

Abstract/Session Information for Program Number 13

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Session Information

Session Title: 11. Intervention and Treatment of Genetic Disorders **Session Type:** Platform

Session Location: Ballroom C, Level 3, Convention Center **Session Time:** Wed Nov 3, 2010 10:30AM-01:00PM

Abstract Information

Program Number: 13 **Presentation Time:** 11:00AM-11:15AM

Keywords: Therapy for Genetic Disorders, KW010 - BONE/JOINT ABNORMALITIES, KW051 - ENZYME REPLACEMENT THERAPY, KW107 - METABOLIC DISORDER, KW158 - SKELETAL SYSTEM, KW168 - THERAPY

Abstract Content

Life-Threatening Hypophosphatasia in Infants and Young Children: Results of Long-Term Treatment with ENB-0040, a Bone-Targeted, Enzyme Replacement-Therapy (ERT), and An Algorithm For Patient Management. C. R. Greenberg¹, S. Craig², M. McGinn², J. Simmons³, W. Russell³, M. Bauer⁴, N. Bishop⁵, J. Taylor⁶, N. J. Salman⁷, M. A. Hamdan⁷, M. Bober⁸, J. Moore⁹, R. Lutz¹⁰, D. Wenkert¹¹, W. H. McAlister¹², A. M. Skrinar¹³, H. Landy¹³, M. P. Whyte¹¹ 1) Dept Pediatrics & Child Hlth, Children's Hosp, Winnipeg, MB, Canada; 2) Royal Belfast Hospital for Sick Children, Belfast, Northern Ireland; 3) Vanderbilt Children's Hospital, Nashville, TN; 4) Arkansas Children's Hospital, Little Rock, AR; 5) Sheffield Children's Hospital, Sheffield, UK; 6) St. Vincent's Hospital, Green Bay, WI; 7) Tawam Hospital, Al Ain, UAE; 8) A.I. duPont Hospital for Children, Wilmington, DE; 9) St. John's Hospital, Springfield, MO; 10) University of Nebraska Medical Center, Omaha, NE; 11) Shiners Hospital for Children, St. Louis, MO; 12) Mallinckrodt Institute of Radiology, St. Louis, MO; 13) Enobia Pharma, Cambridge, MA.

Background: Hypophosphatasia (HPP) is the heritable rickets/osteomalacia due to inactivating mutation(s) within the gene encoding the tissue nonspecific isoenzyme of alkaline phosphatase (TNSALP). This leads to extracellular accumulation of TNSALP substrates, including inorganic pyrophosphate (PPi), an inhibitor of mineralization, and pyridoxal 5'-phosphate (PLP), a form of vitamin B6. HPP severity ranges from perinatal demise due to respiratory compromise, to only dental problems during adult life. Mortality is high when HPP presents in infancy. Survivors can have rachitic deformity, significant weakness with delayed motor milestones, short stature, respiratory insufficiency, musculoskeletal pain, nephrocalcinosis, craniosynostosis, cranial shaping abnormalities and scoliosis. **Results:** Eleven infants and young children ≤ 3 years of age with life-threatening HPP received ERT using ENB-0040. Ten of 11 pts received from 6 to 18 mos of treatment with ENB-0040, 1-3 mg/kg SC thrice weekly, after a single 2 mg/kg IV dose of ENB-0040. One pt withdrew because of a moderate reaction during the infusion. All 10 pts who continued showed radiographic skeletal improvement. Nine demonstrated substantial to near complete healing of rickets and significant respiratory and/or motor improvement. Growth was largely preserved. Skull mineralization improved, but abnormalities of cranial vault shaping persisted and even progressed. One pt with craniosynostosis developed papilledema and underwent successful craniectomy. One pt, 8 mos into treatment, died of acute respiratory compromise and sepsis thought not to be due to ENB-0040. Baseline hypercalcemia, hypercalciuria, and/or suppressed serum parathyroid hormone levels resolved in parallel with skeletal radiographic improvement and declines in circulating PPi and PLP. Thus, restricted dietary calcium intake was liberalized. Nephrocalcinosis, when present at baseline, did not progress, and there was no evidence of ectopic calcification. An algorithm was developed to guide ENB-0040 dosing and dietary calcium management. **Conclusions:** HPP presenting in infancy is often life-threatening. Long-term ERT with ENB-0040 seems safe and well-tolerated. Improvements in mineralization are maintained and correlate with continued functional improvement. Cranial vault shaping abnormalities have not responded. As with other forms of rickets, treatment optimization of severe HPP requires attention to both pharmacological and mineral management.

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