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Disease Burden and Systemic Manifestations of HPP in Children Enrolled in the Global HPP Registry

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INTRODUCTION

- Hypophosphatasia (HPP) is a rare, inherited, systemic disease caused by mutation(s) within the *ALPL* gene, which encodes tissue-nonspecific alkaline phosphatase (TNSALP)[1-3]
- Low TNSALP activity leads to the extracellular accumulation of TNSALP substrates (e.g., inorganic pyrophosphate, pyridoxal 5'-phosphate),[4,5] resulting in bone mineralization defects and other systemic complications, including seizures, pulmonary insufficiency, nephrocalcinosis, craniosynostosis, and fractures[2,3]
- Asfotase alfa is an enzyme replacement therapy approved for treatment of patients with HPP[6,7]
- To improve our understanding of the natural history of HPP and its impact on patients, the Global HPP Registry collects real world data from patients of all ages with HPP, regardless of asfotase alfa treatment status

OBJECTIVE

- To compare and contrast the medical histories of children in the Global HPP Registry by their asfotase alfa treatment status at enrollment

METHODS

- The Global HPP Registry is an observational, prospective, multinational study (NCT02306720; EUPAS13514) enrolling patients of all ages who have a confirmed diagnosis of HPP, regardless of asfotase alfa treatment status
- Patients who were deceased before enrollment are not included in the Registry
- At the time of Registry enrollment, clinical data and information related to HPP disease history were collected based on patient or parent/guardian recall; pretreatment data on HPP disease history were also collected for those who initiated treatment with asfotase alfa before study entry
- Only children (age <18 y) who had a diagnosis of HPP confirmed by low serum age- and sex-adjusted alkaline phosphatase (ALP) activity at any time (but before treatment initiation) and/or an *ALPL* pathogenic variant were included in this analysis

RESULTS

Patient Disposition and Demographics

- A total of 269 patients from 11 countries were enrolled in the Global HPP Registry from January 2015 through September 2017; of these, 121 (45.0%) were children (**Table 1**)
- Of the 121 children, 45 (37.2%) were being treated with asfotase alfa at enrollment and 76 (62.8%) were not being treated with asfotase alfa
  - Of the children being treated with asfotase alfa, 16 had previously participated in an asfotase alfa clinical study

Table 1. Number of Children (Age <18 Years) Enrolled[a] in the Global HPP Registry, by Asfotase Alfa Treatment Status

Country	Asfotase Alfa Treatment Status at Enrollment		Total, n
	Treated, n	Untreated, n	
United States	8	30	38
Japan	28	0	28
United Kingdom	3	21	24
Australia	0	10	10
Canada	6	2	8
France	0	6	6
Spain	0	5	5
Russia	0	1	1
Germany	0	1	1
Total	**45**	**76**	**121**

[a]Enrollment dates: January 2015–September 2017.
HPP=hypophosphatasia.

- Children treated with asfotase alfa were mostly female (66.7%) and most were Asian (67.4%); children not treated with asfotase alfa were mostly female (57.9%) and most were white (73.5%) (**Table 2**)

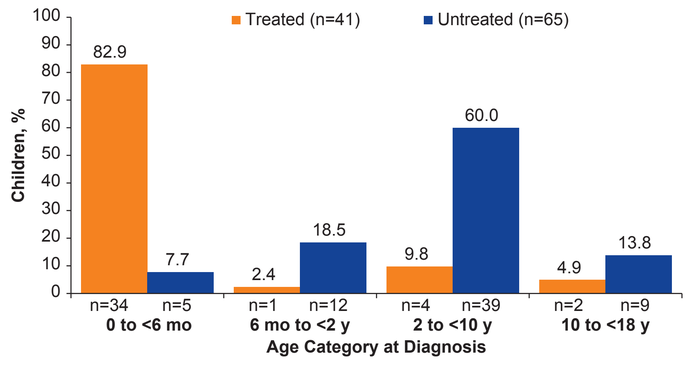
Table 2. Demographics of Children (Age <18 Years), by Asfotase Alfa Treatment Status

Characteristic	Asfotase Alfa Treatment Status at Enrollment		Total (n=121)
	Treated (n=45)	Untreated (n=76)	
Age at enrollment,[a] y	**n=45**	**n=76**	**n=121**
Mean (SD)	4.4 (4.7)	6.6 (4.5)	5.7 (4.7)
Median (min, max)	2.2 (−0.01, 15.4)	5.1 (0.2, 17.3)	4.3 (−0.01, 17.3)
Sex	**n=45**	**n=76**	**n=121**
Female, n (%)	30 (66.7)	44 (57.9)	74 (61.2)
Race,[b] n (%)	**n=43**	**n=68**	**n=111**
White	14 (32.6)	50 (73.5)	64 (57.7)
Asian	29 (67.4)	6 (8.8)	35 (31.5)
Other/multiple	0	5 (7.4)	5 (4.5)
Not reported	0	7 (10.3)	7 (6.3)
Ethnicity,[b] n (%)	**n=45**	**n=76**	**n=121**
Not Hispanic or Latino	45 (100)	58 (76.3)	103 (85.1)
Hispanic or Latino	0	4 (5.3)	4 (3.3)
Not reported	0	14 (18.4)	14 (11.6)
Family history of HPP, n (%)	**n=43**	**n=74**	**n=117**
Yes	10 (23.3)	40 (54.1)	50 (42.7)
No	32 (74.4)	29 (39.2)	61 (52.1)
Unknown	1 (2.3)	5 (6.8)	6 (5.1)

[a]Negative values for age indicate enrollment date occurred during pregnancy.
[b]The race and ethnicity categories used are those recommended by the US National Institutes of Health.
HPP=hypophosphatasia; SD=standard deviation.

- Of the 41 children treated with asfotase alfa, most (82.9%) were diagnosed with HPP before the age of 6 months, whereas the majority (60.0%) of untreated children were diagnosed with HPP between the ages of 2 and <10 years (**Figure 1**)

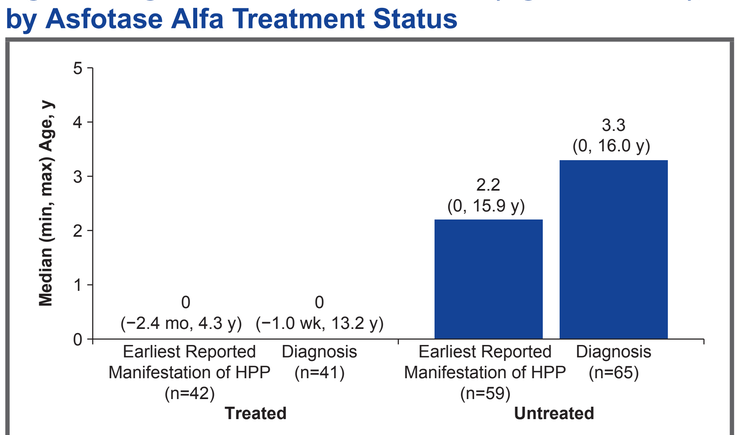
Figure 1. Age Category at Time of Diagnosis of HPP in Children (Age <18 Years), by Asfotase Alfa Treatment Status



HPP=hypophosphatasia.

- Among children treated with asfotase alfa, the median age of earliest HPP manifestation and the median age at diagnosis was at birth (**Figure 2**), and the median diagnostic delay was 1.1 days (range: birth–11.5 y; n=36])
- Children not treated with asfotase alfa had a median age of earliest HPP manifestation of 2.2 years and a median age at diagnosis of 3.3 years (median diagnostic delay: 0.7 y [range: birth–10.7 y]; n=44)

Figure 2. Age at Earliest Reported Manifestation and Age at Diagnosis of HPP in Children (Age <18 Years), by Asfotase Alfa Treatment Status



Negative values for age indicate a date that occurred during pregnancy. A value of 0 indicates the date was at birth.
HPP=hypophosphatasia.

- Skeletal signs and symptoms, failure to thrive, neurologic manifestations, renal/metabolic signs and symptoms, orthopedic procedures and therapies, and respiratory support were more commonly reported in the HPP-related disease history of children treated with asfotase alfa compared with children not treated with asfotase alfa (**Table 3**)

Table 3. HPP-Related Manifestations Based on the Medical History of Children (Age <18 Years), by Asfotase Alfa Treatment Status

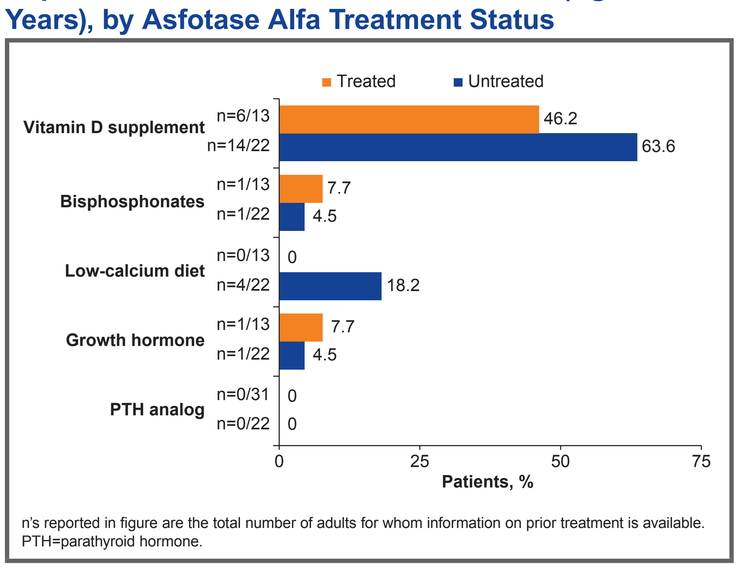
Category[a]: Symptom/Sign	Asfotase Alfa Treatment Status at Enrollment		Total (n=121) n/N (%)
	Treated (n=45) n/N (%)	Untreated (n=76) n/N (%)	
Premature loss of deciduous teeth[b]	**9/36 (25.0)**	**44/74 (59.5)**	**53/110 (48.2)**
Skeletal	**34/45 (75.6)**	**19/75 (25.3)**	**53/120 (44.2)**
Bone deformity	24 (53.3)	15 (20.0)	39 (32.5)
Rickets-like changes (by radiograph)	15 (33.3)	7 (9.3)	22 (18.3)
Recurrent and poorly healing fractures	4 (8.9)	1 (1.3)	5 (4.2)
Pseudofractures	1 (2.2)	0	1 (0.8)
Failure to thrive	**21/45 (46.7)**	**11/75 (14.7)**	**32/120 (26.7)**
Neurologic	**19/45 (42.2)**	**13/75 (17.3)**	**32/120 (26.7)**
Developmental delay	10 (22.2)	6 (8.0)	16 (13.3)
Craniosynostosis	8 (17.8)	4 (5.3)	12 (10.0)
Seizures	7 (15.6)	4 (5.3)	11 (9.2)
Increased intracranial pressure	2 (4.4)	0	2 (1.7)
Renal/metabolic	**14/44 (31.8)**	**14/75 (18.7)**	**28/119 (23.5)**
Hypercalcemia	11 (25.0)	4 (5.3)	15 (12.6)
Nephrocalcinosis	5 (11.4)	6 (8.0)	11 (9.2)
Hyperphosphatemia	3 (6.8)	4 (5.3)	7 (5.9)
Kidney stones	1 (2.3)	1 (1.3)	2 (1.7)
Orthopedic procedures and therapies	**12/45 (26.7)**	**14/75 (18.7)**	**26/120 (21.7)**
Rheumatic	**5/44 (11.4)**	**20/75 (26.7)**	**25/119 (21.0)**
Pain[c]	4 (9.1)	19 (25.3)	23 (19.3)
Fibromyalgia	1 (2.3)	1 (1.3)	2 (1.7)
Pseudogout	0	2 (2.7)	2 (1.7)
Muscular	**7/44 (15.9)**	**16/75 (21.3)**	**23/119 (19.3)**
Abnormal gait[d]	4/23 (17.4)	13/68 (19.1)	17/91 (18.7)
Weakness	7/44 (15.9)	8/75 (10.7)	15/119 (12.6)
Respiratory support	**20/43 (46.5)**	**2/75 (2.7)**	**22/118 (18.6)**
Invasive ventilation	17 (39.5)	1 (1.3)	18 (15.3)
Supplemental oxygen	9 (20.9)	2 (2.7)	11 (9.3)
CPAP/BiPAP	6 (14.0)	1 (1.3)	7 (5.9)

[a]Patients may have had >1 sign/symptom within each category.
[b]Excludes patients aged <6 mo at enrollment.
[c]Combines generalized body pain, chronic bone pain, and chronic muscle pain.
[d]Excludes patients aged <2 y at enrollment.
BiPAP=bilevel positive airway pressure; CPAP=continuous positive airway pressure; HPP=hypophosphatasia.

Medication History

- A large proportion of children, both treated with asfotase alfa (46.2%; 6/13 patients with available data) and not treated with asfotase alfa (63.6%; 14/22 patients with available data), had received vitamin D supplementation (**Figure 3**)

Figure 3. Treatments Affecting Bone Mineralization Reported in Medical Histories of Children (Age <18 Years), by Asfotase Alfa Treatment Status



n's reported in figure are the total number of adults for whom information on prior treatment is available.
PTH=parathyroid hormone.

LIMITATIONS

- Ensuring complete data entry is an inherent challenge with any registry collecting real world data; missing data for the Global HPP Registry were collected retrospectively
- Data collected for the Global HPP Registry may have been subject to recall bias by the patient, parent/caregiver, or clinician
- The Global HPP Registry does not capture data from neonates and young infants, either treated or untreated with asfotase alfa, who died before enrollment, thus potentially underestimating or not reflecting the spectrum of disease burden in pediatric HPP

CONCLUSIONS

- Children with HPP who were not on treatment with asfotase alfa at the time of enrollment in the Global HPP Registry presented at a later age and had more significant diagnostic delays compared with children who were on treatment at the time of enrollment
  - This may reflect that severely affected children have more obvious signs and symptoms compared with less severely affected children, leading to their earlier diagnosis and treatment
- Baseline medical histories for this group of 121 children with HPP suggest that manifestations of HPP beyond the skeletal system are common among children with HPP, highlighting the importance of taking thorough medical histories and recognizing systemic manifestations of HPP to ensure a timely diagnosis

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DISCLOSURES

WH, CL, AL, KO, CRG, LS, and PK are clinical study investigators and have received consultancy fees, and/or institutional research funding and/or grant support from Alexion Pharmaceuticals, Inc. SF and AP are employees of and may own stock/options in Alexion Pharmaceuticals, Inc., which funded the study. At the time of the study, HG was an employee of and may own stock/options in Alexion Pharmaceuticals, Inc.

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