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Continuing XLH Treatment into Adulthood – Evolving the Treatment Goals

Announcer:
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Dr. Filler:
A good day everyone. My second lecture I was asked to do is entitled, Continuing Treatment Into Adulthood-Evolving the Treatment Goals. I'm a professor of pediatrics, medicine, and pathology and laboratory medicine at the Schulich School of Medicine & Dentistry in London, Ontario, which is between Toronto and Detroit.

So I would like to ask a few questions. The first one is, and I'm really inspired by a lecture by Dr. Leanne Ward, what should be our treatment target? We normally have the consensus that we should aim for a normalization of the alkaline phosphatase, and she shared, and I'm grateful for her sharing her slides, that she had the opportunity to do a bone biopsy on an adolescent. And should we, like we do in IBD or other diseases, aim for complete resolution of osteomalacia, or just for the normalization of the alkaline phosphatase?

This is this patient who had been on treatment for a number of years and he was started at the age of 10, he was actually one of the study patients. He needed an orthopedic surgery, so there was an opportunity for him to have a bone biopsy. And as you can see, he was growing quite nicely along the percentiles. The dose was not totally optimized, he occasionally had low normal cell phosphates, but he did have a normal alkaline phosphatase throughout the time, and he had no pain.

I know that you will not be experts in bone mineral density assessment, but there was, on the biopsy, at the time when he was about four and a half years post-treatment start, and a dose of about one milligram per kilo, that there was still mild active osteomalacia, despite of the neutralization of the FGF23 with burosumab. That raises an interesting question as to what we should have as a treatment target.

The next question that comes right along with that is that there are actually developmental changes in the alkaline phosphatase normal values. And also, this was a male, and I have previously talked about dosing for males as compared to females. I want to remind ourselves about the age dependency of the alkaline phosphatase. As you can see, on the left side are the boys and on the right side are the girls, and alkaline phosphatase is quite high early on in life and then drops to low values around the age five to ten, but then when we have our pubertal growth spurs, we have much higher values. And should we be allowing higher alkaline phosphatase values, where exactly in this chart should we aim at this? I think this is an important question that needs to be addressed, especially in view of the possibility to perhaps achieve complete resolution of the osteomalacia.

So should we then have a higher alkaline phosphatase in puberty as a target, or should we actually not use the chronological age, but actually look at the tunnel staging, so that the highest alkaline phosphatase are aimed for when they are going through the stage three of puberty? These are all unanswered questions that may help us to guide an optimal therapy, and perhaps allow for complete resolution of the osteomalacia.

Then another important open question, this is about the body proportions. This was work that was done with Dr. Živičnjak when I was in Berlin a long time ago, but you have very disproportionate body compositions. The sitting height is maintained, but you have short stature and you have, in particular, very short leg lengths, and we have no data on how burosumab would achieve that. But for the quality of life, the final height is actually a very important one, and it seems that the later you start with the therapy, the less you achieve a normal final height. And over time actually, the body disproportion worsens and you get these normal trunks, but you get these very short femurs and tibia, which may be worsened by bowing.

Then the other important question is, we treat children every two weeks, in the original trials, both pediatric and adult dosing was actually started at Q four weeks, but it came out that that is not working and it was shortened, and I know from a lot of parents that they are on treatment and have been switched to twice a month dosing, not just once a month, the other question is what do we do with the dosing? The dosing is 0.8 to 2 milligrams every two weeks in the pediatric age, but then the same dose is applied every four weeks, and should we not maybe taper the transition? This is a very important question that we have no answer for, right? Also, we need more data on the conversion from adult dosing from every four weeks to two weeks, and that was done because they're having symptoms.

So to summarize, patients could be treated with burosumab from birth, or at least six months of age, until their entire life, and there's some uncertainty about how to convert dosing upon transition into adult care. Questions for future research include, should we normalize the alkaline phosphatase, is that enough, and do we need full normalization of the osteomalacia? And then treatment duration, frequency and age/sex differences need to be studied further. Thank you for your attention.

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