

## Authors and Disclosures

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## From Medscape Medical News Enzyme Replacement a Promising Treatment for Children With Hypophosphatasia



Fran Lowry

October 18, 2010 (Toronto, Ontario) — Enzyme replacement therapy using bone-targeted tissue-nonspecific alkaline phosphatase (TNSALP) is a promising treatment for children with hypophosphatasia, according to new research presented here at the American Society for Bone and Mineral Research 2010 Annual Meeting.

Children with hypophosphatasia who were given injections of ENB-40, a bone-targeted human recombinant TNSALP fusion protein, achieved significant improvements in bone health, muscle strength, agility, endurance, and mobility within weeks of beginning treatment, said Michael P. Whyte, MD, from Shriners Hospital for Children, and professor of medicine at Washington University School of Medicine, both in St. Louis, Missouri.

"I have been doing work in this field for 30 years and have tried a variety of things without much success. The results with this new treatment have been extremely gratifying," Dr. Whyte told *Medscape Medical News*.

The moderators of the session and members of the audience were equally enthusiastic after hearing the results of this phase 2 open-label study, which showed that a few weeks after receiving thrice-weekly injections of ENB-40, children who were barely able to walk upstairs were able to climb trees, steal home base, and otherwise act like normal active kids.

"This is a very significant breakthrough in a disease that's been extremely difficult to manage and, in its most severe form, had absolutely no option for even survival for many children," Thomas O. Carpenter, MD, Yale University School of Medicine, New Haven, Connecticut, told *Medscape Medical News*.

Comoderator Laurie K. McCauley, DDS, PhD, from the University of Michigan School of Dentistry in Ann Arbor, was equally enthused. "The study was phenomenal. The results that he showed were quite dramatic. Very compelling results in bone healing, and the mobility in the patients is fantastic," she said in an interview after the presentation.

Hypophosphatasia is a heritable inborn error of metabolism that features paradoxically low serum alkaline phosphatase activity. The condition can occur from earliest infancy, or even manifest as stillbirth, from profound skeletal hypomineralization to osteomalacia presenting late in adult life. So far, there is no established medical treatment.

After successful experiments in TNSALP knockout mice, which showed that daily subcutaneous injections with ENB-40 successfully prevented the skeletal, dental, and neurologic complications of infantile hypophosphatasia, Dr. Whyte and his team of researchers decided to try the enzyme in children.

Eleven children, 5 to 12 years of age, with hypophosphatasia were randomized in an open-label trial to receive either 2 or 3 mg/kg ENB-40 subcutaneously thrice weekly for 6 months.

The primary outcome objective was radiographic skeletal improvement; secondary measures included physical performance on a 6-minute walk test, hand-held dynamometry to test muscle strength, and agility testing.

There were transient dose-dependent injection-site reactions with the higher dose in all of the patients, but these were less prominent and less frequent with the lower dose. There were no serious adverse events and no evidence of ectopic

calcification on renal ultrasound or retinal examination, Dr. Whyte said.

Serum alkaline phosphatase levels were low at baseline, but rose rapidly after the subcutaneous ENB-40 injections and then achieved a steady state. Levels of pyridoxal 5'-phosphate, the principal form of vitamin B<sub>6</sub>, which were significantly elevated at baseline, diminished in all patients by week 6, and remained normal throughout the study period. Inorganic pyrophosphate levels decreased, although they remained detectable. "We believe that this protected against ectopic mineralization, and the reduction was highly significant," Dr. Whyte noted.

In addition, increases in circulating parathyroid hormone from enhanced skeletal mineralization occurred, but no patient developed symptomatic hypocalcemia from hungry bones.

Importantly, all patients showed skeletal radiographic improvement by week 6, and this improvement persisted. All reported increased strength, endurance, and mobility, and some patients improved after a few weeks of ENB-40 treatment.

The average 6-minute walk distance increased from an average of 365 meters at baseline to 490 meters at the end of the study ( $P < .001$ ). "This was an increase of a soccer or football field," Dr. Whyte noted.

Long jump increased from an average of 14 inches at baseline to 33 inches at the end of the study ( $P < .001$ ), and muscle strength also improved significantly for all muscle groups, he said.

"ENB-40 is a promising therapy for these kids. We think there was clear cut radiographic improvement in these patients; walking speed, agility, pain, and disability indices improved, with a high degree of statistical significance. More importantly, their functional improvement was remarkable," Dr. Whyte said.

He added that the study has yielded a number of heartwarming anecdotes. He recounted one of them to *Medscape Medical News*.

"There was a boy who wanted only to be able to make it to first base while playing T-ball before being tagged out. He couldn't really run because of his wobbly gait, but after 3 months of this therapy he improved so much that he became all-county for his T-ball team and ended up representing it at the state level. We've seen parents who were planning to have a disabled, handicapped child for the rest of the child's life and were starting to adapt their homes to accommodate such a child, and suddenly they were very startled to find that they have what is essentially a fully functioning, rambunctious child. Those are the anecdotes that we love to hear, and there are many of them."

*Dr. Whyte reports being a consultant for and receiving research funding from Enobia Pharma, the manufacturers of ENB-40. Dr. Carpenter and Dr. McCauley have disclosed no relevant financial relationships.*

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