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Advances in Treatment of Hypoparathyroidism: Importance of Genetic Testing for Autosomal Dominant Hypocalcemia Type 1

Dr. Collins:
Hello, everyone. Today we're going to be talking about advances in the treatment of hypoparathyroidism, emphasizing the importance of genetic testing for autosomal dominant hypocalcemia type 1. I'm Michael Collins. I'm a special volunteer and a senior clinical advisor at the National Institutes of Health in Bethesda, Maryland. I'm also a consultant to Calcilytix, and encaleret is currently under clinical development, and its safety and efficacy have not been evaluated by any regulatory authority.

Briefly, our learning objectives today are shown here, and they are to describe the pathophysiology and clinical manifestations of ADH1, including its molecular basis; identify the barriers to early diagnosis of ADH1, including overlapping symptoms with other disorders; and general lack of awareness among many frontline clinicians. I'll emphasize the importance of the role of genetic testing in confirming ADH1, including current testing platforms, access to them, and ethical considerations. We'll also evaluate the latest data on the emerging treatments for ADH1 and their potential to restore mineral homeostasis, reduce renal complications, and discuss the mechanism of action, clinical trial data, and potential benefits.

But first, I'd like to review some calcium physiology that emphasizes the importance of and the precision of maintaining blood calcium levels. First of all, we all know calcium is important for neural function, muscle function, cell signaling. The vast majority of the calcium reservoir is in the skeleton, where there's over a kilogram of calcium, complexed largely with phosphate.

But this is one of the important features shown here. And as you can see, blood calcium levels change very little over the course of the day, and it's important that they be maintained in this very narrow normal range. And the primary way in which that is done is by excursions in parathyroid hormone, which you can see here. So very small excursions in calcium result in large excursions of parathyroid hormone to bring that level back to that narrow normal range. So really, in regards to calcium, parathyroid hormone runs the show.

But if parathyroid hormone runs the show, it's the calcium-sensing receptor that controls PTH and overall calcium homeostasis. And as you can see in this cartoon, the calcium-sensing receptor is significantly expressed in the parathyroid glands and in the renal proximal tubule cells.

So through the action of the calcium-sensing receptor, parathyroid hormone release is controlled. Parathyroid hormone acts directly at the bone to release calcium, to increase blood calcium. Parathyroid hormone from the calcium-sensing receptor regulation also acts at the kidney to promote the conversion of 25D to the active hormone 1,25D, which then stimulates the absorption of calcium from the gut.

Importantly to note here, though, is that the kidney has 2 inputs in regard to calcium regulation—both parathyroid hormone as well as the calcium-sensing receptor itself. So the kidney is really a very important regulator of this with this dual regulation, and you'll see how that comes into play when we talk about ADH1.

A little bit about the calcium-sensing receptor—its regulation, the way it controls the cells is very complex. There are multiple signaling pathways that we won't go into. This large extracellular G-protein coupled receptor binds calcium at multiple sites.

But the important thing about this is shown here in this top panel on the right, and that's the very steep dose-response curve to extracellular calcium that the calcium-sensing receptor induces in the cell. So that with very small changes in extracellular calcium, for example, there's large changes in parathyroid hormone. And that's how we accomplish what's shown in the lower panel, this tight regulation of blood calcium levels.

So to get to ADH1, we first need to talk about the differential diagnosis of hypocalcemia, and an outline of that is shown here. So a patient comes into your clinic, they have a low blood calcium. The first thing you do—one of the first things you do—is check the parathyroid hormone levels. And if the parathyroid hormone levels are elevated or not suppressed, then this is secondary hyperparathyroidism, which is caused by something else.

The next step then is to check the 25D levels. If the 25D levels are very low, this indicates that this is a problem of deficient vitamin D, and it can be caused by all the things shown here: malabsorption, liver disease, and abnormal vitamin D and metabolism. If the vitamin D level is only moderately low, this suggests another path: renal failure, severe hypophosphatemia for tumor lysis syndrome or rhabdomyolysis, alcoholism, or malnutrition. And many of these, of course, will be made apparent through a good history with the patient.

So what we're really most interested in, though, are these low PTH ones. So this is hypoparathyroidism, and the vast majority of these, as you can see, are caused by neck surgery. This is a patient who has had neck surgery, typically for thyroid disease, when the parathyroid glands are inadvertently removed. And this accounts for about 75% of all the cases of hypoparathyroidism. Less common causes are shown here: neck radiation, rarely infiltrative diseases with iron, copper, sarcoid, and sometimes severe hypomagnesemia.

And this brings us to the last category, which would be idiopathic, which are primarily genetic. And within this category, we have DiGeorge syndrome, APECED, and X-linked hypoparathyroidism. But far and away, the most common and the most important in terms of our discussion today is autosomal dominant hypocalcemia type 1, which is due to variants in the calcium-sensing receptor and accounts for about 42% of those that have been identified in this category.

Next, I'd like to discuss, I think, what's an extremely informative case of autosomal dominant hypocalcemia type 1. This is a 50-year-old man who enrolled in the study of encaleret at NIH for the study of ADH1. And he presented in childhood with cramping, paresthesias, and so-called foggy thinking. In fact, at the age of 6, because of learning difficulties, he was evaluated further and found to be hypocalcemic with a low PTH, and he was diagnosed with hypoparathyroidism.

From age 6 onward, he was treated with calcium and active vitamin D—calcitriol. Because of the difficulty in managing this condition this way, he developed nephrocalcinosis at 14, which is shown on this CT scan here, and he had to be hospitalized for hypercalcemia at age 20.

What was one of the most striking features of this patient, though, was his family history. He had had 2 older siblings who died in infancy with hypocalcemic seizures, which, after the fact, were suspected to be that they also had ADH1. And his father was diagnosed with ADH1 at the time that his son was diagnosed. So this is very clearly a family that would have benefited from early genetic testing if it had existed at that time as it does now; we could have seen this family relieved of a lot of heartache and pain over the years.

These are the common options for genetic testing today. The first listed is from the company PreventionGenetics. This focuses on hypoparathyroidism testing. And the beauty of this testing is that it not only tests for all the genes that we know that cause hypoparathyroidism—26 genes—but the fact that this is free to anyone who subscribes to it. The other companies are shown here: Ambry Genetics, Invitae Panel, and Sequencing.com.

So enter the calcium-sensing receptor and the activating variants that cause ADH1. So what they do is essentially trick the body, if you will, to think—in the case of the parathyroid hormone secretion—that the blood calcium is actually higher than it is. So this shuts down parathyroid hormone secretion. In terms of the kidney, it thinks blood calcium is higher than it is, and it promotes calcium excretion into the urine. The net result of this is a decrease in PTH secretion, a decrease in blood calcium, and an increase in urinary calcium

excretion.

The clinical manifestations of this are acutely hypocalcemic seizures, paresthesias, tetany, and muscle cramps. Long-term complications, especially with treatment, are nephrolithiasis, nephrocalcinosis, and even chronic kidney disease. And conventional therapy with calcium and calcitriol does not address the underlying pathophysiology and can, in fact, worsen the renal complications.

Enter calcilytics. Calcilytics are a potential treatment for ADH1. They're negative allosteric modulators—antagonists of the calcium-sensing receptor that decrease calcium-sensing receptor sensitivity to extracellular calcium. They normalize calcium-sensing receptor sensitivity, and they could correct the hypocalcemia, hypercalciuria in the low PTH individuals. And as you can see on the 2 panels on the bottom, they shift the dose-response curve for patients with ADH1 back to normal at both the parathyroid gland and the kidney.

So to test this, we conducted a study with an early generation calcilytic called NPS795 from NPS Pharmaceuticals. And the endpoint of this study was percent change in PTH, so we used an intravenous injection of this calcilytic so we could monitor this very closely. And you can see that with this initial dose, 5 mg given 10 minutes IV, there is a significant increase in parathyroid hormone—percent parathyroid secretion, shown in the top panel, and PTH, shown in the bottom panel. A higher dose over a longer period of time resulted in an even greater increase in parathyroid hormone and an even higher dose showed this here.

However, this was not a large enough increase in parathyroid hormone to change the blood calcium, so the plan had been to proceed forward with this compound in patients with ADH1. But as things happen sometimes in the pharmaceutical industry, NPS Pharmaceuticals was bought by one company, which was bought by another company, and they lost interest in this project.

Enter encaleret. So encaleret is a different calcilytic, and so we conducted a phase 2b study in patients with encaleret, also known by CLTX-305-201. The overall design of the study is shown here. There was a Period 1 where dose was escalated for individuals. Period 2 where the dose was titrated. Period 3, outpatient extension. And I'll show you today the results in the long-term extension trial up to 36 months.

Key study objectives was safety and tolerability, blood and urine calcium, and PTH levels, and there were additional measures as well shown here.

So these are the patients, and they had the very typical profile of patients with ADH1. They had low blood calcium, low parathyroid hormone, relatively high phosphate, and already at baseline most of the patients had significant hypercalciuria, and in fact, 77% of them already had some degree of nephrocalcinosis.

Also of interest, note the specific calcium-sensing variants that are shown on the bottom line there. And this is of interest, and I'll talk about that here in a moment.

I did want to show you this slide, though, for a couple reasons. So this is a cartoon of the calcium-sensing receptor. It has, on this cartoon, pretty much all of the known variants, mutations in the calcium-sensing receptor, the little red arrows and red numbers, letters above that. And it shows us several things.

First of all, it shows what a huge molecule this receptor is. It shows you that the mutations can occur most anywhere along the receptor, but there do appear to be a couple areas where they cluster, and that's where most of our patients are, in those areas where they were clustered. And it raises the question, is there a sort of genotype-phenotype relationship between the response to encaleret or calcilytics, and where the mutation is and what that specific mutation does?

And you would get a hint of that in this slide here, where we see these are the individual doses for all the patients who are in the study. And there's a couple of things to note here. First of all, there's a really wide variation in the amount of drug that an individual needed to maintain the blood calcium levels that we are trying to achieve. So while it was a wide range, it is also evident that once you find the right dose for that patient, they're pretty much good to go, and you can keep them on that dose for a long time.

Not shown here, but I can tell you a little bit about because more work needs to be done with this, is that there did seem to be a relationship between individuals who had the same mutation and the amount of drug they needed to maintain their calcium. We think this is probably the case. As I said, more work has to be done. The other confounder with that is that usually if two patients have the

same mutation, at least in this study, they were members of the same family. So there could be other aspects. But nonetheless, it does appear that there could be a genotype-phenotype relationship in terms of response to encaleret.

So here is the money slide. So this is the response of patients in terms of parathyroid hormone and blood calcium to encaleret. And these data were really spectacular. We were very happy to see this. You can see parathyroid hormone levels were very low. They rose into the normal range and stayed in the normal range for the most part. But look how beautifully blood calcium was maintained right in the middle of the normal range. So very, very successful. This was published in *The New England Journal of Medicine*, and we're very proud of these results.

Encaleret also, importantly, as I said, hypercalciuria can be a big problem, and these patients had high urinary calcium at baseline, but in the patients, urine calcium was returned to the normal range throughout the course of the study. Glomerular filtration rate, kidney function was stable throughout as well. Blood phosphate tended to be on the high side. This came down within the normal range. Blood magnesium was slightly low, and it was maintained during the normal range as well.

It's going to be very important to understand what these drugs that treat hypoparathyroidism do to bone in the long term. Shown here are the results of what encaleret did to bone turnover markers. And the way this slide is displayed is that one represents the upper limit of normal for that patient—whether it's a man or a woman, they're young or they're old—because there's very different normal ranges for bone turnover markers. So this allows us to directly compare the effects of the drug on patients, regardless of their age, sex, and gender.

And so what we see here is the fact that bone turnover markers, as is common in patients with hypoparathyroidism, start out in the low range—low into the normal range. And with treatment, they rise, as you see here, and at some points in time, they're above the upper limit of normal. Towards the end of the study, they're trending back to normal, and they're in the normal range for most patients.

CTX is a bone resorption marker. Lower panel P1NP is a formation marker. And it's pretty much the same pattern was seen for both of these bone turnover markers.

Importantly here is the effect on the skeleton in terms of bone density. Whole-body bone density decreased. Again, patients with hypoparathyroidism tend to have high bone mass. This decreased into the normal range and stayed stable—whole-body—throughout the course of the study. The AP spine was slightly high, decreased significantly, again, right near the upper end of the normal.

The one part of the skeleton that is often most reflective of what can be happening in terms of patients, in terms of putting them at risk, though, is the distal third radius, which is slow shown in the right lower panel. It's the part of the skeleton that is least affected at baseline. It was right about at the normal range with a Z-score of 0, and it did decrease slightly over the course of the study, but again, remained well within the normal range. So that was quite reassuring.

The drug was well tolerated. There were no significant serious adverse events caused by the drug. Most of the adverse events were mild. They corrected with the change in the dose of calcium, and none resulted in discontinuation.

So to summarize the efficacy and safety of the encaleret trial, first, in patients with ADH1, encaleret administered twice daily rapidly corrects and maintains mineral homeostasis within normal range, as demonstrated by an increase in normalization of PTH, correction of hypocalcemia, normalization of the 24-hour urine calcium, and reduction in mean blood phosphate.

In addition, bone turnover markers increased, with some participants above the normal range. Bone mineral density Z-scores decreased at 24 months but remained stable at 36 months. Overall, encaleret was well tolerated over 42 months. Participants continue on long-term encaleret treatment in the long-term extension and phase 3 trial, the so-called CALIBRATE trial.

And I'm excited to present the results, the top-line data from the phase 3 trial of encaleret, CALIBRATE. Encaleret met all prespecified primary and key secondary efficacy endpoints. 76% of the patients achieved both serum and urine calcium within the target ranges compared to 4% on conventional therapy. 91% the patients achieved intact PTH above the lower limit of the reference range compared to 7% of those on conventional therapy.

So to conclude, the summary is there have been advances in the understanding of ADH1 in terms of pathophysiology, natural history,

and prevalence. We know that it's mutations in the calcium-sensing receptor that cause ADH1. Patients have worse outcomes than patients with postsurgical hypoparathyroidism.

And just to give you a sense of the prevalence of this, recent studies have shown it's about twice as prevalent as previously expected. About 6 in 100,000 patients have ADH1. This is similar to the prevalence of ALS, for example, or elbow dislocations.

Calcium-sensing receptors shift the dose-response curve in patients with ADH1 towards normal. And in a phase 3 trial, the encaleret showed promise as a treatment for ADH1.

Summary of the advances in ADH1 diagnosis and treatment. This really, I think, emphasizes if you have a patient who has what is sometimes known as idiopathic hypocalcemia or hypoparathyroidism, or they have a family history of hypoparathyroidism, it's really incumbent upon you to perform genetic testing.

Shown here are 4 companies from which you can get genetic testing done. Only one of these is free, and that's PreventionGenetics. They have a program in which they'll perform testing on a panel of 26 genes to attempt to diagnose the cause. These other companies have ones as well, but those aren't free.

And I'll just show you a poster that was recently presented in regard to this genetic testing program. And what it showed, again, on the right lower panel, you can see some of the genes that were tested. Again, clearly the most common one was the calcium-sensing receptor. These AIRE gene mutations are often evident on a clinical basis as well, but you can see that calcium-sensing receptor is the most common. But then again, there are 54% of the patients, about 1/2 of the patients, no variant was identified.

So there's really still a lot more work that needs to be done in this area. But nonetheless, this represents a significant advance in our understanding and treatment of ADH1. And I thank you for your time.