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Best Practice for the Multidisciplinary Team – Starting Transition Early, Tailoring the Specific Timing and Speed to Individual Patients

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCME curriculum.

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Dr. Mahan:
So hello, welcome to our presentation on XLH Best Practices in Treatment and Transition. My name is John Mahan, and I'm a Professor of Pediatrics at Nationwide Children's Hospital, the Ohio State University College of Medicine. And I have the pleasure being the Medical Director of our Metabolic Bone Program at Nationwide Children's Hospital. And I'm delighted today to have the opportunity to talk about XLH care and these advances with someone who's been a devotee, an expert in this field for some time, Dr. Guido Filler. And I'll have Guido introduce himself to you right now.

Dr. Filler:
Yes, well thank you so much. That's a very kind introduction. I'm a Professor of Pediatrics Medicine and Pathology and Laboratory Medicine at the University of Western Ontario in London, Ontario. That is a small town in the middle between Detroit and Toronto. And yeah, I feel very privileged, I have been working on XLH since 1992. I had 66 patients when I was in Berlin and was actually part of the consortium that found the gene. And I have always had a great interest in that and was always very disappointed about the treatment and also wondered whether some of the late complications like hypertension and like nephrocalcinosis are treatment induced. So to have new novel choices for the treatment is actually very exciting.

Dr. Mahan:
Yes Guido, I agree. Living through the frustrations of practice in this condition in the 1980s when I trained and seeing advance over the last four decades has been truly breathtaking. So we're in really a good company here. So first question I would ask you is just to share with us your thoughts about what is the best treatment these days for children and adults with XLH?

Dr. Filler:
Well, in my opinion, I think we should have lifelong therapy with Burosumab, and we can have a conversation about when to start. But especially when you have families, especially when father is having a girl, then it is very clear that they are affected. And I have very limited experience starting under one year, but it has been terrific and they have not had the same secondary things. In my lecture earlier, we talked about the dental issues and they actually increased on the Burosumab therapy, probably more in the older children than the younger children. But most of the dentin formation occurs in the first year of life and it would be good to have a harmonization in the world that everyone has the same age for inclusion. A lot of countries have age one and not six months. In Canada we have six months, but I think we should actually push for starting as early as possible because even after two months the alkaline phosphatase can be very elevated.

Dr. Mahan:

And in the United States of course the FDA approves Burosumab for six months of age and older now. But I agree with you, we have young children, we know they have XLH and it seems unfortunate that they would walk on those legs when we know they're demineralized and don't have the strength and end up having some of the clinical consequences of their disorder. I know I just recently had two boys, mom has XLH, and the second boy we diagnosed in the first couple months of life. And right at six months he got started. And he is straight as can be, where his older brother that took a little while to get in to see us because mom wasn't sure and all of that, does have some bowing that is getting better on treatment. But yeah, it's remarkable to see the difference with a child that starts much earlier.

Dr. Filler:
May I say, the other thing I find a remark remarkable around the two patients I started at six months is the height. So they actually are at the same, so in the first six months you lose a little bit of the hypervelocity but then they are back at the percentile. So one of the two kids has a fairly tall mother, affected father. So we don't know what his target height would be. But she is on the 93rd percentile again, which was the same as at her birth. And she's now two years of age and she never had any dental issues either. But I think actually the dental issues would be a reason because much of the dentin is formed in the first few months of life that we start from birth.

Dr. Mahan:
And Guido, is there any role for conventional therapy in a child with known XLH these days?

Dr. Filler:
Well I am not sure that it really worked, if I may say so. First of all, you give them a huge amount of sodium because most of the phosphate supplements are sodium phosphate supplements and I think complication like hypercalciuria, like nephrocalcinosis and even the hypertension may be driven by that. Because before they start treatment they're actually hypocalciuric, not hypercalciuric, and then you can get it wrong with the mix of an alpha and of the phosphate supplementation. I think that that treatment is today obsolete.

The real challenge is by fault, at least in my country, first reimbursement, because it is expensive and not all provinces have universally approved it yet. And then in Canada I think we are the only country in the world where we have to do the Rickets Severity Score every year and that jacks up the radiation exposure substantially. I calculated actually the lifetime cancer risk from 44% in Ontario to 56% with these annual x-rays. And I think that is ethically unjustifiable. And that brings me to a question, is anyone else requiring the RSS? I mean, don't we just go by alkaline phosphatase?

Dr. Mahan:
Yeah, that is not required in the states, Guido. And certainly different government insurance plans might have different requirements. We've had some that have required an FGF 23 or have required a TMPGFR. I've had patients where I have the abnormal gene and a low serum phosphorus, and in my mind I have the diagnosis but they still require the urine TMPGFR. So I think there's variability even in what's required to initiate therapy. But I agree with you, I really think the conventional therapy is clearly inferior. And when we have something that works as well as what you and I have experienced with Burosumab. We're treating over 30 children right now. No one has asked to go back on conventional therapy.

Dr. Filler:
The convenience of once fortnight with an injection as compared to four times a day, and if they have diarrhea even more than four times a day, taking the sodium phosphate is just unbelievable. The quality of life also has improved so much. And I have never really been able in a severe case with the conventional therapy to prevent that knee pain and that chronic pain or the enthesopathy and all of that later in life. And there's really big hope that the Burosumab therapy long term will ameliorate all of this. And if we start early enough, never ever develops.

Dr. Mahan:
Yes. So that's the point about starting early. Another thing that comes up in our clinic, and I wonder if it does with you, is the parent comes in, is not on any treatment, has been told there was no reason to be on treatment after they were done growing. And yet has back pain, may have had a pseudo fracture in the last year, has enthesopathy. And I believe one of my roles in taking care of the children in these families is to really open the other affected adults, the parents and maybe even in one case we have a grandfather who started therapy as well as his daughter, who's the mother of my patient. So I think part of my role is to really educate them and encourage them to talk to our adult XLH experts in my region.

Dr. Filler:
So I completely agree. I have several kindreds where grandmother and then three children that I treated earlier and then their grandchildren are all on therapy, and the benefits are quite amazing. What is an interesting development, so I work very closely with one adult nephrologist who sees the bulk of the adult patients, is the dosing though. And we are going to talk about transition later, but it seems to be happening at large scale that when the drug was initially introduced, it was in both age groups every four weeks. But then

they figured out that in children it wasn't good enough. And now we have 0.8 to 2.0 milligram per kilo every two weeks for the children. But in adults it's 0.8 to two milligram per kilo every four weeks.

And I know of multiple parents that have been switched to every two weeks with the maximum dose that they can prescribe for four weeks, and they really experience how the pain, especially pre tibial, recurs when they're coming to the end of the dosing interval is the four weeks. So I think there is some work to be done to really tease out what exactly is the best dose. And I think it is probably twofold. One is the sex, the biologic sex. The other one is the severity of the mutation. There is a very interesting paper from China looking at a large cohort comparing C and N terminal mutations. And as you know very well, there are like 770 different mutation. Some of them have a very severe phenotype and some of them have a much milder phenotype. And I think some phenotype genotype correlation also for the dose finding would be very helpful.

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