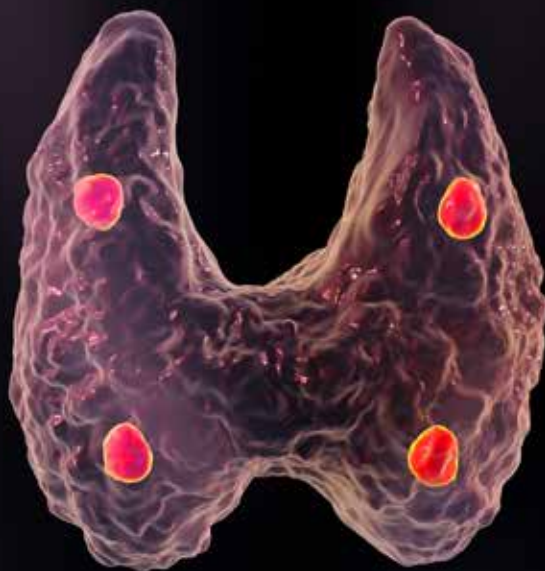


A new pharmacological treatment could provide hope for hypoparathyroidism patients



FOLLOWING UP

Approved a little more than a year ago by the U.S. Food and Drug Administration, palopegteriparatide was lauded by a panel of experts from around the world in a recently published consensus statement on hypoparathyroidism treatment.

Aliya Khan, MD, FRCP, FACP, talks to *Endocrine News* about what this means for these patients' treatment options, quality of life, and other pharmaceuticals on the horizon.

BY DEREK BAGLEY

In August 2022, Aliya Khan, MD, FRCP, FACP, professor of clinical medicine at McMaster University in Ontario, Canada, shared the good news of the molecules that were being investigated and in development to treat hypoparathyroidism — an often-debilitating disease that robs quality of life, impacting both physical and psychological aspects of everyday life. That good news came on the heels of the 2022 Global Hypoparathyroidism Guidelines, which Khan co-authored.

By 2024, Khan was able to share stories of patients who had participated in Phase 3 clinical trials investigating the drug palopegteriparatide: an operating room nurse who had a total thyroidectomy and developed hypoparathyroidism, thoughts so muddled she had to go on disability; a construction worker whose dream was to build houses but was bedridden; a young patient whose calcium was so low he had seizures and was hospitalized time and time again with kidney stones.

On August 12, 2024, the U.S. Food and Drug Administration approved palopegteriparatide for use in adults with hypoparathyroidism. The drug is a sustained release prodrug of active parathyroid hormone (PTH [1-34]) administered once daily. Ascendis Pharma funded the trial and markets the drug as TransCon PTH. The medication is also sold under the brand name Yorvipath.

This past June, Khan and her co-authors published updated recommendations titled “Best Practice Recommendations for the Diagnosis and Management of Hypoparathyroidism” in the journal *Metabolism*. The new recommendations, convened by an international panel of

experts, builds upon the 2022 Global Hypoparathyroidism Guidelines through a structured, consensus-based process. These updates provide practical guidance regarding evaluation and management based on new findings and provide a framework for improving patient care, monitoring protocols, and the use of PTH replacement therapy with palopegteriparatide for chronic hypoparathyroidism.

One surprising result that revealed itself during this guideline-writing process was the improvement in renal function. “The degree of improvement in kidney function was phenomenal,” Khan says. “What we have seen in patients who have been treated with this medication is it’s a life-changing event.”





“It was not expected that this would have such a huge impact on kidney function. And we feel that it’s probably multiple factors. We know that palopegteriparatide drops the urine calcium, **and a high urine calcium is detrimental for kidney function, but we’re also getting these patients off their active vitamin D and their calcium supplements.**”

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

“We felt that we needed to do this because now we actually have an approved drug for hypoparathyroidism, and we wanted to provide information as to when to use it, how to use it, how to start therapy, how to manage therapy,” Khan says.

Lessons Learned

Until fairly 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 again touts the benefits of palopegteriparatide over the conventional therapy mentioned above. She says that patients are able to come off their calcitriol, they’re able to reduce their calcium supplements to 600 milligrams or less, and they’re able to have a significant improvement in quality of life.

One surprising result that revealed itself during this guideline-writing process was the improvement in renal function. “The degree of improvement in kidney function was phenomenal,” Khan says. “What we have seen in patients who have been treated with this medication is it’s a life-changing event.”

Khan says that patients who started palopegteriparatide had improvements in kidney function by five, 10, or even 14 mils per minute. “It was not expected that this would have such a huge impact on kidney function,” she says. “And we feel that it’s probably multiple factors. We know that palopegteriparatide drops the urine calcium, and a high urine calcium is detrimental for kidney function, but we’re also getting these patients off their active vitamin D and their calcium supplements.

“Not only is palopegteriparatide helping them, it also has vasodilatory effects, so it may be helping the kidney, but also getting them off the conventional therapy and is preserving and improving renal function,” Khan continues. “And that was a very important lesson to learn.”

Quality of Life

And of course, quality of life is a huge concern for these patients. After participating in that Phase 3 trial investigating palopegteriparatide, the



operating room nurse returned to work; the construction worker reported that he was building his fifth house; the young patient's kidney stones vanished.

The mental health components of these treatments can't be overlooked. "In the questionnaires, one of them was SF-36, that evaluates overall well-being and function and also the hypoparathyroidism patient experience scale, and what we found was a significant improvement in quality of life," Khan says. "This would also include improvements in anxiety, in symptoms of depression, in overall well-being. This was really a game changer."

Individualized Medicine

The authors of the new recommendations write that they are intended to guide individualized, decision making across diverse patient populations and clinical contexts. "The recommendations address practical clinical concerns including postsurgical risk assessment, genetic evaluation in nonsurgical [hypoparathyroidism], comprehensive management of complications, sick day protocols, dose titration with PTH therapy, transitioning between conventional therapy and PTH, as well as considerations for pregnancy, lactation, and care of children," the authors write.

Khan says that these recommendations were endorsed by 25 international societies — an international working group that represented several major endocrine societies around the world. According to Khan, during a one-day meeting at the Parathyroid Summit, the writing group reviewed and discussed all of the complications of hypoparathyroidism and came up with recommendations for management. "We addressed pregnant women, we addressed children, we addressed adults," Khan says. "We have specific recommendations for children and specific recommendations for pregnant women, because there are changes that happen during pregnancy."

For example, the breast and the placenta produce parathyroid hormone-related protein (PTHrP), which then causes increase in endogenous calcitriol. "Now this pregnant woman has her own PTHrP and 125-D, so her requirements for calcitriol may change, but she also has a developing fetus," Khan says. "The requirements may increase, or they may go down, or they may stay the same. The only way we'll know is if we monitor these people very closely. And we recommend that in a pregnant woman, that we check the lab profile every three to four weeks to make sure that we're keeping that calcium normal."

"Because in pregnancy, if we run the calcium high, the baby's parathyroid glands won't develop," Khan continues. "And if we run the calcium low, then the baby's parathyroid glands become overactive. And so it's important that we run that calcium normal, and it can be a changing target during the woman's pregnancy."

Looking Ahead

Khan and her co-authors also point to emerging therapies to treat hypoparathyroidism. The drug eneboparatide — currently in Phase 3 clinical trials — is also a long-acting PHT, PHTrP analog, and Khan says this molecule has also been shown to be of tremendous benefit in hypoparathyroidism.

For now, Khan says that palopegteriparatide is a major advance in currently available treatments, but the future is looking bright. "We are very enthusiastic that this option is available, and we expect to have other options in addition with eneboparatide. There are other options that will become available over the next five years. But right now, the fact that we can achieve improvements in renal function, quality of life, normalize urine calcium, and serum calcium, and normalize phosphate, it's huge." ^{EN}