Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/clinical-practice/endocrinology/expert-answers-to-your-pressing-questions-on-the-calibrate-trial-in-adh1/60605/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Expert Answers to Your Pressing Questions on the CALIBRATE Trial in ADH1

Announcer:
You're listening to GLC on ReachMD. This DataPulse, titled *Expert Answers to Your Pressing Questions on the CALIBRATE Trial in ADH1*, is provided by Global Learning Collaborative.

Dr. Michael Levine:
Hello from ENDO 2026 here in beautiful downtown Chicago. I'm Dr. Michael Levine, and I'm addressing some of the key questions clinicians may have after the oral presentation of the phase 3 CALIBRATE trial. The data generated significant interest in the potential clinical role of encaleret in autosomal dominant hypocalcemia type 1, or ADH1, as we call it. In this video brief, I'll answer some of the most pressing questions regarding what these findings mean for clinical practice, at least the questions that other clinicians ask me.

So the first question might be, what's the potential benefit and side effect of encaleret? Well, encaleret is a negative allosteric modulator of the calcium-sensing receptor and is designed to reverse the activated state of the calcium-sensing receptor. And the activated state of the calcium-sensing receptor leads to a suppression of PTH secretion and failure of the kidney to reabsorb calcium, so leading to hypocalciuria. Using encaleret reverses both of these manifestations of ADH1. In the parathyroid gland, encaleret leads to a more normal functioning of the calcium-sensing receptor, so that PTH secretion is now restored to a more physiologic manner. PTH levels go up, so serum calcium levels go up, and phosphate levels go down because now the kidney is able to excrete the phosphate load.

And what I think is most important for patients with ADH1 is that using encaleret, as opposed to standard of care with an activated form of vitamin D plus supplemental calcium, with encaleret you can actually reduce the urinary calcium excretion and thereby reduce the likelihood of further calcification in the kidney, both nephrocalcinosis and renal stones.

So I think this is a real game changer compared to standard of care, which leads to normalization of serum calcium levels, but even greater excretion of calcium in the urine, placing the patient at greater risk. Using encaleret places us in a completely different set of physiologic circumstances, where now calcium is normal in the serum and calcium is normal in the urine.

I think this leads us to question 2, and what are the long-term implications of using a drug like encaleret on renal complications? Well, as I've already mentioned, urinary calcium excretion will be normalized in patients on encaleret, even as the filtered load of calcium increases because serum calcium levels are greater. What this means, I think, from a very functional point of view, is that the risk of kidney stone formation and nephrocalcinosis is reduced. Now, whether this translates into improved renal function and a decreased risk of other renal complications, such as renal insufficiency, remains to be seen, and we're looking forward to those data with a great deal of interest. But for now, what we do know is that urinary calcium levels go down, and this is very encouraging.

Now, another question is, can we use genetics, and can we use biochemical testing in order to determine the best patient for encaleret? Well, clearly ADH1 patients will be the focus of our prescribing of encaleret. And we can detect these patients easily using genetic testing that will sequence the calcium-sensing receptor. And at this point we don't have enough information about specific mutations to say this patient will respond better than that patient, so once you have identified a calcium-sensing receptor mutation in a patient, that patient becomes a candidate for encaleret. And then one would have to monitor the response, looking at levels of PTH several hours to days after starting the encaleret, and then looking at serum levels of calcium and phosphorus and ultimately urinary calcium levels.

But once you've identified a patient using genetic testing, you can then look at the rest of their family, you're looking for a mutation, the same calcium-sensing receptor mutation, and you can begin to ascertain patients who would be candidates for encaleret.

And I guess that's leading to the next question, which is what's the role of genetic testing? And I think we live today in a world where genetics, if it doesn't determine your destiny, certainly contributes to your destiny, and where you can use it to employ a strategy of precision medicine, it may in fact declare your destiny. In this case, identifying a calcium-sensing receptor mutation enables us to begin to think about using precision medicine, which will provide, I think, a much more physiologic way to address the hypoparathyroidism and hypercalciuria in a patient with ADH1. And I think this use of the genetics to identify the calcium-sensing receptor mutation enables us quickly to go to, what I would say, is the right medication for patients with ADH1, as opposed to continuing with standard of care or considering a PTH analogue, which would not address the renal problem due to the calcium-sensing receptor.

So I think the most important clinical message here is [that] we need to think more broadly about the utilization of genetic testing in patients who have nonsurgical forms of hypoparathyroidism. And when we identify a patient who has a calcium-sensing receptor, I think we should look closely within their family, because this is an autosomal-dominant condition, so first-degree relatives will be at risk of having perhaps a milder form of the same hypoparathyroidism. But once we use these genetic tests to ascertain patients who have calcium-sensing receptor mutations, we can begin to apply the precepts of precision therapy in order to achieve an optimal pharmacological result.

This is Michael Levine at ENDO 2026. Thanks for your attention. See you next time.

Announcer:
You've been listening to GLC on ReachMD. This DataPulse is provided by Global Learning Collaborative. Thank you for listening.