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Review article

Monitoring guidance for patients with hypophosphatasia treated with asfotase alfa

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ABSTRACT

Hypophosphatasia (HPP) is a rare, inherited, systemic, metabolic disorder caused by autosomal recessive mutations or a single dominant-negative mutation in the gene encoding tissue-nonspecific alkaline phosphatase (TNSALP). The disease is associated with a broad range of signs, symptoms, and complications, including impaired skeletal mineralization, altered calcium and phosphate metabolism, recurrent fractures, pain, respiratory problems, impaired growth and mobility, premature tooth loss, developmental delay, and seizures. Asfotase alfa is a human, recombinant enzyme replacement therapy that is approved in many countries for the treatment of patients with HPP. To address the unmet need for guidance in the monitoring of patients receiving asfotase alfa, an international panel of physicians with experience in diagnosing and managing HPP convened in May 2016 to discuss treatment monitoring parameters. The panel discussions focused on recommendations for assessing and monitoring patients after the decision to treat with asfotase alfa had been made and did not include recommendations for whom to treat. Based on the consensus of panel members, this review provides guidance on the monitoring of patients with HPP during treatment with asfotase alfa, including recommendations for laboratory, efficacy, and safety assessments and the frequency with which these should be performed during the course of treatment. Recommended assessments are based on patient age and include regular monitoring of biochemistry, skeletal radiographs, respiratory function, growth, pain, mobility and motor function, and quality of life. Because of the systemic presentation of HPP, a coordinated, multidisciplinary, team-based, patient-focused approach is recommended in the management of patients receiving asfotase alfa. Monitoring of efficacy and safety outcomes must be tailored to the individual patient, depending on medical history, clinical manifestations, availability of resources in the clinical setting, and the clinician's professional judgment.

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1. Introduction

Hypophosphatasia (HPP) is a rare, inherited, systemic, metabolic disorder that is sometimes life-threatening in infants and can lead to disability at any age. HPP is characterized by low activity of the enzyme tissue-nonspecific alkaline phosphatase (TNSALP), resulting in a broad range of signs, symptoms, and complications [1,2]. Deficient TNSALP activity in HPP is caused by autosomal recessive mutations or a single putative dominant-negative mutation in the liver/bone/kidney alkaline phosphatase (ALP) gene (*ALPL*) encoding TNSALP [3,4] and leads to extracellular accumulation of TNSALP substrates, chiefly inorganic pyrophosphate (PPi; an inhibitor of hydroxyapatite crystal formation and bone mineralization) [2,5,6] and pyridoxal-5′-phosphate (PLP; the circulating form of vitamin B_6, which without TNSALP activity is thought to fail to cross the blood-brain barrier, as well as cell membranes) [2,7,8]. Phosphoethanolamine (PEA; a degradation product of cell surface phosphatidylinositol-glycan anchors) is also a substrate, although not exclusively, of TNSALP in vitro [9–11].

Depending on the patient's age, the signs, symptoms, and complications of HPP can include bone anomalies detected in utero, premature tooth loss (exfoliation of the entire tooth including root), impaired skeletal mineralization, bone deformities, fractures, bone/joint/muscle pain, respiratory compromise that may require ventilation, impaired growth and mobility, vitamin B_6-dependent seizures, craniosynostosis, substantial morbidity, and, in some cases, death [2,12,13].

The clinical presentation of HPP is possibly influenced by autosomal dominant versus autosomal recessive inheritance [14,15], as well as environmental and epigenetic factors and modifier genes [16]. HPP has been clinically classified according to age at first sign or symptom onset: perinatal (in utero and at birth), infantile (age $<$ 6 months), childhood (age $\geq$ 6 months to $<$ 18 years), and adult (age $\geq$ 18 years) [1,2,15,17]. HPP presenting primarily with dental manifestations has been described as odontohypophosphatasia [18–20]. Skeletal manifestations of HPP in utero have been observed, which in some cases may resolve spontaneously after birth; this has been described as benign prenatal HPP [21,22]. These categories are helpful in describing the disease; however, the clinical presentation of HPP is variable [23] and the disease burden throughout an individual patient's life is not well understood [12,14,24]. Substantial morbidities may develop during the lifetime of a patient with HPP [25], who may have increasing disease burden resulting from joint problems, fractures, orthopedic/dental surgeries, pain, muscular insufficiency, decreased functional status, and impaired mobility [1,25,26].

Until recently, treatment of HPP consisted largely of supportive care [2]. Use of bisphosphonates has not been rigorously studied in patients with HPP [27]; in case studies of adults with previously undiagnosed HPP, treatment with bisphosphonates potentially led to an increase in and/or worsening of fractures [28,29]. Teriparatide (recombinant human parathyroid hormone [PTH] 1–34) has shown some benefit in case studies of adults with HPP [30,31], although one case report described no benefit [32]. Teriparatide is contraindicated in pediatric and young adult patients with open epiphyses; studies in rats showed an increase in the incidence of osteosarcoma that was dose and treatment duration dependent [27,33]. Teriparatide is currently not recommended for use in the treatment of osteoporosis for longer than 2 years over a lifetime [33]. Case reports for other approaches, such as bone marrow and stem cell transplantation, in infants and children with HPP have described some improvement in skeletal mineralization and survival to at least age 3 to 7 years in patients with life-threatening disease; however, the improvement in skeletal mineralization was not necessarily associated with an improvement in ALP activity [34–36].

Asfotase alfa (Strensiq®; Alexion Pharmaceuticals, Inc., New Haven, CT, USA), a human, recombinant TNSALP replacement therapy, replaces deficient TNSALP activity in patients with HPP and reduces the accumulation of extracellular TNSALP substrates [37]. The efficacy and safety of asfotase alfa was assessed in 5 prospective, open-label, Phase 2, multinational clinical studies in infants and adolescents with perinatal, infantile, or childhood HPP [37–40]. In these studies, asfotase alfa improved bone mineralization based on radiographic and biopsy findings and improved growth, respiratory function, and mobility. A study of asfotase alfa in adolescents and adults with HPP has been completed, and the results are being prepared for publication.

No published guidelines are available for monitoring patients with HPP being treated with asfotase alfa. To address this unmet need, in May 2016, Alexion Pharmaceuticals, Inc., convened an international panel of physicians to discuss treatment monitoring parameters for patients with HPP who are receiving asfotase alfa. For this discussion, it was presumed that the decision to treat with asfotase alfa had already been made; other possible therapeutic approaches, symptom management with other treatments, and general management of HPP were not discussed and are beyond the scope of this report. It should also be noted that access to and experience with this drug currently vary from country to country. Further, the decision to discontinue treatment is complex and also beyond the scope of this paper; the decision is multifactorial and should be considered using a case-by-case approach based on discussions and understanding between the patient, family, and physicians. The intention of this consensus report is to provide guidance on the monitoring of patients with HPP receiving treatment with asfotase alfa, including clinical recommendations concerning laboratory, efficacy, and safety assessments and the frequency with which these should be performed during the course of treatment.

1.1. Methodology

All physicians involved in the panel discussions were experienced in the management of HPP. Their areas of expertise included pediatrics, metabolic bone disease, endocrinology, gastroenterology, genetics, clinical biochemistry, and orthopedic surgery. After the meeting, nurses experienced in administering asfotase alfa were consulted to obtain feedback on their recommendations for injection technique.

During the meeting, panel members reached consensus on the monitoring of infants, children, and adults with HPP treated with asfotase alfa and prioritized the importance of assessments for each age group. Evidence from the asfotase alfa clinical studies was used where available and appropriate to guide recommendations. A comprehensive review of the literature was undertaken to establish the foundation for diagnosis and genetic testing for HPP. All authors reviewed and unanimously approved these recommendations.

Although these recommendations provide a basic framework, the signs, symptoms, and complications of HPP vary widely from patient to patient. Thus, treatment and monitoring ultimately should be tailored to the patient based on the individual's medical history, clinical manifestations, and the clinician's professional judgment.

1.2. Diagnosis

Considerations for the diagnosis of HPP have been reviewed in other publications [1,12] and were not a primary focus of the panel discussions. Briefly, the diagnosis of HPP in patients of any age can be established based on characteristic signs, symptoms, and complications of HPP (Table 1) [1,2,9,13,26,39,41–52] in combination with consistently low age- and sex-adjusted serum ALP activity [1,13] after exclusion of other causes of low ALP activity and skeletal diseases with similar presentations [2]. Because the lower limit of normal for ALP activity varies by age and sex [53], measured activity must be compared with the lower limit and range appropriate for the patient [13]. Physicians should be aware that many institutions do not routinely flag low ALP activity [2] and may incorrectly use adult ALP reference ranges and apply them to patients of all ages. It should be emphasized that age- and sex-adjusted ALP reference intervals are critical to making an accurate diagnosis of HPP. Obtaining activity of the bone isoform of ALP is generally not necessary or helpful, although it too would be expected to