. Doghramji:
Okay, and once a patient is receiving treatment for ALD, what are some of your next steps? For instance, how long after the treatment do you typically meet with the patients?

Dr. Escolar:
So they usually are in the hospital anywhere from three to six months depending how they do. The patients are typically assessed by a group like ours right after referral. Then, we recommend the transplant to proceed or not based on our testing. We follow them three months later when they usually leave the transplant unit, but they're still near the hospital or once they're seen in the clinic. So we see them three months later, then six months later, and then we follow them once a year. So, typically they're sent back home once their immune system has been reconstituted and they have been re-immunized so now they can go back to school and have a normal life, and then what we continue to follow them yearly just to make sure that they don't have any issues and that all the endocrine part is in control.

Dr. Doghramji:
Okay. Well, Dr. Escolar, unfortunately we're almost out of time today, but before we close, is there anything else you'd like to share with our audience regarding the treatment of ALD?

Dr. Escolar:
I just wanted to emphasize that because of newborn screening, our approach really has changed drastically, and now many doctors are going to be seeing in their practice children that have been picked up through a newborn screening that are needing monitoring, and so it's important to understand well what are those early signs and also how to interpret the changes in the MRI. Those are the two things that I want to disseminate as much as possible for doctors treating these patients.

Dr. Doghramji:
So, with that parting comment, I'd like to thank Dr. Maria Escolar for joining me today to review the two treatment options available for ALD, and I certainly hope that one day in the future we can have you on again to unveil another new treatment or maybe even a cure. It was great having you on the program today, Dr. Escolar.

Dr. Escolar:
Thank you very much.

Dr. Doghramji:
I'm Dr. Paul Doghramji, and you've been listening to Clinician's Roundtable on ReachMD. To access this episode and others in this series, visit ReachMD.com/CliniciansRoundTable where you can be part of the knowledge. Thanks for listening.