Treatment of hypophosphatasia

Lothar Seefried

Orthopedic Department, University of Würzburg, Würzburg, Germany

ABSTRACT

Hypophosphatasia is a systemic metabolic disorder due to genetically determined deficient activity of the tissue non-specific alkaline phosphatase (TNAP). The phenotypic presentation is characterized by a wide spectrum of clinical manifestations regarding both, affected body systems and organs as well as the severity of associated deficits. Appropriate treatment strategies thus have to be multimodal in order to cover individual disease manifestation.

For patients with disease onset before adulthood, enzyme replacement therapy with asfotase alfa is approved in Europe to treat the bone manifestations of the disease. Available data from clinical trials as well as real-word evidence confirm encouraging results of this treatment in severely affected children with substantial improvement regarding radiographic and functional outcome parameters as well as overall survival. In adult patients with disease manifestation pursuant to the label, published results also report substantial amelioration of disease-specific deficits along with functional improvements. Meanwhile, there is are also data supporting the safety and efficacy of long-term treatment with asfotase alfa over several years.

While inflammatory muskuloskeletal pain - seemingly the most prevalent clinical manifestation along with exhaustion - can transiently be mitigated with on-demand NSARs, essential treatment options to causatively overcome that issue are still lacking. Accordingly, maintenance of musculoskeletal health and functionality requires sustained supportive treatment including physiotherapy and individually adjusted technical orthopedic support. The use and potential clinical impact of phosphate and vitamin B6 on the course of the disease requires further investigation. Current data regarding the use of bone-targeted compounds established for osteoporosis is critical in terms of antiresorptive, while osteoanabolic treatment strategies appear feasible. Considering further organ manifestation including orodental, gastrointestinal and neurological symptoms etc., the entirety of therapeutic measures should be coordinated among a multidisciplinary team and overlooked at an experienced center, while individual tasks can preferably be accomplished at local facilities near the patient's home.

KEYWORDS

Hypophosphatasia, HPP, alkaline phosphatase.

Background

Hypophosphatasia (HPP) is a genetic disorder due to loss-of-function variants in the *ALPL* gene on chromosome 1p36.12 (OMIM#171760), encoding for the tissue-nonspecific alkaline phosphatase (TNAP).

While pathogenic changes in both alleles reflecting autosomal recessive disease are often associated with very substantial impairments in enzyme activity and more severe, clinical manifestations at an early age, heterozygous, monoallelic changes are often associated with a more subtle, clinically less obvious manifestation [1-4]. However, depending on the severity and localization of the variant, there are exceptions to this rule of thumb in both directions. Furthermore, individual manifestations and clinical courses can be variable over lifetime. Accordingly, the traditional classification of the severity of the disease based on the age at first manifestation [5] is of limited help in everyday clinical practice, and it is important to establish optimal therapy based on the individual patient's situation instead of providing onset-category based standard treatment.

Given the almost ubiquitous expression of the enzyme throughout the body and its pivotal role in processing phosphoric acid monoesters in a large number of metabolic settings, numerous, partially hypothetical concepts to explain the broad spectrum of clinical manifestations. In that regard, deficient skeletal mineralization in most severe cases due to accumulation of inorganic pyrophosphate (PPi) and supposedly phospho-osteopontin as well as the role of ALP concerning the dephosphorylation of pyridoxal-5-phosphate (PLP), the main circulating form of vitamin B6, are well established. In contrast, further investigations are required to clarify the influence of ALP deficiency on purinergic signalling, the interconversion of neurotransmitters, the relevance for energy turnover and the specifically the turnover of energy-rich, proinflammatory nucleotide triphosphates and potentially deficient provision of anti-inflammatory adenosine. In addition, the clinical signifi-

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Contact

Lothar Seefried: l-seefried.klh@uni-wuerzburg.de

Orthopedic Department, University of Würzburg, Würzburg, Germany

Phone: +49 (0) 931/803-3575, Fax: +49 (0) 931/803-15 98

cance of ALP activity on specifically neuronal tissue formation and regeneration, neurotransmitter metabolism and for the detoxification of bacterial lipopolysaccharides deserve further attention. Overall, a better understanding of the mechanisms by which a lack of ALP activity and the consecutive accumulation of certain – as yet unidentified - metabolites can induce clinical symptoms via direct, receptor-mediated and/or indirect, tissue-associated effects was essential to enable the development of novel causative treatment concepts for the majority of patients. Moreover, gene based therapeutic concepts and the idea of improving enzyme expression on a transcriptional or translational level are of course attractive options for HPP treatment and respective developments are on the way.

Still, beyond these pathophysiological and scientific challenges and prospects, which will certainly provide novel insights and enable better treatment options for the future, the pleiotropic spectrum of clinical disease manifestations already requires therapeutic answers today.

Figure 1 provides an overview of common signs and symptoms reported by patients and which can therefore be seen as the challenge for caregivers [6-9]. Accordingly, the overview here focuses on therapeutic options that we have available based on the current state of knowledge and can be offered to patients. A graphical outline it provided in Figure 2.

Enzyme replacement therapy

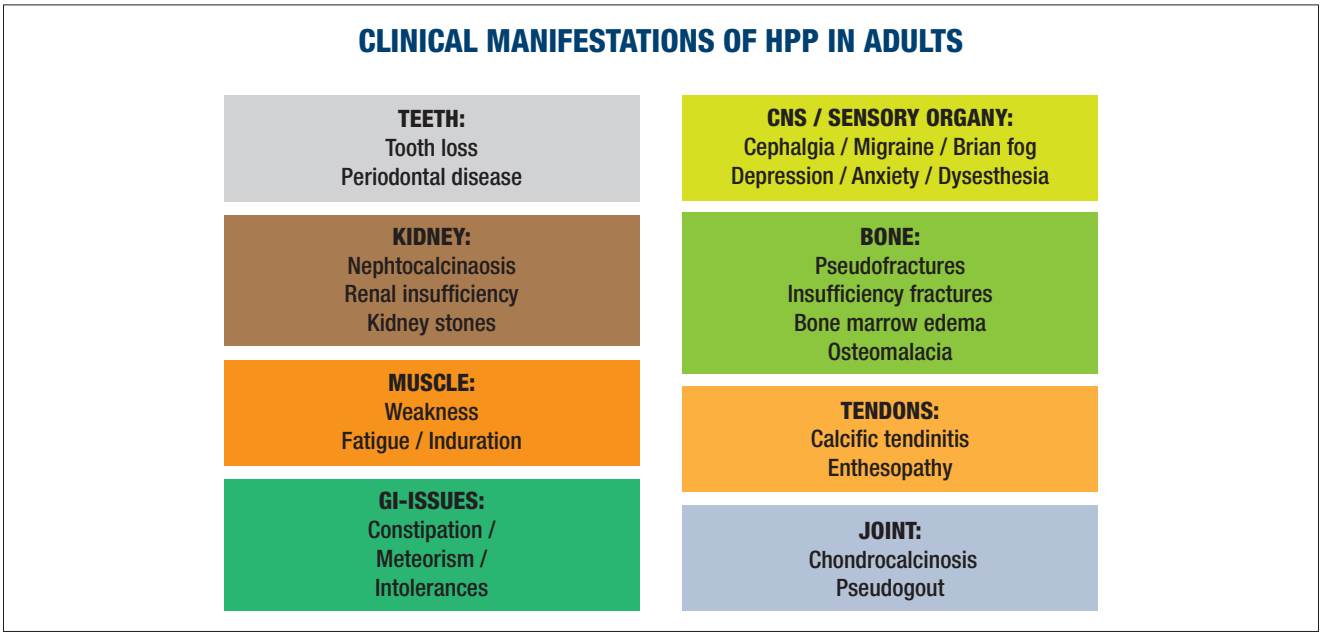
With the approval asfotase alfa for long-term enzyme replacement therapy (ERT) to treat the bone manifestations in pediatric-onset HPP a first-in class causal therapeutic approach has become available for most severe cases [10]. Asfotase alfa is the recombinant human TNSALP enzyme coupled to an IgG1-Fc fragment and a deca-aspartate anchor, enabling its anchorage at the calcium hydroxyapatite surface of bone tissue to ensure persistence of the compound. The drug is applied subcutaneously, in weight-adapted dosage of recommended 6 mg/kg body weight (bw) per week, distributed over three or six weekly doses i.e., 2 mg/kg 3x/week or 1 mg/kg 6x/week. Available data confirms that this dosage, which was primarily established in children, also appears to be also adequate in adult patients.

The study results underlying approval underscore a beneficial radiological and also functional response along with respiratory improvements and, in particular, an improved overall survival in severely affected children as compared to a natural history cohort [11-14].

Further to that, real word data of individual, severely affected patients substantiate that substantial additional benefit can be achieved through the therapy. In fact, one study showed that older children (6-12 years, *n*=12) also had a radiological response and an improvement in muscle strength and growth as well as motor skills and, as a result, improved quality of life [15]. Data on enzyme replacement therapy in mostly severely affected adolescents and adults (13-65 years, *n*=19) also show the achievable goals with adequate dosage, although it turns out that individual variability of the response in this and other studies underline the need for careful patient selection to identify those who will eventually benefit [16]. Various case reports also confirm the beneficial effect of ERT on bone healing also in adult patients [17-19] and even with long-term persistent pseudofractures. First evaluations of the 12-month data of 14 participants (19-78 years) of a longer-term treatment course study in severely affected adult patients (EmPATHY) with pediatric onset also show significant functional improvements, especially with regards to parameters evaluating everyday mobility such as the chair-rise test and the 6-minute walk test [20].

Over time, it will be interesting to better understand to what extent this is directly associated with improved bone resilience or whether there is also an indirect effect on the muscles and other soft tissues and organ structures, for example through

Figure 1 Spectrum of common organ manifestations in hypophosphatasia.



changes in the concentrations of substrates or through circulating enzyme activity. This also implies the question of possible undesired effects of the therapy.

Despite the recommended rotation between different injection sites (3x or 6x weekly injections), alterations of skin and subcutaneous tissue at the injection sites with discoloration and the development of lipodystrophy appear common, specifically in adult patient requiring high absolute amounts of drug but exhibit inferior tissue regeneration capacity. In individual cases, anaphylactoid reactions have also been reported.

Changes of laboratory parameters after treatment initiation appear consistent largely consistent and include a transient increase in PTH in the first few weeks and months along with an increase in bone turnover markers implying healing of preexisting osteomalacia.

Clinical follow-up visits should be scheduled e.g., at 3 and 6 months after treatment initiation every 6 months thereafter to check for both treatment-related benefits including laboratory and ideally functional assessment to support continuation and but also check for untoward events that might require adjustments of the treatment strategy. Treatment monitoring should regularly include checkups for ectopic calcifications specifically in the kidneys and the eyes [21]. In children regular, additional emphasis has to be put on ruling out evolving or progressive craniosynostosis.

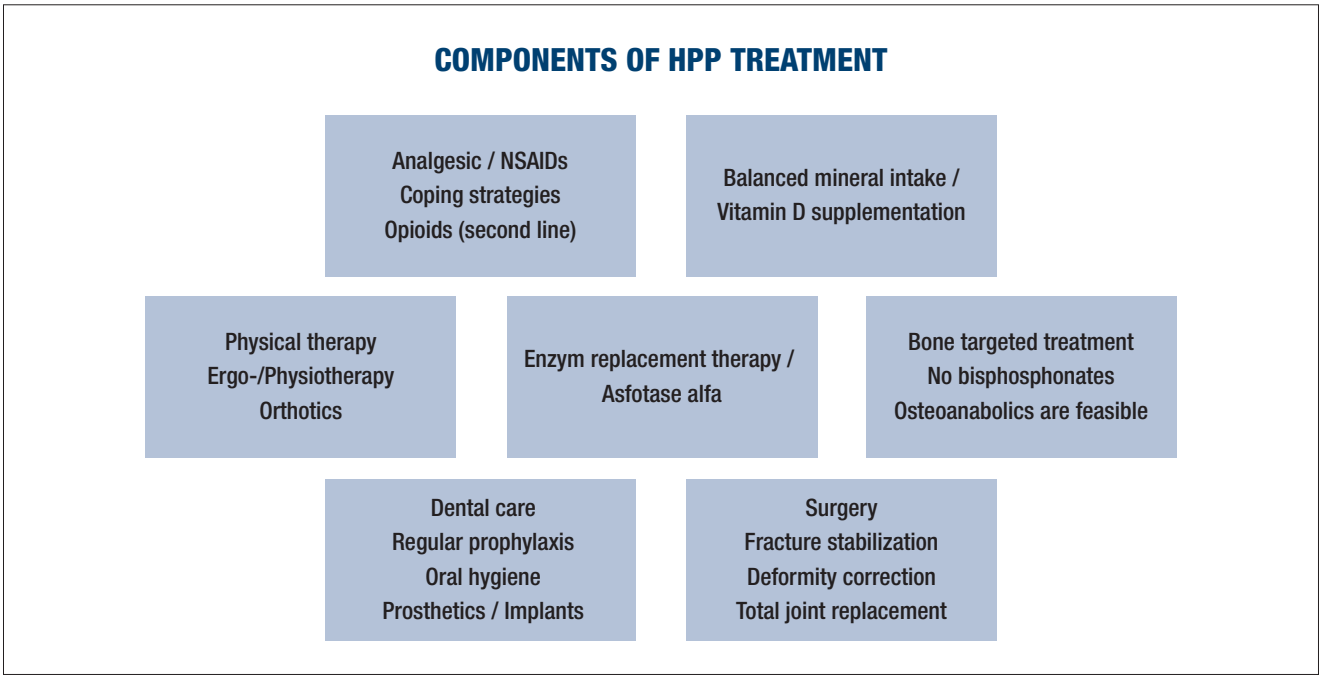
In that regard, it is essential to ensure interdisciplinary care, especially for patients on enzyme replacement therapy, and to define clear treatment goals right at the start of therapy, the achievement of which should also be regularly monitored as the basis for a responsible individual benefit/risk assessment [22, 23]. The question of long-term benefits of ERT will further be clarified by ongoing studies and the global HPP register (NCT02306720) which will provide valuable information. This will also bring new insights regarding the clinical significance of antidrug antibodies which have been described to potentially limit long term efficacy.

Beyond the overall promising data on the effectiveness of enzyme replacement therapy for the underlying bone pathology and potential positive off-target effects in most severely affected patients, further challenges remain concerning the need for appropriate treatment for the majority of patients not qualifying for ERT under the current label. In this respect, the interdisciplinary, multimodal, symptomatic treatment concept is of utmost importance.

Exercise, sport and physiotherapy

Muscular weakness and exhaustion compromising everyday activity are among the most prevalent clinical complaints reported by patients [24]. In the context of the compromised phosphate metabolism, it appears conceivable that this might be associated with deficient supply/replenishment of energetic phosphate compounds, specifically ATP within the exercising muscle. This concept could explain both, limited endurance resilience as well and protracted reconvalescence following exercise [25, 26]. Still, this is only theory and alternative explanations like an insufficient/protracted degradation and accumulation of toxic metabolites limiting further performance are equally conceivable. One aspect all these potential hypotheses have in common is that they cannot be just overcome by intensified, vigorous training and this actually matches clinical experience specifically with adult patients. Accordingly, it doesn't appear helpful to push patients to exercise beyond their limit. However, since the development of mobility and strength in childhood and the maintenance of physical fitness in adulthood are central determinants for the quality of life perceived by patients and the burden of the disease [27, 28] physiotherapy and medical

Figure 2 Components of HPP treatment.



training therapy under expert guidance and with an instructive component appear to be empirically helpful without risking undesirable side effects [29]. For frequently reported muscular indurations and tension complaints, accompanying detoxing measures (manual therapy, heat therapy, etc.) in order to reduce muscular hypertension and associated pain should also be included [30, 31].

Current experience with enzyme replacement therapy reveals that muscular issues, which contribute significantly to motor deficits in children and training intolerance in adults, can be improved during enzyme replacement therapy, although this effect appears to be inconsistent between individuals. While functional improvements in children appear quite obvious, revealing these in adult patients requires more diligent assessments and in sometimes hard to prove.

Orthopedic technical care

Especially in the case of severely affected patients with significant skeletal involvement, i.e., childhood rickets, consecutive deformities and deviations of the axial skeleton along with (pseudo-)fractures, concomitant orthopedic technical support is critical. Distinguished evaluation of the correction potential during growth can help to make surgical interventions and correction superfluous. In addition, supportive technical measures can also help to limit sequelae of functional incapabilities.

Supplements and nutrition

In the neonatal setting, treatment with parenteral high-dose pyridoxine-HCL (unphosphorylated vitamin B6) is well established to control for Vit B6 dependent seizures. The concept behind is based on the assumption that due to compromised dephosphorylation in ALP deficiency, pyridoxal-5-phosphate (PLP) cannot cross the plasma membrane or the blood-brain barrier causing a state of intracellular deficiency of the Vitamin B6 while circulating levels are elevated. This may also have impact on the conversion of neurotransmitters and thus the seizure threshold in the brain may lowered.

In addition, severely affected infants and young children often have a failure to thrive, sometimes associated with nausea and nutritional difficulties. To this end, an adequate, age-appropriate diet is critical and may require professional nutritional support and guidance in individual cases. Most severely affect infants even require enteral feeding via a tube, at least intermittently. In individual cases, a diet with a low-calcium and/or low-phosphate or the use of phosphate binders appear may also be reasonable in the case of hypercalcemia and/or phosphataemia specifically for children. In the case of pronounced hypercalcemia in infancy, additional drug measures may be necessary (e.g., i.v. fluids, furosemide, if necessary short-term glucocorticosteroids, etc.).

In adult patients, a cross-sectional survey revealed that both very high but also a very low dietary phosphate intake and also a deficient or increased calcium intake are associated with clinical symptoms compared to well-balanced calcium and phosphate amounts and specifically a balanced Ca/P ratio. Furthermore, in this study, in line with an earlier evaluation, there was no evidence for a therapeutic benefit of increased dietary intake of zinc and magnesium [32, 33].

Recommendation on vitamin D supplements should be based on the recommendations for healthy people or dosed according to individually assessed serum level for both, children as well as adults.

Analgesic-antiphlogistic therapy

Musculoskeletal pain is probably the most prevalent symptom in HPP patients and affecting particularly the large muscle groups of the thighs and spine, as well as the shoulder girdle and neck [34]. In earlier studies, NSAIDs were shown to be effective in treating these symptoms in children and adolescents. Against the background of the presumed inflammatory origin of the pain, as well as the symptoms described by the patients, analgesic therapy using NSAIDs appears reasonable and expedient to ameliorate these. However, considering side effects of long-term treatment, thoughtful application in situations of actual need is preferable to continuous, long-term treatment [35]. In the event of intolerance to the most common preparations in the setting of HPP like Ibuprofen and Naproxen, other painkillers may be considered, although experience is limited. Empirically, opioids have only limited benefit regarding mitigation of HPP-associated pain.

Bone-targeted treatment

In addition to the HPP-related mineralization disorders, coincident osteoporosis and osteoporotic fractures, i.e. vertebral compression fractures and metaphyseal fractures at the proximal femur (femoral neck, per trochanteric region) or the proximal humerus may be prevalent in adult patients with ALPL variants. In that regard, DXA values at the proximal femur appear to more meaningful than the lumbar spine. In light of the reduced bone remodeling activity owing to accompanying HPP, treatment with antiresorptive preparations in general and application of bisphosphonates in particular appears relatively contraindicated, especially when deficient enzyme activity appears severe enough to cause relevant pyrophosphate accumulation, since this may promote occurrence or progression of the focal, diaphyseal demineralization, commonly referred to as pseudo-fractures or Looser's remodeling zones [36-38].

In contrast, the use of osteoanabolic therapeutic agents seems plausible and in fact, there are ublished and reportedly even more unpublished cases of successful use of teriparatide and more recently romosozumab. However fortunately, the reported effects are comparatively inconsistent and, as expected, only transient, i.e. a lasting effectiveness beyond the duration of the actual therapy cannot be expected, which against the background of the limited total duration of therapy severely limits the benefit measured over the lifetime and suggests a differentiated use [39-42]. Regarding the use of a sclerostin antibody, effectiveness of this principle in HPP patients in terms of an im-

provement in bone mineral density and increase in bone formation with good tolerability has been demonstrated in a phase II study. Therefore, this is another option in a setting of coincident osteoporosis and HPP or when necessary to increase bone formation and bone mineral density in case of underlying HPP [43].

Dentistry

Since dental problems are one of the characteristic manifestations of HPP, a lifelong dedicated dental care is recommended. Dental implants and corrective interventions for misaligned teeth are basically feasible but should be coordinated by an orthodontist experienced in the treatment of HPP patients [44, 45].

Surgical measures

While pediatric patients with craniosynostosis require regular neurological or neurosurgical care as well as ophthalmoscopic control in order to not miss relevant neurological symptoms such including headaches, paralysis or numbness in the arms or papilledema which may warrant neurosurgical intervention [46, 47] this is less of an issue in adult patients.

For adult patients, stabilization of fractures represents one of the majors challenges, since compromised bone quality and prolonged healing must be assumed, especially in severely affected patients. However, most HPP-related fractures are not primarily due to actual trauma but rather occur as a consequence of latent pseudo-fractures, typically in the diaphyseal area of the long bones. In such instances, the use of extramedullary devices such as plates appears to be associated with a higher risk of complicated courses and in thus, adequately dimensioned intramedullary nails should be preferred [38]. Similar principles apply with regards to endoprosthetic care.

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