Tx May Be First for Severe Hypophosphatasia

BY MIRIAM E. TUCKER

NEW YORK — The investigational bone-targeting enzyme replacement therapy ENB-0040 was associated with significant bone mineralization and clinical improvements at 6 months in five infants with life-threatening hypophosphatasia who were given the compound in a phase II open-label trial.

The 24-week study initially enrolled six patients (five girls) aged 6-36 months at baseline who were all symptomatic early in life, with severe rickets, respiratory insufficiency, hypercalcemia, and nephrocalcinosis. All had a high likelihood of death or significant morbidity. Dosing was 2 mg/kg given once intravenously, followed by subcutaneous doses of 1 mg/kg thrice weekly for 23 months, with the possibility of dose adjustment depending on clinical response.

Marked improvements were seen in the radiographic appearance of rickets in three infants, with increased mineralization, resolution of radiolucencies, physeal narrowing, and less flaring. There were no new fractures. Another infant showed substantial improvement that was not quite as dramatic as the other three. The fifth infant, with profound hypomineralization, had no radiographic improvement, Dr. Michael P. Whyte said at a joint meeting of the Lawson Wilkins Pediatric Endocrine Society / European Society for Pediatric Endocrinology.

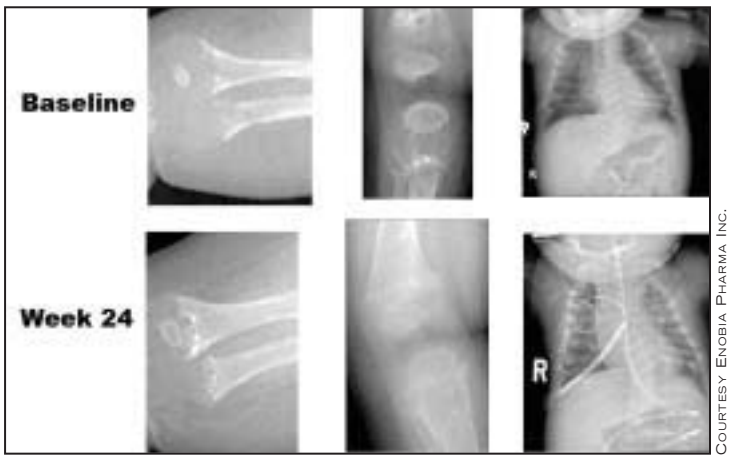
Radiographic evidence of skeletal mineralization was associated with reduced plasma levels of pyridoxal 5´-phosphate and increased levels of parathyroid hormone, which was initially suppressed in all patients. There was a concurrent decline in the calcium to creatinine ratio, "as though bone and mineral were moving into the skeleton, a sign of hungry bones," accompanied by a need to increase dietary calcium, said Dr. Whyte, medical / scientific director of the center for metabolic bone disease and molecular research at Shriners Hospitals for Children, St. Louis.

Evidence of improved growth, including linear growth, head circumference, and growth catch-up appearing in later assessments, was seen in all five patients. Respiratory problems, present in four of the five infants at baseline, improved in three infants after 6 months of therapy. One patient, who had been on continuous positive airway pressure and bilevel positive airway pressure and was on the verge of endotracheal intubation, was able to be treated with just nighttime nasal oxygen after 6 months of ENB-0040. Motor function, assessed by Bayley scores, also improved in all five patients.

There were no drug-related serious adverse events and the subcutaneous doses were well tolerated, with only mild redness and swelling seen at the injection site. There were no clinical signs or symptoms of hypocalcemia or of increased intracranial pressure. No anti–ENB-0040 antibodies developed. One infant was withdrawn after showing signs of distress during treatment, leaving five for subsequent analysis.

There is currently no established treatment for hypophosphatasia (HPP), an inborn error of metabolism resulting from a mutation within a gene that codes for tissue-nonspecific alkaline phosphatase (TNSALP). Mortality among infants less than 6 months of age with the perinatal form of the disease is around 50%, he said.

Manufactured by Montreal-based Enobia Pharma Inc., ENB-0040 is a subcutaneously administered recombinant compound of TNSALP fused to a patented bone-targeting peptide, designed to replace the missing enzyme in HPP patients. It was given an orphan drug designation in the United States and the European Union in 2008 and was granted fast-track status for HPP treatment by the Food and Drug Administration in May 2009, according to the company Web site. Dr. Whyte is a consultant for Enobia Pharma and received grant support for this study. ■



COURTESY ENOBIA PHARMA INC.

X-rays above show response to treatment using a recombinant compound of TNSALP fused to a bone-targeting peptide.

Low Bone Density, Vitamin D Common in Children With CF

BY DOUG BRUNK

SAN DIEGO — Reduced bone mineral density is common in children with cystic fibrosis, and few have normal serum concentrations of vitamin D, based on the results of a multicenter, cross-sectional study of 100 children with cystic fibrosis.

"The most important factors influencing bone mineral density are glucocorticoid use, poor nutrition, hypogonadism, physical inactivity, and malabsorption of vitamin D, [but] the exact pathogenesis of low bone mineral density in patients with cystic fibrosis is still unclear," said lead investigator Dr. Dorota Sands of the department of pediatrics at the Institute of Mother and Child, Warsaw, Poland.

The average age of the patients (51 boys and 49 girls) was 13 years, and all had severe pancreatic insufficiency and were compliant with vitamin supplementation. All patients completed a 3-day dietary questionnaire and underwent standard biochemical blood tests and bone mineral density (BMD) testing with dual-energy x-ray absorptiometry, Dr. Sands reported in a poster session at the annual meeting of the Society for Inherited Metabolic Disorders.

Results of the cross-sectional component of the study revealed that 55 patients had a BMD within the normal range and 45 had a *z* score of –1 or below. The mean body mass index (BMI) for the group was 17.5 kg/m^2. Sixty-five percent of the patients had normal nutritional status, and their mean values of calcium and phosphorus blood concentrations were within normal limits. However, only 13% of patients had a vitamin D blood concentration within normal limits, 21% had high levels of parathyroid hormone, and 77% had osteocalcin levels that exceeded normal limits.

"Only 12% had a sufficient dietetic supply of vitamin D," Dr. Sands added. "Dietetic supply of vitamin D was on a low level, providing on average only 37% of [the] Recommended Daily Allowance [RDA]; 55% of patients did not achieve [the] RDA for calcium intake."

A longitudinal analysis was performed in the 45 study participants who had a *z* score of –1 or below. These patients received an intervention consisting of 0.25 mcg of vitamin D_3 for 1 year. The mean age of this subgroup of patients was 15 years, their mean BMI was 17 kg/m^2, and more than half (24) were female. After 1 year of treatment with vitamin D, the mean *z* scores were –1.87, and in 51% of patients, the *z* scores worsened. Only three patients had a normal BMD score; in 31% the *z* score improved but not to a normal level. Nearly three-quarters of patients (70%) did not achieve the RDA for calcium intake, and the mean values of calcium and phosphorus blood concentration remained within normal limits. The parathyroid hormone level was high in 23% of the patients, and osteocalcin exceeded the normal limit in 67%. The study was supported by the Nutricia Research Foundation. ■

Project Aims to Coordinate Newborn Screening Data

BY DOUG BRUNK

SAN DIEGO — A population-based monitoring program is underway in four states to develop clinical data on metabolic conditions screened at birth using tandem mass spectrometry.

The goal is to develop sustainable, population-based longitudinal monitoring that includes measures of clinical and public health impact, researchers led by Dr. Lorenzo D. Botto reported during a poster session at the annual meeting of the Society for Inherited Metabolic Disorders.

"There are major data gaps on metabolic conditions diagnosed by newborn screenings, [including] few data on clinical and public health impact and long term outcomes," the researchers stated. "To better prevent disease and improve health it is crucial to have a strong evidence base to know what to test, what we find, what to treat, [and] what benefits to expect."

Funded through September 2011 by the Centers for Disease Control and Prevention, the pilot study is assessing how existing birth defect surveillance programs in California, Iowa, New York, and Utah can expand to monitor 19 metabolic disorders identified by the American College of Medical Genetics.

At the meeting, Dr. Botto of the division of medical genetics at the University of Utah, and his associates presented preliminary data from 461,226 babies born in the four states in 2006 on the prevalence of four common conditions: glutaric aciduria type 1 (GA-1), 3-methylcrotonyl-CoA carboxylase deficiency (3-MCC), medium chain acyl-CoA dehydrogenase deficiency (MCAD), and phenylketonuria (PKU).

In 2006, there were 33 cases of 3-MCC (a rate of 7.2 per 100,000 births); 27 cases of PKU (5.9 per 100,000 births); 17 cases of MCAD (3.7 per 100,000 births), and 3 cases of GA-1 (0.7 per 100,000 births). The cases occurred in predominantly non-Hispanic white infants.

The next steps are to collect health, outcomes, and use of medical services data on the 2006 cohort; add the 2007 birth cohort; and, for the combined 2006-2007 cohort, evaluate morbidity, mortality, disability, and health service use through the second year of life.

"Funding challenges persist, even for pilot studies," the researchers noted. "Integrating funding and activities between different public agencies and professional organizations would be very beneficial."

The work is funded by a grant from the CDC's National Center on Birth Defects and Developmental Disabilities. ■