



FIRST **SCIENTIFIC** MEETING
SUMMARY

www.SoftBones.org

CHICAGO | JUNE 8-10
2018
USA

TO THE SOFT BONES COMMUNITY,

As the mom of a child with a rare disease, I never like to test the odds. The chances of having a child with HPP are very low. And having founded a patient advocacy organization at the same time that a treatment for HPP was in clinical development was also a very rare experience. Today, Soft Bones has chapters in four countries, and we are nearing our tenth anniversary. We also reached a major milestone for both Soft Bones and HPP: hosting a Global Scientific Meeting focused on HPP, an act that was called “unprecedented and historic.” What are the odds?

Our Scientific Advisory Board was up for the challenge. Without hesitation, they stepped in to create an agenda and enthusiastically spent the time and energy to invite colleagues and champion the meeting. Before we knew it, the meeting was a reality. Having completed it, we can now say it was a wild success.

From June 8-10, our first Global Scientific Meeting brought together 50 HPP experts from around the world to talk specifically about the latest findings in HPP. People generously gave of their time to travel to Chicago to share clinical experiences and identify research gaps to improve treatment of patients moving forward. The agenda was very robust and there was much active discussion and engagement throughout the two-day meeting. This publication captures the highlights.

There was much interest and discussion in having another meeting, and Dr. Michael Whyte wondered about this as soon as next year! Now I’m wondering what the odds are that we will be able to raise the funding! But then again, I never test the odds. We are blessed as an HPP community and I am beyond grateful for the support of our Scientific Advisory Board, our Soft Bones staff, and the patient community.

Thank you.

Be well,

Deborah Fowler
Founder and President, Soft Bones

FOREWORD

During June 8-10, 2018 in Chicago, Illinois, USA, a multinational group of 50 clinicians, clinical investigators, and basic scientists gathered with other interested individuals to convene the First Scientific Meeting of the Soft Bones Foundation. They reviewed current understanding and uncertainties concerning hypophosphatasia (HPP) and planned work necessary to improve the lives of people with this inborn error of metabolism. The importance for such a meeting was perceived by Ms. Deborah Fowler, President and Founder of the Soft Bones Foundation, and was brought to success with the help of Ms. Denise Goodbar and Ms. Charlene Waldman and support from Alexion Pharmaceuticals, PANTHERx Specialty Pharmacy, and Charles River Laboratories, Inc. Session moderators Matthew Drake, MD, PhD; Eric Rush, MD; Frank Rauch, MD; Mark Nunes, MD; Katheryn Dahir, MD; Craig Langman, MD; and Susan Ott, MD expertly kept to time the considerable enthusiasm of all attendees.

Graham Russell, MD, PhD gave a historical review of inorganic pyrophosphate, its action as an inhibitor of mineralization, excess in HPP, and early experiences following its modification to become the bisphosphonates. Michael Whyte, MD described the discovery in 1923 of alkaline phosphatase (ALP), the first report in 1948 of HPP, and the many important lessons from investigation of patients, including major insight concerning the pathogenesis of the defective hard tissue mineralization leading to tooth loss and rickets during childhood and osteomalacia during adult life as well as identification of its etiology. The expanded clinical nosology of HPP was validated after using the now-delineated clinical, biochemical, radiological, and histopathological features of this metabolic bone disease.

Stephen Coburn, PhD discussed the derangement of vitamin B6 metabolism leading to extracellular accumulation of the deficient tissue-nonspecific ALP isoenzyme (TNSALP) substrates including pyridoxal 5'-phosphate, and the pathogenesis of the vitamin B6-dependent seizures. José Luis Millan, PhD reviewed the importance of mouse models for HPP, including their role in preclinical studies of asfotase alfa (AA) enzyme-replacement therapy for HPP, and investigation of other molecules that regulate skeletal mineralization. Larry Suva, PhD described the recent development of the first large- animal model (i.e., sheep) for HPP, and the early findings concerning the clinical and biochemical phenotype.

Deborah Kraków, MD discussed the considerable uncertainties with prenatal radiological imaging of HPP, and Deborah Wenkert MD defined and reviewed the management of the not uncommon “benign prenatal” form. Steven Mumm, PhD provided an overview concerning the Mendelian inheritance of HPP, and what can be said concerning genotype/phenotype correlations. Treatment for HPP now includes the benefits from enzyme replacement using AA (Strensiq™), approved multinationally in 2015 typically for pediatric-onset HPP.

Philippe Crine, PhD reviewed the recombinant DNA structuring of AA as a TNSALP targeted to hydroxyapatite. Jill Simmons, MD described the improvements in skeletal mineralization, respiratory and motor function, and growth observed during AA treatment studied initially for the life-threatening perinatal and infantile forms of HPP and followed to seven years of therapy. Nicholas Bishop, MD and Vrinda Saraff, MD reported experience with such patients in the United Kingdom. Keiichi Ozono, MD, PhD presented the Japanese experience with severe pediatric HPP. Then, Gary Gottesman MD provided an overview concerning AA treatment for older children debilitated by HPP, including the problems as well as the benefits.

FOREWORD (cont'd)

Donna Griffin, PT, PCS reported how a modification of the Performance-Oriented Mobility Assessment-gait (mPOMA-G) could assess in real-time baseline and treatment responses of children with HPP. Lothar Seefried, MD discussed the orthopedic complications and management of adults with HPP, including experience with AA treatment. The broad range of HPP severity encountered in this age group was reviewed by Peter Tebben, MD, and Frederick Singer, MD discussed the difficulties with diagnosis and treatment of these individuals. Priya Krishnani, MD outlined the importance of functional testing of adults with HPP, and what improvements have been observed with AA treatment.

Pauline Camacho, MD discussed “off-label” use of parathyroid hormone given to adults with HPP. Mark Rallo, OD discussed occurrences of ectopic calcification on conjunctiva naturally in HPP, and perhaps increased with AA treatment but largely microscopic and asymptomatic. Timothy Wright, MS, DDS reviewed oral and craniofacial issues of HPP, and emphasized how much more must be learned about these complications especially in adults. Brian Foster, PhD discussed the importance of TNSALP in dentoalveolar tissue formation, and the consequences of TNSALP deficiency in HPP. Clifford Rosen, MD reviewed early work concerning a potential role for ALP in fat metabolism, including fat accumulation at sites of AA injection in patients with HPP. Isabel Orriss, PhD provided an overview of skeletal mineralization controlled by TNSALP and pyrophosphate, and other factors.

Progress reports, summarized in their abstracts compiled herein, were provided by the past recipients of research awards from the Soft Bones Foundation: Steven Mumm, PhD; Luke Mortensen, PhD; Brian Foster, PhD; and Kathryn Dahir, MD.

Finally, means to advance the treatment or to cure HPP, including by gene editing, ALP transfection, and mesenchymal stem cell therapy were discussed by José Luis Millan, PhD and Luke Mortensen, PhD.

In this document we provide the highlights of the meeting. The abstracts of the presentations will be published in *JBMR Plus*, so that they can be accessed worldwide.

Michael P. Whyte, MD
Chair, Scientific Advisory Board
Soft Bones Foundation

Executive Summary

On June 8, 2018, a major milestone was reached for the thousands of children and adults who live with hypophosphatasia (HPP). On that day, and for the next two days, the world's scientific experts on HPP gathered, for the first time, specifically to share their knowledge, exchange ideas, and create a platform for going forward with a strategy to tackle the most pressing issues that can improve the quality of life for people living with HPP.

The participants included clinicians involved in patient care, physician-researchers, and basic scientists. They journeyed from three continents. They represented such disciplines as dentistry, orthopedics, rehabilitation medicine, pediatrics, genetics, and internal medicine.

HPP is a rare, inherited “inborn error of metabolism” that can result in impaired bone mineralization. In individuals with HPP, bones may be soft, fracture easily, and heal slowly. With the greatest range of severity of all skeletal diseases, HPP displays signs and symptoms that vary greatly, ranging from very mild to severe and even life-threatening. There's no cure, but patients can be treated. The disease is life-long.

The topics discussed at the First Scientific Meeting spanned the body of knowledge from the earliest characterization of HPP, in 1948, to what we know at present—and what the future may hold. During these past 70 years our understanding of HPP has progressed to discover its etiology, define its principal clinical and laboratory manifestations, and significantly (but not perfectly) understand its pathogenesis.

There's been recent unprecedented growth of knowledge and a growing commitment by many in the scientific community to improve the lives of HPP patients everywhere. A major advance has been the multinational introduction, in 2015, of an enzyme replacement therapy (asfotase alfa), typically for pediatric-onset HPP.

Still, there is much ground to cover, and the mechanism for several complications of HPP remains poorly understood, such as the muscle weakness, scoliosis, and craniosynostosis that affect some children, and the dental problems of many affected adults.

The dynamic, informative meeting was based on 26 abstracts, each with extensive discussion. This document includes the key takeaways of the Soft Bones First Scientific Meeting.

What We Learned

The meeting was packed with interesting and informative scientific information. We have pulled out the top points that we learned, or that we feel need further emphasis. Here they are:

- We still have much to learn about the relationship between HPP genotype and phenotype, and to know if it provides clinically useful information. It has not seemed helpful for closely predicting HPP severity.
- The vitamin B6 story has been confusing for some patients. Further research would be welcomed. Currently, no formal recommendations have been conveyed to patients. Vitamin B6 has been used to treat seizures in life-threatening HPP. Otherwise, some clinicians would see supplementation as a concern. Soft Bones relies on research as a foundation, and does NOT advise patients to supplement with vitamins without conclusions of evidence-based research.
- Sheep may be useful to research HPP gene therapies. Unlike mice, sheep have a set of deciduous teeth and two sets of incisors, providing an opportunity to gauge the effects of treatment. In addition, they also replicate the hypotonia and waddle gait of HPP.
- Suspicion of HPP in utero is helped by examining the hands on ultrasound images. Prenatally, on ultrasound, HPP is often mistaken for OI. In HPP, the hand may not be mineralized, while it is mineralized in OI.
- Lethality cannot be predicted early on from in utero skeletal abnormalities; HPP manifestations are highly variable after birth, and thus the disease is classified based on the presentation of signs and symptoms after birth.
- Long-term treatment—up to 7 years—with asfotase alfa appears to demonstrate continued benefit in patients with perinatal and infantile HPP.
- In Japan, the c.1559delT mutation is the one commonly associated there with severe HPP. It could be the target of gene correction in the near future.
- Over the last 10 years, the plight of severely affected patients with HPP has changed dramatically with the successful testing and, in 2015, the multinational approval of asfotase alfa therapy. Formerly, only supportive measures were the available interventions. Now, asfotase alfa can enable not only survival but also a fulfilling early childhood for severely affected babies.
- New techniques to assess patients' functionality, before and during therapy, have been developed by physical therapists, in St. Louis, to provide a benchmark for how well therapy is working.
- Harboring a single deleterious heterozygous variant in ALPL is relatively common in the general population and explains the prevalence of HPP "carriers", but also underlies adults who manifest signs and symptoms of HPP.
- Uncertainty surrounds what is appropriate for an asymptomatic adult, with genetic or biochemical evidence of HPP, who may have low bone density, because osteoporosis is much more common than HPP and might benefit from certain medications that would potentially be contraindicated in HPP. This is an area that warrants further study.
- Regarding orodental health, critical gaps in knowledge remain, including that no study has correlated HPP dental complications with musculoskeletal, biochemical, or genetic findings.
- We still do not know the cause of fat deposition at injection sites in patients taking asfotase alfa.
- In exploring future HPP therapies, one exciting area of research is a single-injection, life-long treatment, explored in mice. It creates an alkaline phosphatase replacement therapy manufactured within the host's own body.

KEY TAKEAWAYS FROM PRESENTATIONS

Overview of Hypophosphatasia

Inorganic Pyrophosphate: Nature's Water Softener

R. Graham G. Russell, MD, PhD, FRCP, FRS

The Mellanby Centre, Sheffield University, and the Botnar Research Centre
Oxford University, UK

- Role of inorganic pyrophosphate in HPP uncovered in scientific research journey beginning in 1965, with fruition coming from the first treatment of HPP reported in 2012
- 1966: Inorganic pyrophosphate (PPi) was discovered as a key regulator of biological calcification
 - Seminal paper: Fleisch H, Russell RGG, Straumann, F. Effect of pyrophosphate on hydroxyapatite and its implications in calcium homeostasis. *Nature*. 1966;212:901-903
- 1965: HPP identified as first of the pyrophosphate diseases
 - Russell RGG, Excretion of the inorganic pyrophosphate in hypophosphatasia. *Lancet*. 1965;ii:461-464
- This established the notion that alkaline phosphatase (ALP) was an important enzyme in regulating extracellular pyrophosphate levels
- Mineralization abnormalities caused by single-gene defect affecting PPi:
- Led to eventual findings:
 - Pyrophosphate (PPi) clearance is reduced in HPP
 - PPi affects bone mineralization
 - Treatment of HPP using enzyme replacement with alkaline phosphatase, verifies TNSALP's role in mineralization: Whyte MP, Greenberg CR, Salman NJ, et al. Enzyme Replacement in Life-Threatening Hypophosphatasia. *N Engl J Med*. 2012;366:904

KEY TAKEAWAYS FROM PRESENTATIONS

Overview of Hypophosphatasia

What Patients With Hypophosphatasia Revealed About the Alkaline Phosphatase They Need

Michael P. Whyte, MD

Center for Metabolic Bone Disease and Molecular Research, Shriners Hospital for Children, and Division of Bone and Mineral Diseases, Dept of Internal Medicine, Washington University School of Medicine, St. Louis, MO, USA

- Physiological role of alkaline phosphatase (ALP) revealed through hypophosphatasia
- P_{Pi} – pyrophosphate—the biochemical villain in HPP
- 1948, JC Rathbun coined “hypophosphatasia” to describe the lethal rickets and epilepsy of an infant paradoxically lacking serum and skeletal ALP activity
 - Characterized in this paper—Rathbun JC. Hypophosphatasia: A new developmental anomaly. *Amer J Diseases Children*. 1948; 75:822-31
- Later autopsy studies show global deficiency of TNSALP activity
- Years later, mutation analysis confirmed that all HPP patients carry one or two defective ALPL (TNSALP) alleles. This finding verified, after its discovery in 1923, that ALP acts in bone mineralization
- ALP is one of the extensively investigated enzymes, and the most frequently assayed
- ALP can be tissue-specific or tissue-nonspecific
- HPP: Greatest range of severity of all skeletal diseases
- Last type of rickets/osteomalacia to have a medical treatment
- Clinical forms in decreasing degree of severity: Perinatal, Infantile, Childhood, Adult, Odonto
- Severe: Autosomal Recessive
- Mild: Autosomal Dominant or Autosomal Recessive
- HPP patients are hyperphosphatemic—high phosphate—due to enhanced kidney reclamation of phosphate

KEY TAKEAWAYS FROM PRESENTATIONS

Overview of Hypophosphatasia

Vitamin B6 and Hypophosphatasia

Stephen Coburn, PhD

Indiana University – Purdue University

Fort Wayne, IN, USA

- Plasma concentrations of pyridoxal (PL), a form of vitamin B6, and 4-pyridoxic acid, a product of and marker for B6 typically, remain normal in HPP
- In HPP, vitamin B6 (pyridoxal 5'-phosphate) is high but PL pyridoxal and 4 pyridoxic acid remain normal. In HPP, no other vitamin B is known to be affected
- Role of vitamin B6 remains under study
 - Developing a physiologically based pharmacokinetic model of vitamin B6 metabolism which hopefully will provide additional insights into vitamin B6 metabolism in normal and pathological conditions
- Vitamin B6 is still an area that needs further research

Hypophosphatasia - Lessons From Mice

Stephen Coburn, PhD

José Luis Millán, PhD, Sanford Burnham Prebys Medical Discovery Institute

La Jolla, CA, USA

- Rationale for the current therapeutic intervention for pediatric-onset HPP arises from an understanding of pathophysiology
 - Mouse studies show that HPP skeletal and dental manifestations are primarily caused by accumulation of extracellular inorganic pyrophosphate (PPi), a physiological substrate of TNAP and a potent inhibitor of mineralization
 - Phosphorylated osteopontin (OPN), another potent inhibitor of mineralization, also accumulates, further impairing mineralization
 - Disturbances in purinergic signaling caused by an increased ATP/adenosine ratio underlie the pathophysiology of pain and seizures in murine HPP
 - Accumulation of ATP and LPS may contribute to the pathophysiology of nephrocalcinosis in murine HPP
 - Phospho1*, *ENPP1* and *OPN* are modifiers of the HPP phenotype in mice

KEY TAKEAWAYS FROM PRESENTATIONS

Overview of Hypophosphatasia

Lessons to be Learned From New and Improved Models of Human Hypophosphatasia in Sheep

Larry Suva, PhD

University of Texas A&M

College Station, TX, USA

- Created a large-animal model of HPP (sheep) to study the disease
- Sheep are a helpful model because, unlike mice, bone and tooth remodeling are analogous to that in humans
- HPP modeled in sheep using CRISPR/Cas9 technology, which changes genes within an organism. HPP mutation-specific replacements were inserted into the sheep genome to develop this large-animal model that has the bone and tooth features of HPP
- Because sheep have deciduous teeth including two pairs of permanent incisors, researchers can study effects of treatment on all these sets of teeth
- Unpredicted bonus: HPP sheep also replicate the hypotonia and waddling gait of patients and need ankle-foot orthoses (AFO) to walk. The sheep measure decreased muscle tone and the waddling gait on enzyme replacement therapy. All improved as in human infants
- Additional findings from the sheep model
 - Highly disordered mitochondria observed in muscle biopsies (misshapen with disordered cristae)
 - To examine the mitochondrial effects of the ALPL mutations, semen is a convenient cell type to measure the effects on mitochondria and consequences of impaired energy metabolism. It is a proxy for understanding what might be wrong in the muscle. Sperm viability and mobility are low, consistent with impaired energy metabolism

KEY TAKEAWAYS FROM PRESENTATIONS

In Utero HPP

Hypophosphatasia and Prenatal Diagnosis

Deborah Krakow, MD

Department of Obstetrics and Gynecology, Human Genetics and Orthopaedic Surgery

David Geffen School of Medicine at UCLA

Los Angeles, CA, USA

- Skeleton: Second-largest organ after skin; thus a target for many disorders
- Obstetricians lack exposure to these bone diseases, although often recognized on prenatal ultrasound
- Carrier frequency of HPP=1/150
- Skeletal dysplasias account for 0.15 percent of all birth defects and are a heterogeneous group of more than 450 distinct disorders; many present prenatally
- HPP is one of them
- Can be passed on through recessive or dominant form of heredity
- Perinatal form of HPP is severe, often lethal
- Now that we have treatment, genetic counseling has to change
- HPP often mistaken for OI; differentiation: OI hand is normally mineralized; severe HPP, no hand mineralization. HPP can often be diagnosed in utero by examining hands for lack of mineralization
- Goal: to identify at-risk families, identify fetuses that may benefit from early post-natal treatment

Bent But Not Broken (Benign Prenatal) Hypophosphatasia

Deborah Wenkert, MD,

Wenkert & Young, LLC and Shriners Hospital for Children

St. Louis, MO, USA

- Benign prenatal HPP
- 5-10% of all pediatric HPP
- Typically improves during third trimester (when placental ALP rises and ALP substrates in a carrier-mother fall), as well as ex utero after birth
- In utero skeletal abnormalities do not necessarily signal lethal HPP; lethality cannot be predicted from in utero manifestations
- Highly variable after birth, and thus the disease type should be reclassified based on signs and manifestations after birth

KEY TAKEAWAYS FROM PRESENTATIONS

In Utero HPP

ALPL Genotype/Phenotype Correlations in Hypophosphatasia

Steven Mumm, PhD

Division of Bone and Mineral Diseases, Department of Internal Medicine,
Washington University School of Medicine at Barnes-Jewish Hospital USA
and Center for Metabolic Bone Disease and Molecular Research,
Shriners Hospital for Children St. Louis, MO, USA

- There is still much we do not know about the relationship between genotype and phenotype
- Extraordinarily broad range of severity—from early tooth loss without skeletal disease to complete lack of skeletal mineralization—is now being largely explained by the number and nature of the ALPL mutations
 - Cause of HPP is loss-of-function mutations in ALPL, the gene encoding the tissue- nonspecific isoenzyme of alkaline phosphatase (TNSALP)
- 355 different mutations have been reported
- The relationship between the particular genetic mutation and the various manifestations of HPP is an active area of research
- Focusing on the two common dominant American mutations (Asp378Val and Asn417Ser)
- Most common dominant mutation (Asp378Val) in U.S. usually shows mild phenotype when inherited singly, but severe when accompanied by second defect
- Common recessive defects (Glu191Lys, Ala176Thr, Asp294Ala, respectively) show increasing disease severity, semi-independently of second mutation
- Phenotype of untreated HPP generally remains stable throughout childhood, but sometimes appears to progress throughout adulthood

KEY TAKEAWAYS FROM PRESENTATIONS

Treatment of HPP Babies

Improvements in Skeletal Mineralization, Respiratory and Motor Function, and Growth during Seven years of Treatment of Perinatal and Infantile Hypophosphatasia

Jill Simmons, MD

Vanderbilt University Medical Center

Nashville, TN, USA

- Asfotase alfa (Strensiq): FDA approval in the US and elsewhere in October 2015
 - First-in-class bone-targeted enzyme replacement therapy for HPP
 - This was a seven-year, open-label study with 11 patients (Whyte et al, *The Lancet Diabetes and Endocrinology* (in press, 2018))
- Results: Improved survival, skeletal manifestations, respiratory function, growth, and motor function in infants and young children with life-threatening HPP
- Patients with severe perinatal/infantile HPP treated with asfotase alfa for up to 7 years demonstrated
- Early and sustained improvements in skeletal mineralization
 - Improvements in respiratory function, growth, cognitive and motor function
 - Early access likely important for improved outcomes
 - Long-term treatment up to 9.5 years appears to demonstrate continued benefit in patients with perinatal and infantile HPP
 - One-year findings published as: Whyte MP, Greenberg CR, Salman NJ. Enzyme-Replacement Therapy in Life-Threatening Hypophosphatasia. *N Engl J Med.* 2012;366:904-913.
<https://www.nejm.org/doi/full/10.1056/NEJMoa1106173>

KEY TAKEAWAYS FROM PRESENTATIONS

Treatment of HPP Babies

Asfotase alfa, a Bioengineered Form of Tissue Non-specific Alkaline Phosphatase Targeted to Bone

Philippe Crine, PhD

Chief Operating Officer, PreciThera Inc.

Montreal, QC, Canada

- Asfotase alfa is a bone-targeted, bioengineered form of tissue non-specific alkaline phosphatase (TNSALP)
- Marketed at Strensiq™, commercialized by Alexion
- How it came about:
 - Enobia Pharma Inc. – founded company in 2003
 - Cloned an enzyme involved in bone mineralization; when inactivated, it caused XLH; goal was to reintroduce the enzyme back into the bone – unsuccessful
- However, same technique and approach for TNSALP proved to be of great benefit to HPP patients

Hypophosphatasia Infants—the United Kingdom Experience

Nick Bishop, MB ChB MRCP, MD, FRCPCHh, FMedSc; Vrinda Saraff, MD

University of Sheffield and Sheffield Children’s Hospital On behalf of the NHSE

Sheffield, UK

Highly Specialised Service for Hypophosphatasia with contributions from Wolfgang Hogler (Birmingham), Raja Padidela (Manchester) and Paul Arundel (Sheffield)

- 15 patients, at three centers, with perinatal or infantile onset HPP have been managed with asfotase alfa treatment in UK
- Lessons learned:
 - Early diagnosis and treatment in infants essential to prevent respiratory deterioration
 - Quality-of-life outcomes very important at early stage because payers are reluctant to fund without these data

KEY TAKEAWAYS FROM PRESENTATIONS

Treatment of HPP Babies

Perinatal and Infantile Hypophosphatasia: The Japanese Experience

Keiichi Ozono, MD, PhD

Osaka University Graduate School of Medicine Taichi Kitaoka

Takuo Kubota, Japan

- Phenotype of HPP varies and is usually classified into six forms based on age at onset and severity of clinical features: perinatal, benign pre-natal, infantile, childhood, adult, and odonto
- In Japan, two mutations causing HPP (c.1559delT and p.F327L) are common and associated with a perinatal severe and a mild type, respectively
- Clinical trial to evaluate safety and efficacy of asfotase alfa
 - 13 patients ages 0 days to 34 years at baseline were enrolled and treated
- The clinical trial revealed improvement of skeletal and respiratory manifestations, adding support to the safety and efficacy of AA therapy for HPP patients
 - The number of patients with HPP who are surviving with no respiratory support is increased by treatment with asfotase alfa
 - Guidelines on the management of HPP are necessary in the new era of enzyme replacement therapy
 - Because c.1559delT is common and associated with severe HPP, it may be the target of gene correction in the near future. ALP activity may be restored by gene correction
- Since AA therapy was approved, in Japan in July 2015, more than 50 patients have been treated

KEY TAKEAWAYS FROM PRESENTATIONS

Treatment of HPP Children

Asfotase Alfa Therapy for Children With Hypophosphatasia: The Good, The Bad, and The Unsightly

Gary S. Gottesman, MD, FAAP, FACMG

Center for Metabolic Bone Disease and Molecular Research

Shriners Hospital for Children

St. Louis, MO, USA

- Over the last 10 years, the plight of severely affected patients with HPP has changed dramatically with the availability of asfotase alfa therapy
- Formerly, supportive measures were the only interventions
- AA can enable not only survival but also a fulfilling childhood for even the most severely affected babies
- Shriners Hospital for Children, St. Louis has cared for 281 children with HPP during the last 35 years, and studied an even greater number of family members
- We have treated 25 children with HPP using AA. Thus, a broadening appreciation has been acquired of the response to AA therapy, factors that may interfere, sibling variation in response to treatment, and soft tissues changes with uncertain pathogenesis. Rapid improvement of the radiographic skeletal changes continues in concert with improved functional capabilities
- Early intervention is important
- Nuances of selecting appropriate patients for AA, monitoring their response to therapy, and modifying treatment accordingly requires ongoing assessment and awareness and expertise concerning these clinical issues

The Modified Performance-Oriented Mobility Assessment-Gait (mPOMA-G) is a Real Time Assessment of Gait in Children with Hypophosphatasia

Donna Griffin, PT, PCS

Rehabilitation Services Shriners Hospital for Children

St. Louis St. Louis, MO, USA

- Shriners Hospital for Children, St. Louis, USA administers a physical therapy protocol for children with HPP that evaluates their range of motion, strength, endurance, development, and gait
- The HPP researchers here modified the Performance-Oriented Mobility Assessment-gait subset (POMA-G)—a standard tool used to assess gait impairments in adults—for use for patients with HPP
- By validating the modified scale for HPP, it was determined that the mPOMA-G can be applied in real time for patients with HPP to provide objective and qualitative gait data for supporting the initiation and continued treatment of HPP

KEY TAKEAWAYS FROM PRESENTATIONS

HPP Adults

Orthopedic Management of Adult Hypophosphatasia

Lothar Seefried, MD
University of Würzburg
Würzburg, Germany

- Orthopedic surgery to correct deformities in HPP patients should be considered cautiously; can be performed with benefit with thoughtful indication and diligent planning at experienced centers
- Preliminary experience suggests that asfotase alfa can enhance fracture consolidation and even supersede the need for surgery in certain settings
- Osteoarthritis is sometimes seen in HPP patients even at a young age
- To correct skeletal deformities, conservative options like physiotherapy and orthoses/braces should be considered first before planning corrective surgery
- If corrective surgery is to be performed, minimally invasive procedures with limited soft-tissue damage and/or without the need for osteotomies could provide helpful alternatives
- Soft tissue surgery in HPP can be necessary, specifically in otherwise treatment refractory situations in order to remove heterotopic calcifications, particularly at the shoulder in the rotator cuff
- Arthroscopic approaches, avoiding additional soft tissue damage, can yield rewarding results
- Where osteoarthritis has taken hold, joint replacements may be necessary

Hypophosphatasia in Adults: The Broad Range of Severity

Peter Tebben, MD
Mayo Clinic College of Medicine Departments of Internal Medicine and Pediatrics Division of Endocrinology
Rochester, MN, USA

- Although perinatal and infantile HPP are rare, harboring a deleterious heterozygous variant in ALPL is relatively common
- Given limited data on treatment efficacy in adults, it is challenging to identify an appropriate threshold for treatment across the disease severity spectrum in adults
- Among adults diagnosed with HPP, expression of disease is variable. HPP diagnosed during adulthood encompasses:
 - those with unrecognized childhood HPP (adults diagnosed with HPP who have a history of bone pain, rickets, or abnormal gait and weakness during childhood should be classified as having childhood onset HPP
 - Those who are truly asymptomatic until 18 years of age or later

KEY TAKEAWAYS FROM PRESENTATIONS

HPP Adults

Difficulties With Diagnosis and Treatment of Adults With Hypophosphatasia

Frederick R. Singer, MD

John Wayne Cancer Institute at Providence Saint Johns Health Center, and David Geffen School of Medicine at UCLA Santa Monica
Los Angeles, CA, USA

- Diagnosis of HPP in adults is more difficult than in children
 - Adults may have few or no signs and symptoms
 - Clinicians may pay little attention to serum alkaline phosphatase levels
 - Low ALP may be a finding in many other medical conditions
- Genetic testing would be the most definitive means of defining HPP, but a positive result does not establish the presence of disease
- It can be difficult to determine what treatment should be offered an asymptomatic adult
- Uncertainty surrounds what to do with an asymptomatic adult who may have low bone density. This situation warrants clinical trials

Off-Label Use of Teriparatide for Hypophosphatasia

Pauline M. Camacho, MD, FACE

Loyola University Medical Center, Loyola University Osteoporosis and Metabolic Bone Disease Center
Chicago, IL, USA

- Several reports of “off-label” use of teriparatide for HPP were published before the availability of asfotase alfa
- In this study, adults with HPP ages 50 to 75 years were treated with teriparatide for 18 to 34 months
- Teriparatide led to clinical improvement, with decreased pain as early as six weeks of therapy, and healing of fractures by 4 to 16 months
- Teriparatide showed clinical and biochemical improvements in adults with HPP
 - Changes were not sustained after discontinuation of the drug
 - Teriparatide cannot be taken long-term

KEY TAKEAWAYS FROM PRESENTATIONS

HPP Adults

Functional Testing in Adults with Hypophosphatasia (What Responds?)

Priya S. Kishnani, MD

Division of Medical Genetics, Department of Pediatrics

Duke University Medical Center

Durham, NC, USA

- There are gaps and challenges in the data concerning how well adults function in HPP
- This is a review of data concerning functional measures in HPP
- Physical therapy assessments can document using quantitative parameters endurance, muscle strength, pain level, and functional deficits
- Scorings are integral to managing disease progression and treatment response
- Adults with HPP can have a varied yet significant burden of disease that compounds over time, affecting daily function
- Functional deficits can be a significant cause of reduced quality of life
- Functional measures are an objective and quantitative method of tracking functional abilities of pediatric and adult patients with HPP prior to, and during treatment
- Functional measures provide “real world” data over time
- —Further characterize disease burden and progression
- —Monitor response to treatment
- —Help reinforce improvements in function and quality of life for the patient and insurance companies

KEY TAKEAWAYS FROM PRESENTATIONS

Complications (Pathogenesis and Management)

Hypophosphatasia and Ectopic Calcification: Ocular Findings From the Enobia Study

Mark S. Rallo, OD

Washington University Department of Ophthalmology

St. Louis Children's Hospital Eye Center

St. Louis, MO, USA

- HPP can cause ectopic calcification of the eyes
- Enobia Pharmaceuticals, Montreal, Canada, studied asfotase alfa for HPP including assessment for any ocular complications, in 21 patients ages 3 to 16 at St. Louis Children's Hospital
 - All 21 patients were placed on treatment
 - One aspect of this study involved the observation and monitoring of abnormal calcium deposition in the eye
- It is possible that treatment with AA can cause ectopic calcification of the eyes, but it is inconclusive. Further study is needed, although it must be noted that ectopic calcification has not posed any issues with vision

Hypophosphatasia: Oral and Craniofacial Issues

Tim Wright MS, DDS

University Of North Carolina Chapel Hill, School of Dentistry

Chapel Hill, NC, USA

- Dental and craniofacial manifestations of HPP can include premature loss of primary teeth (before 5 years of age), early loss of permanent teeth, and abnormal craniofacial morphology
- Early tooth loss is considered a critical diagnostic feature for the early identification of HPP

Dental professionals are front-line diagnosticians for HPP
- Treatment to prevent dental caries and periodontal involvement should be optimized for all HPP patients
- There is need for detailed phenotyping of the oral and craniofacial manifestations of individuals diagnosed with HPP

KEY TAKEAWAYS FROM PRESENTATIONS

Complications (Pathogenesis and Management)

Hypophosphatasia and the Functional Importance of Tissue-nonspecific Alkaline Phosphatase in Dentoalveolar Tissues

Brian Foster, PhD
The Ohio State University
Columbus, OH, USA

- Studies of teeth from individuals with different forms of HPP were performed in parallel with development of novel mouse models of HPP for studies of enzyme replacement therapy
- Dental defects in HPP cause lifelong difficulties, the most common being premature tooth loss due to reduced cementum
- Despite these recognized negative effects on orodental health, critical gaps in knowledge remain, including that no study has correlated HPP dental phenotypes with musculoskeletal, biochemical, or genetic findings
- Now, effective enzyme replacement therapy for HPP is available in the U.S., Canada, Europe, and Japan. Nevertheless, the efficacy of asfotase alfa treatment on repairing dentoalveolar tissues remains poorly defined
- Analysis of HPP dental tissue mineralization will clarify the mechanisms and provide insights for therapeutic interventions
 - A new mouse model provides an improved and longer-lived way for studying dental developmental defects and timing of ERT

KEY TAKEAWAYS FROM PRESENTATIONS

Complications (Pathogenesis and Management)

Asfotase Alfa Injection Site Fat: But Elsewhere?

Clifford Rosen, MD

Maine Medical Center Research Institute

Scarborough, ME, USA

- Asfotase alfa has led to remarkable treatment effects in the skeleton
- However, fat deposition at injection sites is a common side effect
 - Cause has not been elucidated
- Several relevant observations could provide potential insights
- Further studies will be needed in mice, and humans in particular, to determine if this side effect expands the therapeutic potential of asfotase alfa

Regulation of Skeletal Mineralisation by ATP, NPP1 and PPI

Isabel R Orriss, PhD

Dept of Comparative Biomedical Sciences, Royal Veterinary College

London, UK

- This basic science was presented concerning the regulation of bone mineralization
- Role of PPI in controlling bone mineralization
 - Inhibitor of mineralization
 - Why we otherwise need inhibitors
- All bone cells release ATP constitutively
- ATP is an extracellular signaling molecule
- ATP is very rapidly broken down
- There is some evidence that PPI has direct effects on bone cells

KEY TAKEAWAYS FROM PRESENTATIONS

Prospects For New Treatments and Cure

What Might a Second Generation Enzyme Replacement for HPP Look Like?

José Luis Millán, PhD

Sanford Burnham Prebys Medical Discovery Institute

La Jolla, CA, USA

- Concern about asfotase alfa (AA) treatment includes its mineral-seeking properties. Mineral-targeted AA may not only bind to the skeleton and teeth, but also to sites of medial vascular calcification in adult HPP patients with diabetes or kidney disease—or in patients with pediatric-onset HPP undergoing life-long AA treatment
- Recently, a non-targeted chimeric alkaline phosphatase ChimAP, (aka: RecAP) entered clinical trials for the treatment of acute kidney injury
- ChimAP might be explored as an alternative for patients in whom AA becomes contraindicated
- Exploring different treatment options to reduce frequency of injections
 - One study looked at a single-injection therapy in mice that treats them for life, as it creates a biologic replacement therapy manufactured within the host's own body—an in vivo therapy in which the body produces the recombinant enzyme

Mesenchymal Stem Cell Therapy for Hypophosphatasia

Luke J. Mortensen, PhD

Regenerative Bioscience Center, School of Chemical, Materials and Biomedical Engineering

University of Georgia

Athens, GA, USA

- A type of stem cell called “bone-forming mesenchymal stem cell” (MSC) is a promising therapeutic approach to prevent or ameliorate HPP
- Asfotase alfa has begun to save the lives of severe HPP sufferers, and to improve the quality of life for patients with more mild forms of the disease
- However, asfotase alfa is expensive and must be injected multiple times a week for sustained therapy, with symptoms reemerging if treatment is stopped
- Therefore, work has continued to find alternate therapies for long-term correction of the mineralization and craniofacial defects of HPP
- MSCs hold great promise for treatment of bone-related disorders
- Future work with MSCs could provide new insights into mechanisms of cell therapy and could potentially lead to a safe and effective treatment for HPP

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