
Getting Back to



NORMAL:

Options for Treating Hypoparathyroidism

Endocrine News talks to Aliya Khan, MD, about the debilitating effects of hypoparathyroidism, new treatment guidelines she helped create, and exciting news from trials that showed promising results that could allow these patients to have a much-improved quality of life, both physically and psychologically.

BY DEREK BAGLEY

Due to his idiopathic hypoparathyroidism, a patient of Khan's couldn't even go swimming or have a driver's license since he was prone to seizures due to having abnormal calcium levels. However, that has all changed since the young man has been a part of the phase 3 PaTHway Trial of palopegteriparatide, an investigational prodrug with sustained release of active parathyroid hormone (PTH [1-34]) administered once daily.

“I wish I had this medicine when I was a kid,” a young patient with hypoparathyroidism tells his endocrinologist, Aliya Khan, MD, FRCP, FACP, professor of clinical medicine at McMaster University in Ontario, Canada, as he participates in a clinical trial investigating a prodrug that replaces parathyroid hormone (PTH). Because of his condition and subsequent treatment, this young man experienced calcium fluctuations so severe that he experienced frequent seizures due to low serum calcium. Because of the seizures, he had difficulty concentrating and was unable to finish school. He couldn't drive; he couldn't even go swimming. He also had recurrent kidney stones and was often hospitalized.

“If you can't drive, you can't get to work or you're dependent on someone else,” Khan says. “If you're having seizures and you don't know when you could have a seizure, that affects your ability to swim or do sports activities that other people take for granted because they know they're not going to have a seizure. He could have a seizure if he was swimming. What if he had a seizure and he died in the pool?”

The young man is participating in the ongoing Phase 3 PaTHway Trial of palopegteriparatide, an investigational prodrug with sustained release of active parathyroid hormone PTH (1-34) administered once daily. Ascendis Pharma is funding the trial of TransCon PTH and marketing the drug as Yorvipath®.

Khan presented 52-week data from the open-label extension period of the trial at the American Society for Bone and Mineral Research (ASBMR)'s 2023 in Vancouver last October, showing that adults with chronic hypoparathyroidism, whose bones tend to be over-mineralized due to insufficient parathyroid hormone-(PTH)-exposure, trended toward a new skeletal steady state closer to age-appropriate norms with continued use of TransCon PTH. The results were consistent regardless of sex, menopausal status, or duration of disease and were consistent with results previously reported through Week 110 in the Phase 2 PaTH Forward Trial.

“When we put him into this study, it was like a new person walked in,” Khan says. “He said, ‘I haven't had to go to the hospital. I haven't had any more seizures. And guess what? I haven't had any more kidney stones.’”

Khan says that the young man has idiopathic hypoparathyroidism, and he has had symptoms since he was a child – basically being unable to function because his calcium levels weren't normal. “Now he's saying, ‘I feel that I missed out on my education, but now that my calcium levels are stable and they're normal, and I don't need to worry



Aliya Khan, MD



Until very recently, many hypoparathyroidism patients were treated with calcium (bottom) and vitamin D (top). However, since that treatment can elevate phosphate levels, it increases the risk of myriad long-term debilitating complications.

about having a seizure, and he's getting his driver's license and he's in university," she says. "It's a life-changing event to be able to restore normal, or as close to normal as possible, parathyroid function that we are able to provide at this time with modern medicine."

Myriad Impacts

Until very recently, patients with hypoparathyroidism were treated with active vitamin D and calcium, but that treatment can increase the risk of long-term complications because it can further elevate phosphate, which can cause calcium and phosphate to deposit in the brain, behind the eyes, and in the kidneys, which can cause nephrocalcinosis, with the whole renal parenchymal calcifying.

Khan says that 95% of participants in this current clinical trial were able to come off of vitamin D, while stabilizing calcium and bone density with palopegteriparatide. "This is really reassuring data, and it's nice to be able to replace PTH, be able to normalize calcium levels, be able to correct the urine calcium, correct the phosphate levels, and improve quality of life," she says. "We've seen significant data showing improvements in quality of life and bring bone remodeling and the bone density values similar to the age-matched and gender-matched norms."

Reflecting on the clinical 52-week data on palopegteriparatide and its potential impact, Khan says, "Treatment with TransCon PTH in this clinical trial showed the positive physiological effects on bone in patients treated for the full year as well as in those switching from placebo after the 26-week blinded period. These results underscore the importance of providing the missing hormone to address the significant impacts of hypoparathyroidism, including decreased bone remodeling leading to a dense, over-mineralized bone structure."

And again, the impacts of hypoparathyroidism — and its treatment — are significant for the patients and their families. Khan says it's important to look at the complications of hypoparathyroidism, because it affects so many systems — vision, kidneys, lungs, heart, even mental health. "All of these need to be evaluated," she says, "Physicians need to look at that, and we need to also ask, 'How is it affecting you? And not just you personally, but your job, your school, your education, your family? What if you've got kids? How are you able to handle your kids?'"

“ I think that we've been able to make an impact on the diagnosis and awareness [of hypoparathyroidism]. Endocrinologists are aware and obviously know how to make the diagnosis, **but primary care physicians may not have considered the possibility that someone's calcium could be low, especially in young people who haven't had any medical problems so far.**”

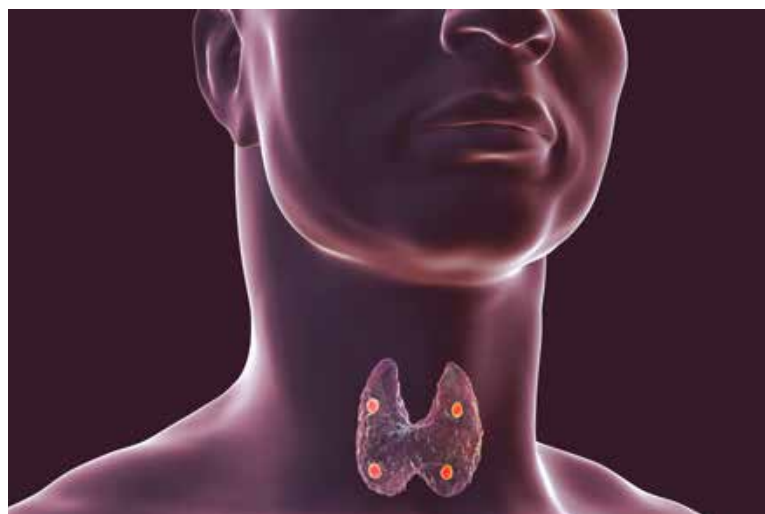
— ALIYA KHAN, MD, FRCP, FACP, PROFESSOR OF CLINICAL MEDICINE, MCMASTER UNIVERSITY, ONTARIO, CANADA

Khan says she treats young mothers with hypoparathyroidism who have just had a baby, and newborns aren't exactly known for sleeping through the night. "It's very difficult," she says "We need to recognize the impact on the person and their family and their whole situation. Look for the multi-system complications, including skeletal complications, renal complications, and neurologic complications, and ensure that we're addressing all of those."

Khan is happy to report that palopegteriparatide has improved patients' mental health as well. "And their social function," she says. "It's definitely making an impact on clarity of thinking, their ability to concentrate, their mood, their functioning. We know that it's not just calcium that's important for brain function. We also know there are PTH receptors in the brain, so if we give back PTH, we're giving back the missing hormone that's affecting brain function and cognition, and those are all critical aspects that need to be addressed."

"Valuable Treatment Options Available"

Khan presented 26-week data from the Phase 3 PaTH Trial at ENDO 2022, as well as Clinical Endocrinology Update (CEU) that same year, with a talk titled "Diagnosis and Management of Hyperparathyroidism & Hypoparathyroidism," in which she



Although relatively rare, hypoparathyroidism occurs when the body produces abnormally low levels of parathyroid hormone (PTH), which regulates the levels of calcium and phosphorus in the body. Khan says it's important to look at the complications of hypoparathyroidism, because it affects so many systems – vision, kidneys, lungs, heart, and mental health.



AT A GLANCE

- ▶ Hypoparathyroidism can be a debilitating disorder, and treatment can increase the risk of long-term complications and is difficult to follow due to the very large number of calcium and active vitamin D pills needed every day.
- ▶ Clinicians are investigating a prodrug that replaces parathyroid hormone in patients with hypoparathyroidism, and the results so far have been promising.
- ▶ Clinicians should be up to date on the latest guidelines, published in late 2022. Conventional treatment remains the first-line therapy, but PTH should be considered if conventional therapy fails.



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pointed to new drug agents like palopegteriparatide as a welcome alternative to conventional therapy, since, again, that treatment can only compound the problem. "We want to improve patients' well-being from day to day, and we can normalize calcium with calcium and active vitamin D, but we're not helping the long-term complications with conventional therapy," she told *Endocrine News* ahead of her CEU presentation. "And if we're making that likelihood of chronic kidney disease earlier and more severe, then we're not really helping our patients."

Khan says that since her presentations in 2022 and 2023, she sees improved awareness among providers, where there might have been some knowledge gaps before. Hypoparathyroidism can be easy to dismiss as anxiety for a physician who might not be up to date with the new recommendations and guidelines. "I think that we've been able to make an impact on the diagnosis and awareness," she says. "Endocrinologists are aware and obviously know how to make the diagnosis, but primary care physicians may not have considered the possibility that someone's calcium could be low, especially in young people who haven't had any medical problems so far."

Khan and her co-authors published the updated guidelines for the evaluation and management of hypoparathyroidism in November and December 2022 — 17 articles across two volumes in *ASBMR's Journal of Bone and Mineral Research*. "We went crazy," she laughs.

The three key highlights from the guidelines are: diagnose the condition as early as possible, understand what the cause is (idiopathic or postsurgical), and treat according to the guidelines. "You can start with conventional therapy and monitor patients closely," she says. "And if you're making changes in their management, make small changes with close follow-up. Don't make big changes and then not see them for three months. They'll end up in the ER. Small changes with closer follow-up."

"And if they're not doing well," Khan continues, "if their calcium levels are fluctuating, their cognition is poor, and they're having complications or kidney stones or decline in renal function, switch to PTH, and don't neglect the fact that we do have valuable treatment options available." 

— BAGLEY IS THE SENIOR EDITOR OF *ENDOCRINE NEWS*. IN THE NOVEMBER ISSUE, HE WROTE ABOUT POTENTIAL PHARMACOLOGICAL OPTIONS FOR PREVENTING DIABETES.