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Individualized Treatment Approaches for Optimal Lifelong Management of Children and Adults with XLH

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

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Dr. Filler:
Good day everyone. My name is Guido Filler. I'm a pediatric nephrologist in London, Ontario, which is between Detroit and Toronto. And I was asked to talk about individualized treatment approaches for optimal lifelong management of children and adults with X-linked hypophosphatemic rickets. Unfortunately I do not treat a lot of adults, so most of this will be on pediatrics.

The first question I want to raise is when to start treatment. Because this is obviously now an innate disease that is heritable, and the problems begin very early in life, but most of the time the diagnosis will only be made when they are one year old and start to weight bear. And one of the points I want to really point to is the dental findings with X-linked hypophosphatemic rickets. You get very characteristic changes, you get a reduced enamel density with normal thickness, you get a reduction of the mean dentin density, and then you get crown and root dentin densities that will be reduced.

And then there's a bad dentin, called the interglobular dentin, which accumulates throughout the dentin, which has been described as a 585-fold volume increase. And they have a lot of dental problems. Perhaps the most prominent findings are these dental abscesses that you can see here. And they're sterile abscesses, but they frequently result in extraction of the teeth. One of my patients will get five teeth removed in the very near future, even though she had been on the modern treatment with Burosumab for three years.

Most of the dentin is being formed in the very early period of life. In Canada, Burosumab is licensed starting at as early as six months, but there are many countries where it's only started at one year of life. And so these dental issues, which were actually quite high in the trial that was initially done, 28 patients had dental abscesses and they were actually significantly more prevalent than conventional therapy, it may well be that dentin formation in the first few months of life is the problem, and is not ameliorated with the virtualization of FGF-23.

Another question is the craniostenosis that these patients often have. And then the other one is the final height. I want to give you an example of a patient whom I started at six months of age. She had no signs of rickets, but as you can see, her growth was already falling behind her biological potential. And then when we started Burosumab we were actually able to get her to her biological target height, which based on the mother, who was not affected, could be as high as the 95th percentile. The father is of course affected and has a low potential. I am really wondering that patients in whom you can make the diagnosis congenitally, they should be started at as early as possible. This patient never had any dental issues so far.

The other question is about sex-based dosing. As you know, this is an X-linked disease, and while females can be as severely affected as males, when you look at siblings or if you look at kindred with the same mutation, then there is the impression that the boys are more severely affected. We therefore conducted a study that was just convenient, because we had five females and five males of

approximately the same age. The median time of starting was about two years of age. We were interested in comparing the sex-based differences in the treatment. They all had normal, except for two patients, vitamin D levels and active vitamin D levels, and they normalized after treatment. But what we noted is that the phosphate levels were lower in the males before starting, and they're age-matched so we don't need to do the Z scores.

The girls on the normal dose of 0.8 milligram per kilo normalized their phosphate after two weeks of dosing, whereas the males did not, and we kept increasing the doses. Also, despite the increase of the doses, the TmP/GFR did not normalize in the males and was significantly lower than in the females. So all males required a dose increase. At the last follow up the males actually had an average dose of 1.68 plus/minus 0.6 milligram per kilo, every two weeks. And they had also a much slower response. We have recently got this accepted for publication, and conclude that males should be started on a higher starting dose of 1.2 milligram per kilo to shorten the time to reach full therapeutic management. Of course, the mutation severity also plays a role, and N and C-terminal mutations have different adjustment.

So to summarize, patients should be treated with Burosumab as early as possible, at least at six months of age, and it should be harmonized. In our world and in our experience males require higher doses. And there is definitely a very important question that is for future research, what are the dental complications of XLH and how can we prevent them? Thank you for your attention.

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