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HYPOPHOSPHATASIA AND X-LINKED HYPOPHOSPHATEMIA

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Key Points

- Hypophosphatasia is a rare, inherited metabolic disorder in which patients have deficient tissue nonspecific alkaline phosphatase (TNAP) enzymatic activity. Oral manifestations characteristic of various forms of hypophosphatasia can include early loss of deciduous teeth, severe dental caries, and alveolar bone loss.
- In its severest forms (occurring in 1 in 100,000 live births), hypophosphatasia is associated with impaired bone/tooth mineralization and rickets-like symptoms, seizures, and failure to thrive; based on historical data, patients with severe, early onset (i.e., younger than 6 months) forms of the disorder have a high 5-year mortality rate (73%), generally from respiratory failure.
- In 2015, the U.S. Food and Drug Administration (FDA) approved a recombinant form of TNAP enzyme replacement therapy called asfotase alfa (Strensiq®, Alexion Pharmaceuticals, Inc.) for subcutaneous administration in patients with perinatal, infantile, and juvenile-onset forms of hypophosphatasia.
- Treated patients show improvements in overall survival and survival free from invasive mechanical ventilation compared with historical controls.
- Adverse events include injection-site and hypersensitivity reactions and ectopic calcifications in the eye and kidneys.
- X-linked hypophosphatemia, also known as vitamin D-resistant rickets, is an inherited disorder characterized by low levels of phosphate in the blood due to abnormal processing in the kidney, leading to phosphate wasting and resulting in soft, weak bones (rickets).
- X-linked hypophosphatemia is usually diagnosed in childhood and its features can include bowed or bent legs, short stature, bone pain, and severe dental pain, as well as other oral manifestations that include spontaneous dental abscesses.
- In 2018, the FDA approved burosumab-twza (Crysvita™, Ultragenyx Pharmaceuticals, Inc.), a monoclonal antibody that inhibits activity of excess fibroblast growth factor 23, thereby restoring normal renal phosphate processing for adult and pediatric individuals with X-linked hypophosphatemia.
- Treated patients show improvements in serum phosphate levels and radiologic findings, compared to placebo treatment or to historical controls.
- Adverse events include injection-site reaction, headache, and decreased circulating levels of vitamin D.

INTRODUCTION

Phosphate is among the most abundant minerals in the body.[1] It is important for a variety of processes including energy metabolism, protein synthesis, skeletal and tooth development, as well as maintaining bone integrity.[1]

Hypophosphatasia and X-linked hypophosphatemia are both genetically inherited conditions that affect phosphate homeostasis and are characterized by abnormal development of bone and teeth.[1] In hypophosphatasia, mineralization is disrupted affecting a number of tissues, including bone and teeth. With X-linked hypophosphatemia, an inability of the cells in the body to properly process phosphate causes circulating levels of phosphate to be low, resulting in problems with bone and tooth development.[1]

Hypophosphatasia

Hypophosphatasia is a rare, inherited, progressive metabolic disorder. In its most severe form, it is an ultra-rare disease, occurring in approximately 1 in 100,000 live births and is characterized by defective bone/tooth mineralization, weakness, seizures, respiratory failure, and premature death.[2] Less-severe forms of the disease occur more frequently, although still uncommonly.[3] In a natural history study, infants who had their first symptom of hypophosphatasia within the first 6 months of life had an overall mortality rate of 73% at 5 years, primarily due to respiratory failure.[4]

Hypophosphatasia is caused by loss-of-function mutation(s) in the gene that encodes the tissue-nonspecific isozyme of alkaline phosphatase (TNSALP or TNAP).[3,5] Marked reduction in alkaline phosphatase activity results in elevated circulating serum levels of inorganic pyrophosphate (PPi) and pyridoxal-5'-phosphate (PLP; the principal circulating form of vitamin B6), and elevated urine levels of PPi and phosphoethanolamine (PEA), all molecules presumed to be substrates of TNAP.[6] High extracellular levels of PPi block hydroxyapatite crystal growth, resulting in impaired bone/tooth mineralization and rickets-like symptoms;[5] severely affected patients can develop hypercalcemia and hyperphosphatemia.[5] The derangement in vitamin B6 metabolism can result in pyridoxine-responsive seizures.[5] Hypomineralization of the ribcage ("rachitic chest") results in hypoinflation of the lungs and respiratory failure.[3]

Hypophosphatasia can manifest as neonatal death with almost no skeletal mineralization to dental problems in adults without any bone symptoms. The disease has generally been classified according to patient age when the first signs and symptoms manifest; six clinical forms are currently recognized (Table 1). These clinical subtypes can overlap, e.g., infantile and childhood hypophosphatasia share some clinical symptoms, and patients with adult hypophosphatasia often had some clinical symptoms already in childhood.[3] Oral manifestations characteristic of various forms of hypophosphatasia can include early loss of deciduous teeth, severe dental caries, improperly formed teeth, and alveolar bone loss.[3]

Oral manifestations characteristic of various forms of hypophosphatasia can include early loss of deciduous teeth, severe dental caries, improperly formed teeth, and alveolar bone loss.[3,8,9]

Enzyme-Replacement Therapy for Hypophosphatasia. Asfotase alfa (Strensiq®, Alexion Pharmaceuticals, Inc.) is the first agent approved for the treatment of perinatal, infantile, and childhood-onset forms of hypophosphatasia.[2,5,10] A recombinant form of TNAP, asfotase alfa is intended to enhance deficient alkaline phosphatase enzyme activity in patients with these forms of hypophosphatasia.[2, 10] Safety and efficacy of asfotase alfa were established in patients with perinatal, infantile- or juvenile-onset hypophosphatasia who received treatment for up to 6.5 years during four prospective, open-label studies.[2,5,10] Results showed that patients with perinatal- and infantile-onset hypophosphatasia treated with asfotase alfa had improved overall and ventilator-free survival compared with historical controls; patients with the juvenile form of the disease showed improvements in growth and bone health compared to control patients selected from a natural history database.

Asfotase alfa is administered as a subcutaneous injection (3 to 6 injections per week) in weight-based dosing regimens.[10] Warnings and precautions include hypersensitivity reactions, lipodystrophy at injection sites (i.e., abnormal thickening or thinning of the skin), and ectopic calcifications in the eye and kidneys.[10] The most common adverse reactions occurring in 10% or more of patients include injection site reactions, lipodystrophy, ectopic calcifications, and hypersensitivity reactions.[10]

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