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Research Article

Change in fracture rate and healthcare resource utilization among patients with hypophosphatasia following initiation of asfotase alfa: a retrospective US claims database analysis

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Abstract

Hypophosphatasia (HPP) is a rare, inherited, systemic disease characterized by skeletal and systemic manifestations. Asfotase alfa (AA) is the only US Food and Drug Administration-approved treatment for perinatal/infantile- and juvenile-onset HPP. Real-world data are scarce on fracture rates and healthcare resource utilization (HCRU) in patients treated with AA. This retrospective, observational study evaluated fracture-related outcomes and HCRU in patients with HPP treated with AA from January 2016 to December 2022 using the US Medicare Fee-for-Service and Inovalon Medical Outcomes Research for Effectiveness and Economics closed claims databases. Patients (≥2 yr of age) treated with AA (≥1 pharmacy claim for AA between January 2017 and December 2021 [identification period]) and ≥12 mo of continuous enrollment with medical and pharmacy coverage pre- and post-AA initiation were included. Clinical outcomes (change in fractures, types of fractures, and fracture event rates) and HCRU were assessed. Statistical analyses were performed to compare outcomes before and after initiation of AA. One hundred forty-nine patients (65.1% females, 69.1% adults; mean age, 39.6 yr) met the inclusion criteria. The proportion of patients experiencing fractures in the 12 mo following AA initiation significantly decreased compared to the 12 mo prior to treatment (18.1% vs 8.1%; $p = .004$). The mean fracture rate per patient per year nominally decreased post-AA initiation (0.24 vs 0.14; $p = .096$). The decrease was significant in fragility fracture rates (0.08 vs 0.02; $p = .019$). Most prescribed concomitant drugs at baseline were opioid analgesics (36.9%), nonopioid analgesics (34.2%), and antidepressants (34.9%). At baseline, 38.2% of patients were continuously using opioids and 21.8% were using high-dose opioids. Asfotase alfa initiation was associated with a statistically significant reduction in the proportion of patients experiencing fractures and fragility fracture rates, underscoring its potential therapeutic benefits.

Keywords: hypophosphatasia, asfotase alfa, real world evidence, fracture, healthcare resource utilization

Lay Summary

Hypophosphatasia (HPP), a rare disease, affects the bone, organs, and soft tissues. Its only approved treatment is asfotase alfa (AA). Information on how often fractures occur or how healthcare services are used in patients with HPP receiving AA treatment are limited. Asfotase alfa treatment reduced the number of patients with fracture substantially (18.1% vs 8.1%). Patients had fewer fractures per year on average, though the difference was not statistically significant. The number of fragility fractures, caused by minor falls or injuries, also decreased substantially. These findings suggest potential therapeutic benefits of AA for patients with HPP.

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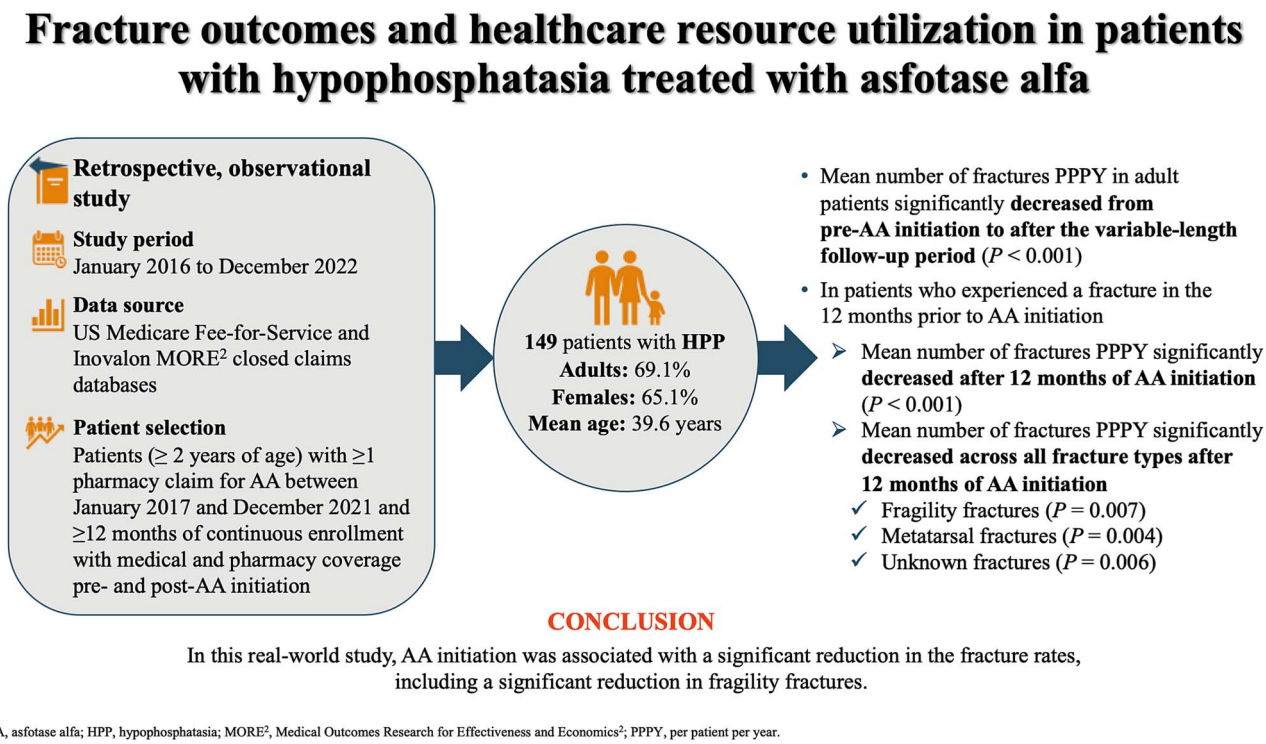
Graphical Abstract



AA, asfotase alfa; HPP, hypophosphatasia; MORE², Medical Outcomes Research for Effectiveness and Economics²; PPPY, per patient per year.

Introduction

Hypophosphatasia (HPP) is a rare, inherited, systemic, metabolic disease caused by deficient activity of tissue-nonspecific alkaline phosphatase (ALP) due to loss-of-function mutations in *ALPL*.[1,2] Reduced tissue-nonspecific ALP (TNSALP) activity results in the accumulation of its substrates (inorganic pyrophosphate and pyridoxal 5′-phosphate), causing bone mineralization defects and systemic complications.[2,3]

The clinical manifestations of HPP vary by age and can include bone anomalies that can be detected in utero in some patients, impaired bone and tooth mineralization (rickets, osteomalacia, and recurring/poorly healing metatarsal and femur fractures), chronic bone/joint/muscle pain, fatigue, muscle weakness, seizures, impaired growth development and mobility, hypercalcemia, and hypercalciuria.[4–7]

The only US Food and Drug Administration-approved therapy for the treatment of HPP is asfotase alfa (AA; Strensiq), a bone-targeted, human recombinant enzyme (ie, TNSALP) replacement therapy for patients with perinatal/infantile- and juvenile-onset HPP.[8,9] Clinical studies involving infants, children, and adults treated with AA have demonstrated improvements in skeletal manifestations, growth, mobility, and respiratory symptoms.[10–15] In adults, however, data on improvements in bone mineralization and fracture healing are limited, with few cases describing enhanced bone healing or healing of nonunions, particularly following femoral and tibial fractures.[15–19]

The heterogeneous nature of the disease may result in variable utilization of healthcare resources.[20] Specifically, there is a scarcity of real-world data on fracture rates and healthcare resource utilization (HCRU) in patients with HPP treated with AA.[20] Therefore, the aim of this retrospective, observational claims database study was to analyze fracture patterns and HCRU and to assess changes following initiation of AA.

Materials and methods

Study design and database

In this descriptive, retrospective, noninterventional, and observational cohort study, we included administrative claims data extracted from Inovalon's Medical Outcomes Research for Effectiveness and Economics closed claims database and the Medicare Fee-for-Service (FFS) database from the Centers for Medicare & Medicaid Services (CMS) between January 1, 2016, and December 31, 2022. Closed claims data, sourced from health insurers (payers), captures nearly all of a patient's healthcare activities during their enrollment period.[21]

Patient selection criteria

There are no *International Classification of Diseases*, *Tenth Revision*, *Clinical Modification* (ICD-10-CM) diagnosis codes for HPP. Prescription claims for AA, the approved drug for HPP, were used as a proxy to identify patients with HPP using National Drug Codes (Appendix 1).[14] Therefore, the selection criteria were: ≥1 pharmacy claim for AA between January 1, 2017, and December 31, 2021; age ≥2 yr at first AA fill; and ≥12 mo of continuous enrollment with medical and pharmacy coverage before and after AA initiation. Patients less than 2 yr of age were excluded from the study due to their distinct disease burden and insufficient sample size, which prevented separate analysis.

The index date was the date of the first AA fill. Data were collected during the baseline period (pre-AA initiation) of 12 mo prior to and excluding AA initiation and 3 follow-up periods (post-AA initiation) of (1) 12 mo, (2) 24 mo, and (3)

variable length (at least 12 mo after AA initiation to the end of enrollment, study end, or death whichever occurred first). Patient counts <11 were suppressed based on the CMS cell size suppression policy.[22]

Baseline clinical conditions and comorbidity burden

Baseline clinical conditions, including musculoskeletal, rheumatic, mental health, renal, and dental conditions; kidney stones or hypercalciuria; attention-deficit/hyperactivity disorder; bursitis and calcific tendonitis; respiratory failure; chondrocalcinosis; calcium pyrophosphate deposition disease; and other crystal arthropathies, were identified using ICD-10-CM diagnostic codes. Musculoskeletal conditions included osteoporosis, osteomalacia, other disorders of bone density and structure, osteomyelitis, osteonecrosis, other osteopathies, and joint disorders (eg, pain in joint, spondylosis, myositis, congenital malformations of the musculoskeletal system, and dislocation/sprain of hand/foot). Rheumatic conditions included rheumatoid arthritis, psoriatic arthritis, inflammatory arthritis, and systemic lupus erythematosus. Mental health conditions included depression, anxiety, and bipolar disorder, but did not include developmental/intellectual disabilities. Depression was defined as major depressive disorder, not otherwise specified (NOS), depression NOS, or premenstrual dysphoric disorder. Anxiety was defined as generalized anxiety disorder, panic disorder, agoraphobia, specific phobias, social phobias, or anxiety disorders NOS. Bipolar disorder was defined as Bipolar I (BP I), BP II, and BP NOS. Renal conditions included CKD, acute kidney failure, end-stage renal disease, and other renal conditions included in the Charlson–Deyo comorbidity index.[23]

Outcomes

Fractures

Fractures were identified using ICD-10-CM diagnostic codes. As a single fracture may generate multiple diagnostic codes across different types of visits, including initial, specialist, and follow-up, not all diagnosis codes constitute unique fractures. Fractures were restricted to unique, incident fractures, defined as diagnosis codes not categorized as subsequent/sequelae, and there were no previous encounters for the same fracture location within 90 d (Figure S1). Fragility fracture was defined as a unique incident fracture at sites commonly considered osteoporotic (hip, vertebrae, distal forearm, and proximal humerus), as well as additional sites (feet and femoral shaft) based on ICD-10 coding. Metatarsal fracture was defined as a unique incident fracture with a diagnosis code specifying a metatarsal bone had been fractured. Unknown fracture type was defined as all other fractures with insufficient specificity in the diagnosis coding to ascertain if they were traumatic or fragility fractures. This would include some traumatic fractures as well as some femoral fractures, although the sample size was too low to report these individually. One hundred eighty-seven ICD-10 diagnosis codes that were found in this patient population were used to identify fractures. We ensured de-duplication of fractures that fell into multiple categories to avoid double counting.

A subanalysis was performed on patients who experienced fractures during the 12-mo baseline period before AA initiation.

Changes in the number of patients experiencing fractures after initiation of AA, stratified by fragility, metatarsal, and/or unknown fracture types, were assessed. Fracture event rates per patient per year (PPPY) were evaluated from initiation of AA until the end of the study period, death, or disenrollment (12 mo, 24 mo, and variable-length follow-up periods).

Healthcare resource utilization

All-cause HCRU was assessed 12 mo before and after the initiation of AA. Healthcare resource utilization included physician office/outpatient visits, emergency department (ED) visits, inpatient hospitalizations, mental health/behavioral health visits, orthopedic surgery visits, physical medicine and rehabilitation visits, and pain management-related visits (Appendix 2). Medical procedure utilization (imaging, physical/occupational therapy, fracture surgeries, bone density testing, laboratory testing, and functional testing) were assessed prior to and after the initiation of AA.

Baseline concomitant medication use and opioid sparing

The use of concomitant medications before the initiation of AA was assessed. The number and proportion of patients with at least 1 medical or pharmacy claim for pain medications, such as opioid (oral or transdermal) analgesics, nonopioid analgesics, gabapentin (Neurontin), as well as other treatments, such as muscle relaxants, bisphosphonates, antidepressants, and anabolic agents for osteoporosis, were evaluated. Because HPP is frequently misdiagnosed as osteoporosis, which can lead to bisphosphonate prescriptions in this population, we captured data on bisphosphonate use to evaluate its relevance in our cohort. For the subset of individuals with an opioid claim during the pre-AA initiation period, opioid use and sparing were assessed. The total morphine milligram equivalents (MMEs) were calculated.[24] To determine the MME per day, the denominator for total days' supply was adjusted to account for overlapping prescriptions. It was assumed that a patient started taking their prescription on the fill date. If a patient received 2 prescriptions on the same day, it was assumed that they would take them simultaneously. High levels of opioid use were defined as >90 MME/d. Patients who did not have a gap of ≥60 d in opioid prescription were categorized as having continuous opioid use.

Statistical analysis

Descriptive statistics, including means, SDs, and medians with IQRs for continuous variables, and frequencies and relative frequencies (%) for categorical variables, were presented for demographics, baseline clinical characteristics, AA treatment patterns, concomitant drug treatments, HCRU, and fracture outcomes. As the pediatric population with fractures included fewer than 11 patients, their exact count was suppressed to protect patient privacy. However, the pediatric count could be inferred by subtracting the adult population from the overall total if the data were not suppressed. Pre- and post-AA patient counts and proportions were compared using appropriate statistical tests, including Wilcoxon signed rank test, chi-square test, and paired *t*-test. Wilcoxon signed rank tests were used, where appropriate, to compare patient counts between the pre- and post-AA initiation periods. A chi-square

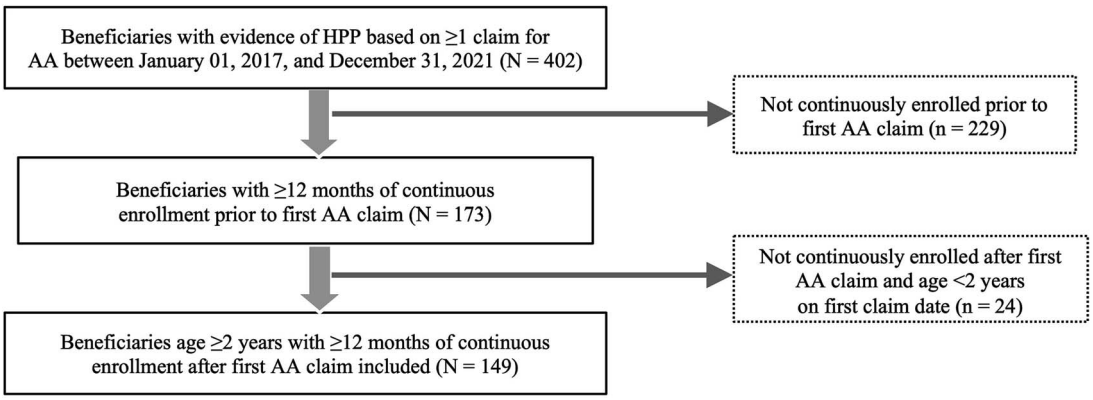


Figure 1. Study population. Abbreviations: AA, asfotase alfa; HPP, hypophosphatasia.

test was used to assess differences between categorical single-cell counts in the results tables that were ≥5. A paired *t*-test was used to determine significant differences in normally distributed continuous variables between the pre- and post-AA initiation periods.

Results

Study population

One hundred forty-nine (37.1%) of the 402 patients with ≥1 pharmacy claim for AA during the identification period met all study criteria (Figure 1). The majority of patients (mean [SD] age: 39.6 [26.6] yr) with HPP were adults (103/149, 69.1%) and female (97/149, 65.1%; Table 1). Approximately one-third were enrolled in Medicare FFS (53/149, 35.6%) and 34.2% (51/149) were commercial payers (Table 1). Of 53 Medicare FFS beneficiaries, 33 (62.3%) were initially eligible for Medicare based on age and survivor's insurance, while the remaining 20 (37.7%) were originally entitled due to disability. Patients were followed for an average of approximately 3 yr (Table 1).

Baseline clinical condition, comorbidity burden, and concomitant medical utilization

The most prevalent baseline clinical conditions were musculoskeletal conditions (111/149, 74.5%), including osteoporosis, osteomalacia, osteomyelitis, and joint disorders; rheumatic conditions (59/149, 39.6%), including rheumatoid arthritis, psoriatic arthritis, inflammatory arthritis, and systemic lupus erythematosus; and mental health conditions (55/149, 36.9%), including anxiety, depression, and bipolar disorder. Renal conditions, including CKD, acute kidney failure, and end-stage renal disease, affected 9.4% (14/149) of patients (Table 1).

The most common medications prior to AA initiation were opioid analgesics (55/149, 36. 9%), antidepressants (52/149, 34.9%), and nonopioid analgesics (51/149, 34.2%, Figure 2). Data on other antiresorptives, including denosumab and romosozumab, were captured. However, the findings were comparable to those observed with bisphosphonates and thus are not reported separately. In the year following the index date, while treated with AA, the number of patients did not change, and remained at <11.

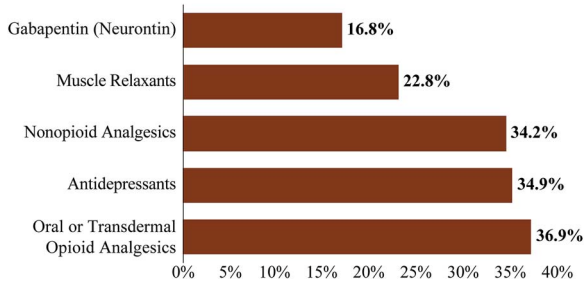


Figure 2. Baseline concomitant medical utilization prior to AA initiation in patients with HPP. Data on other antiresorptives, including denosumab and romosozumab, were captured. However, the findings were comparable to those observed with bisphosphonates and, therefore, are not reported separately. In the year following the index date, while treated with AA, the number of patients did not change, and remained at <11. Abbreviations: AA, asfotase alfa; HPP, hypophosphatasia.

Fracture outcomes

Fractures 12 mo after AA initiation

In the year prior to the initiation of AA, 18.1% of patients experienced at least 1 unique fracture. This does not include the full history of fracture at any point prior to initiation of AA. The number of patients experiencing unique fractures significantly decreased after 12 mo of AA initiation (27 [18.1%] vs 12 [8.1%]; $p = .004$; Table 2). The number of adult patients experiencing unique fractures significantly decreased after 12 mo of AA initiation (>16 [>15.5%] vs <12 [<11.7%]; $p = .004$). The number of pediatric patients experiencing unique fractures was similar to baseline after 12 mo of initiating AA treatment (Table 2). When stratified by fracture type, the number of patients experiencing unique fractures decreased in those with fragility fractures 12 mo after initiating AA ($p = .031$; Table 2). Other fracture types, including femoral fractures, were not analyzed because of insufficient sample size.

Among patients with a unique fracture prior to initiation of AA, significantly fewer patients experienced fractures within 12 mo after AA initiation (27 [100%] vs <11 [<40.7%]; $p < .001$). The number of patients experiencing fractures decreased across all fracture types 12 mo after initiating AA, with significant reductions in those with fragility (<11 vs <11; $p = .031$) and unknown (15 [100%] vs <11 [<73.3%]; $p = .001$) fracture types.

Table 1. Patient characteristics.

Patient characteristics	Patients (age ≥ 2 yr) ($N = 149$)
Age at index date, yr	
Mean (SD)	39.6 (26.6)
Median (IQR)	41.0 (54.0)
Age group at index date, *n* (%), yr	
2-5	18 (12.1)
6-10	15 (10.1)
11-17	13 (8.7)
18-29	13 (8.7)
30-39	15 (10.1)
40-49	12 (8.1)
50-64	18 (12.1)
65+	45 (30.2)
Sex, *n* (%)	
Female	97 (65.1)
Male	52 (34.9)
Payer, *n* (%)	
Medicare FFS	53 (35.6)
Commercial	51 (34.2)
Medicare advantage	<11 (<7.4)
Managed Medicaid	>34 (>22.8)
Census region, *n* (%)	
Northeast	>20 (>13.4)
Midwest	32 (21.5)
South	57 (38.3)
West	29 (19.5)
Unknown	<11 (<7.4)
Dual eligible status, (Medicare FFS only), *n* (%)	
Dual	<11 (<20.8)
Nondual	>42 (>79.2)
Original reason for Medicare entitlement, (Medicare FFS only), *n* (%)	
Old age and survivor's insurance	33 (62.3)
Disability insurance benefit	20 (37.7)
Deyo CCI score	
Mean (SD)	1.4 (2.1)
Median (IQR)	1.0 (2.0)
Baseline clinical condition, *n* (%)	111 (74.5%)
Musculoskeletal[a]	59 (39.6)
Rheumatic[b]	55 (36.9)
Mental health[c]	14 (9.4)
Renal[d]	12 (8.1)
Dental	12 (8.1)
Kidney stones or hypercalciuria	12 (8.1)
ADHD	11 (7.4)
Bursitis and calcific tendonitis	<11 (<7.4)
Respiratory failure	<11 (<7.4)
Chondrocalcinosis, CPPD, and other crystal arthropathies	
Duration of follow-up, mo	
Mean (SD)	35.5 (16.3)
Median (IQR)	35.4 (24.5)

Patient or event counts <11 were suppressed to protect patient privacy. [a] Musculoskeletal conditions include osteoporosis, osteomalacia, other disorders of bone density and structure, osteomyelitis, osteonecrosis, other osteopathies, and joint disorders (eg, pain in joint, spondylosis, myositis, congenital malformations of the musculoskeletal system, and dislocation/sprain of hand/foot). [b] Rheumatic conditions include rheumatoid arthritis, psoriatic arthritis, inflammatory arthritis, and systemic lupus erythematosus. [c] Mental health conditions include depression, anxiety, and bipolar but do not include developmental/intellectual disabilities. Depression was defined as MDD, MDD NOS, depression NOS, and premenstrual dysphoric disorder. Anxiety was defined as generalized anxiety disorder, panic disorder, agoraphobia, specific phobias, social phobias, and anxiety disorders NOS. BP was defined as BP I, BP II, and BP NOS. [d] Renal conditions include CKD, acute kidney failure, end-stage renal disease, and other renal conditions included in the Deyo CCI. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BP, bipolar; CCI, Charlson comorbidity index; CPPD, calcium pyrophosphate deposition disease; FFS, Fee-for-Service; MDD, major depressive disorder; NOS, not otherwise specified.

Fracture event rates PPPY

The mean number of fractures PPPY decreased after 12 mo (0.24 vs 0.14; $p = .096$) and significantly decreased after 24 mo (0.24 vs 0.13; $p = .033$) following AA initiation. The mean number of fractures PY also decreased after the variable-length follow-up period (0.24 vs 0.07; $p < .001$) following AA initiation (Figure 3A). In other words, patients experienced an average of 1 fracture per 4.2 patients PY pre-AA initiation, 1 fracture per 7.1 patients PY in the year following AA initiation, and sustained this rate through the end of follow-up, ultimately resulting in 1 fracture per 14.3 patients PY based on the variable follow-up period.

The mean number of fractures PPPY among adult patients decreased nominally but was not statistically significant after

Table 2. Fracture outcomes among patients 12 mo after AA initiation.

	Patients (age ≥ 2 yr)			Adult patients (age ≥ 18 yr)			Pediatric patients (age 2-17 yr)		
	N = 149			*N* = 103			*N* = 46		
	Pre-AA initiation[a]	Post-AA initiation[b]	*p*-value	Pre-AA initiation[a]	Post-AA initiation[b]	*p*-value	Pre-AA initiation[a]	Post-AA initiation[b]	*p*-value
Patients with unique incident fracture,[c] *n* (%)									
Overall	27 (18.1)	12 (8.1)	.004	>16 (>15.5)	<12 (<11.7)	.004	<11 (<23.9)	<11 (<23.9)	1.000
Fragility	<11(<7.4)	<11(<7.4)	.031	<11 (<10.7)	<11 (<10.7)	.063	<11 (<23.9)	0 (0)	1.000
Metatarsal	<11(<7.4)	<11(<7.4)	.219	<11 (<10.7)	<11 (<10.7)	.219	0 (0)	0 (0)	NA
Unknown[d]	15(10.1)	<11(<7.4)	.332	>11 (>10.7)	>11 (>10.7)	.455	<11 (<23.9)	<11 (<23.9)	1.000

Patient or event counts <11 were suppressed to protect patient privacy. [a]Pre-AA initiation: 12 mo of data prior to AA initiation. [b]Post-AA initiation: 12 mo of data after AA initiation. [c]Unique fractures were identified via claims for initial encounters for fractures that occurred during the measurement period: 12 mo pre-AA and 12 mo post-AA initiation. Fractures include new fractures in the 12 mo pre-AA initiation and do not include all historical fractures prior to AA initiation. [d]Fractures were classified as unknown type when they were neither metatarsal nor fragility fractures. Abbreviations: AA, asfotase alfa; NA, not available.

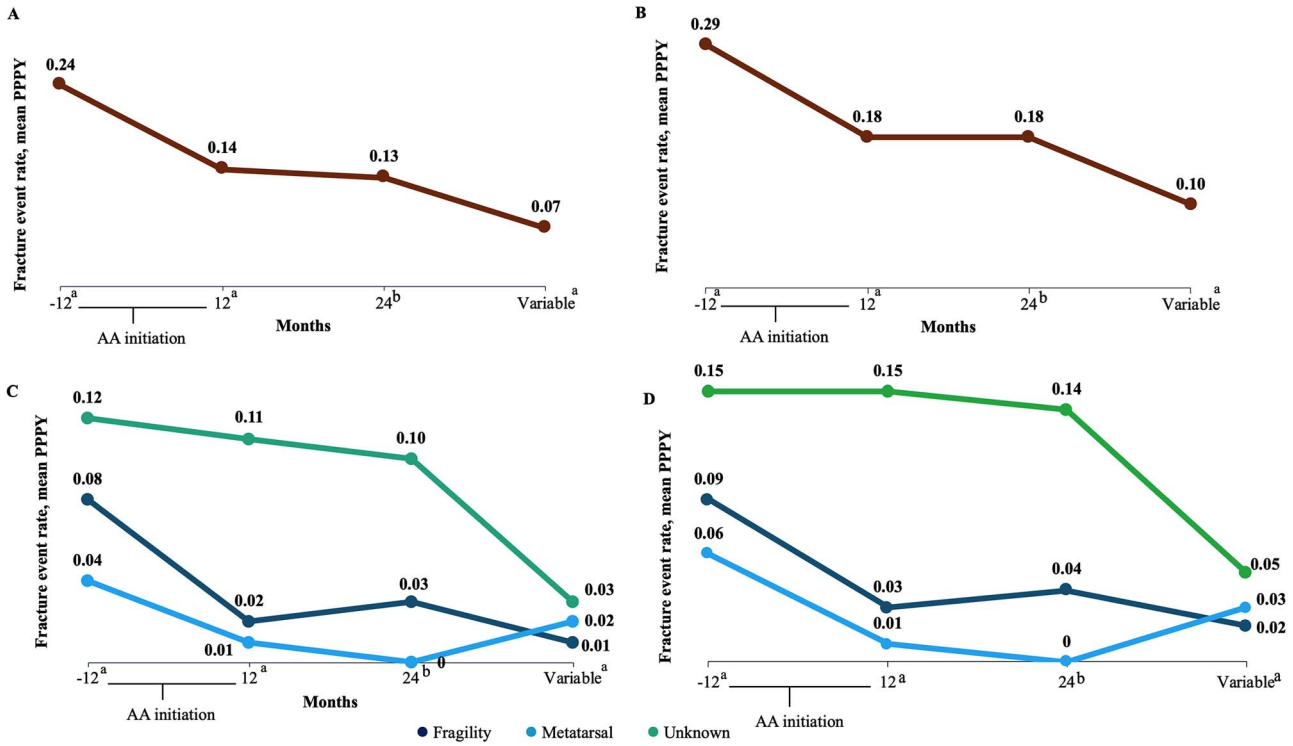


Figure 3. Overall fracture event rates after AA initiation in (A) all patients with HPP (B) and adult patients with HPP; fracture event rates across different fracture types after AA initiation in (C) all patients with HPP and (D) adult patients with HPP. Variable months: patients were followed for a minimum of 12 mo post-AA initiation, with some patients having follow-up data extending beyond 12 mo. Fractures may fall into multiple fracture categories. Patients may have more than 1 type of fracture. Fractures were classified as unknown type when they were neither metatarsal nor fragility fractures. [a]*N* = 149. [b]*N* = 104. Abbreviations: AA, asfotase alfa; HPP, hypophosphatasia; PPPY, per patient per year.

12 mo (0.29 vs 0.18; $p = .139$) and 24 mo (0.29 vs 0.18; $p = .139$) following AA initiation. A statistically significant reduction was observed after the variable-length follow-up period (mean [SD]: 0.29 [0.55] vs 0.10 [0.48]; $p < .001$; Figure 3B). The mean number of overall fractures per pediatric patient PY decreased after 12 mo, though the change was not statistically significant (0.13 vs 0.04; $p = .439$).

When stratified by fracture type, the mean number of fragility fractures PPPY significantly decreased after 12 mo (0.08 vs 0.02; $p = .019$), 24 mo (0.08 vs 0.03; $p = .025$), and the variable-length follow-up period (0.08 vs 0.01; $p = .014$) following AA initiation (Figure 3C). The mean number of fragility fractures per adult patient PY significantly decreased after 12 mo (0.09 vs 0.03; $p = .014$), 24 mo (0.09 vs 0.04; $p = .024$), and the variable-length follow-up period (0.09 vs 0.02; $p = .025$; Figure 3D). The mean number of fragility fractures for pediatric patients PPPY decreased, but was not statistically significant, after 12 mo (0.07 vs 0.00; $p = .323$) following AA initiation.

In the subanalysis of patients who experienced a fracture in the 12 mo pre-AA initiation, the mean number of overall fractures PPPY significantly decreased after 12 mo of AA initiation (1.33 vs 0.37; $p < .001$; Figure 4A). The mean number of fractures PPPY significantly decreased across all fracture types after 12 mo of AA initiation: fragility fractures (1.50 vs 0.38; $p = .007$), metatarsal fractures (1.20 vs 0.00; $p = .004$), and unknown fractures (1.20 vs 0.47; $p = .006$; Figure 4B). Patients experienced an average of 1.33 fractures PY

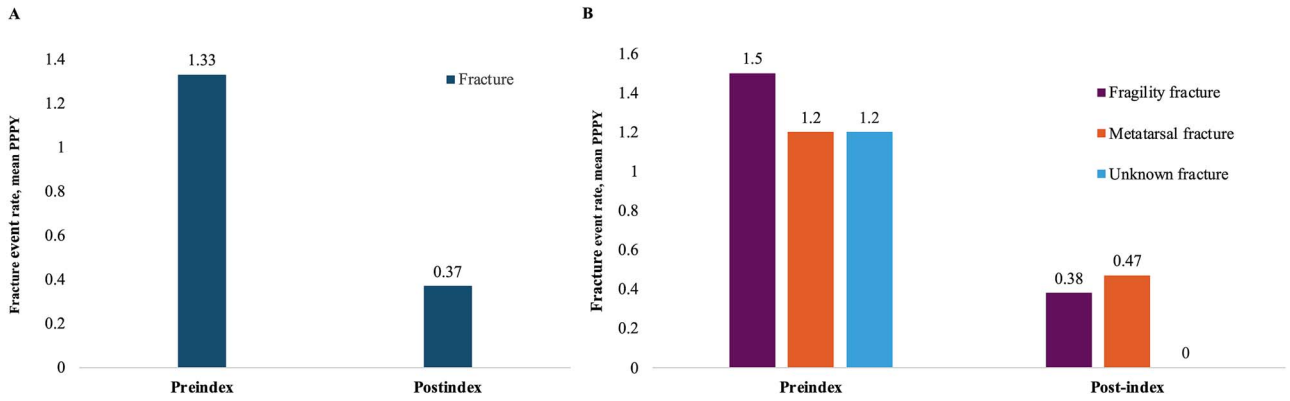


Figure 4. (A) Overall fracture event rates after AA initiation in all patients with HPP who experienced a fracture in the 12 mo pre-AA initiation. (B) Fracture event rates across different fracture types after AA initiation in all patients with HPP who experienced a fracture in the 12 mo pre-AA initiation. Preindex, 12 mo before AA initiation. Postindex, 12 mo after AA initiation. Fragility fracture sites include spine, hip, and wrist. Fractures were classified as unknown when they were neither metatarsal nor fragility fractures. Abbreviations: AA, asfotase alfa; HPP, hypophosphatasia; PPPY, per patient per year.

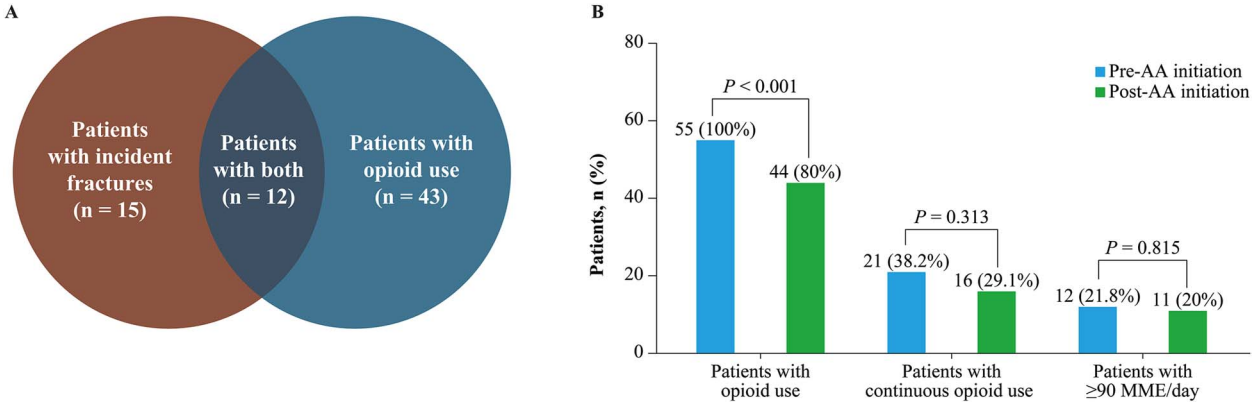


Figure 5. (A) Association of fractures and opioid use, and (B) opioid sparing in patients after 12 mo of AA initiation. Patients who did not have a gap of ≥60 d in opioid use were categorized as having continuous opioid use. Abbreviations: AA, asfotase alfa; MME, morphine milligram equivalent.

pre-AA initiation and an average of 0.37 fractures following AA initiation.

Opioid sparing

Fracture incidence among patients with opioid use prior to AA initiation

Twelve (21.8%) patients with baseline opioid usage experienced a fracture during the baseline period (Figure 5A). No association was found between the incidence of fractures and the use of opioids among patients pre-AA initiation ($p = .370$), suggesting that most patients using opioids may have experienced HPP-related pain unrelated to fracture.

Opioid sparing in patients who used opioid pre-AA initiation (baseline period)

Of patients using opioids before AA initiation, 20.0% lacked a claim for opioids after initiation of AA (Figure 5B). A total of 38.2% of patients during the baseline period did not have a 60-d gap in opioid supply, compared with 29.1% after initiation of AA (Figure 5B). Of patients using opioids at baseline, 21.8% were taking high-dose opioids (≥90 MME/d; Figure 5B). An additional 7% of patients filled opioid prescriptions during the follow-up period who had not filled opioid prescriptions during the baseline period.

Healthcare resource utilization

All-cause HCRU

At baseline, most patients had at least 1 physician office/outpatient visit (145/149 [97.3%]) or pain management-related visit (105/149 [70.5%]). Many patients also had at least 1 mental/behavioral health visit (64/149 [43.0%]), ED visit (55/149 [36.9%]), or physical medicine or rehabilitation visit (26/149 [17.4%]). Fewer patients had an inpatient hospitalization (<11/149 [<7.4%]) or orthopedic surgery visit (<11/149 [<7.4%]).

Medical procedure utilization

Fewer patients received imaging (122/149 [81.9%] vs 108/149 [72.5%]; $p = .040$) and bone density testing (59/149 [39.6%] vs 37/149 [24.8%]; $p = .005$) after initiating AA (Table 3).

Discussion

This retrospective claims study provides valuable insights into the effectiveness of AA treatment on fracture outcomes, opioid usage, and HCRU among patients with HPP in the United States. Our study population predominantly consisted of adults, most of them females, with a considerable proportion of patients enrolled in Medicare FFS and commercial insurance plans. These findings align with earlier studies

Table 3. Procedure utilization in patients after initiation of AA.

Patients receiving medical procedure of interest,[a] *n* (%)	Patients with HPP (age ≥ 2 yr) (*N* = 149)				
	Pre-AA initiation[b]		Post-AA initiation[c]		*p*-value
Imaging	122	(81.9)	108	(72.5)	.040
Physical/occupational therapy	62	(41.6)	59	(39.6)	.728
Fracture surgeries	<11	(<7.4)	<11	(<7.4)	.803
Laboratory testing	49	(32.9)	43	(28.9)	.391
Bone density testing	59	(39.6)	37	(24. 8)	.005
Functional testing	<11	(<7.4)	<11	(<7.4)	.501

[a]Patients may fall into multiple procedure categories. [b]Pre-AA initiation: 12 mo of data prior to AA initiation. [c]Post-AA initiation: 12 mo of data after AA initiation. Abbreviations: AA, asfotase alfa; HPP, hypophosphatasia.

evaluating the safety and efficacy of AA in patients with HPP, which similarly reported that most patients were adults and predominately female.[2,15] In the current study, the high prevalence of musculoskeletal and mental health conditions observed at baseline in patients with HPP receiving AA treatment is consistent with findings from the existing body of literature, including Global HPP Registry data.[25] This underscores the multifaceted clinical profile of patients with HPP requiring AA treatment.

Following 12 mo of AA treatment, there was a statistically significant reduction in patients experiencing fractures, particularly a pronounced reduction in those experiencing fragility fractures. These results suggest that AA may play a crucial role in mitigating fracture risk, particularly among patients with a history of fracture. A phase 2 interventional study reported improved skeletal mineralization associated with AA treatment in patients with HPP.[14] Additionally, a notable reduction in mineralization lag time from baseline was observed in adults and adolescents with HPP treated with AA for 12 mo.[15] Our study further demonstrates that the fracture rate decreased after 12 mo of AA initiation and decreased substantially after 24 mo and during the variable-length follow-up period. Our study showed a sustained reduction in fracture rates, reinforcing the potential long-term benefits of AA. This corroborates previous studies demonstrating improvements in skeletal manifestations in patients with HPP treated with AA for a median of 2.3 yr, and up to 6 yr of treatment.[10] To the best of our knowledge, these are the first real-world data demonstrating the efficacy of AA in reducing fracture rates in patients with HPP.

Opioids have long been used as analgesics for pain management.[26] While opioid analgesics were commonly used prior to AA initiation, our results suggest no significant association between opioid use pre-AA initiation and fracture incidence. This indicates that patients included in the current study may be using opioids to manage nonfracture-related pain. Opioid use is seen among patients with fractures, but it may also be utilized by patients with HPP for diffuse pain related to their underlying musculoskeletal disease, making it challenging to distinguish the extent to which opioid use reflects fracture-related pain vs pain from the broader disease process.[27] Among patients with opioid claims prior to AA initiation, a reduction in opioid claims was observed post-AA initiation. However, a small proportion of patients initiated opioid use post-AA initiation. This finding is particularly relevant in the context of ongoing efforts to reduce opioid dependency among patients.

The heterogenous clinical burden of HPP exerts a considerable impact on HCRU among patients.[20] Approximately 40% of patients qualified for Medicare due to disability and presented with several clinical conditions at baseline, including musculoskeletal and rheumatic conditions. Notably, 37% of patients had a mental health condition, exceeding the 23% prevalence observed in the general US population. In addition, there was substantial use of antidepressants and opioid analgesics at baseline. This distinction underscores the significant disease burden within this cohort, potentially influencing their healthcare needs.

Our study documents a substantial proportion of patients with outpatient visits and pain management-related visits at baseline. These findings are consistent with a previous case study on HCRU, particularly outpatient visits, as observed in patients with HPP in the United Kingdom.[20] Earlier reports have documented that patients with HPP frequently undergo imaging procedures and bone density testing as a part of their clinical management.[20] Our study reported a substantial reduction in the proportion of patients receiving imaging and bone density testing after initiation of AA; however, this may be attributed to the standard frequency of diagnostic interventions, which may decrease as the patient's condition stabilizes, as well as the standard frequency of routine scans. Bone density scanning is covered every 2 yr by Medicare and is not routinely conducted every year. Moreover, the clinical utility of DXA in assessing bone density in adults with HPP appears to be compromised. Once the diagnosis of HPP is established, reliance on DXA as a surrogate marker for treatment response or fracture risk assessment becomes questionable.[28]

Study limitations

The claims databases used in the current study include insured patients. Therefore, the findings from this study may not be generalizable to uninsured individuals, self-pay patients, military or veteran health services, or healthcare systems outside of the United States. This was a descriptive study, and the results were not statistically adjusted for potential confounding factors. There are no ICD-10-CM diagnosis codes for HPP. Consequently, prescription claims for AA, which is used exclusively to treat HPP, were used as a proxy to identify patients with HPP. Since administrative claims data were generated for billing and reimbursement purposes, some data captured may not be documented correctly. As the unique fractures are not explicitly coded in the claims database, they

were identified using an algorithm based on ICD-10 diagnostic codes and may not be precise counts. Fractures occurring >12 mo before the index date were not captured. Patient or event counts <11 were suppressed to protect patient privacy, and thus exact values could not be reported in some cases. Medication usage for this study was based on filled outpatient prescriptions and medical claims for physician-administered medications; patients were assumed to take the medications as prescribed, although this could not be confirmed. The reason for cessation of opioid use in patients is not captured in the claims database. Additionally, the use of over-the-counter pain medications was not captured in the claims database. This study did not include information about the time of fracture healing or major osteoporotic fractures, which could be a promising area of future research.

Conclusions

This observational, retrospective administrative claims study highlights the association between AA treatment and reduced fracture rates in patients with HPP. Many patients had clinical conditions, including mental health disorders, highlighting the disease burden in this population. While not a comparative effectiveness study, these findings support the consideration of AA for patients at high risk of fractures, to improve outcomes and reduce healthcare burden.

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Author contributions

Genevieve Lyons (Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Supervision, Validation, Writing—review & editing), Toby Bates (Conceptualization, Formal analysis, Writing—review & editing), Jon Vlasnik (Conceptualization, Formal analysis, Writing—review & editing), Craig Wakeford (Conceptualization, Formal analysis, Writing—review & editing), Elizabeth A. Donckels (Data curation, Formal analysis, Methodology, Writing—review & editing), Philip K. Chan (Data curation, Formal analysis, Methodology, Writing—review & editing), Scott B. Robinson (Data curation, Formal analysis, Methodology, Writing—review & editing), and Kathryn M. Dahir (Conceptualization, Supervision, Writing—review & editing)

Supplementary material

Supplementary material is available at *JBMR Plus* online.

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Conflicts of interest

G.L., T.B., J.V., and C.W. are employees of Alexion, AstraZeneca Rare Disease and hold stock in the company. E.A.D. and P.K.C. are employees of Inovalon. Inovalon received funding to perform this study. P.K.C. holds stock in AstraZeneca. S.B.R. was an employee of Inovalon at the time of this study. K.M.D. is a clinical trial investigator and has received institutional grant support from Alexion, AstraZeneca Rare Disease, Kyowa Kirin, Ultragenyx, Sanofi, and Regeneron. She serves on scientific advisory boards and acts as a consultant for Alexion, AstraZeneca Rare Disease, Kyowa Kirin, and Ultragenyx.

Data availability

Alexion, AstraZeneca Rare Disease will consider requests for disclosure of clinical study participant-level data provided that participant privacy is assured through methods like data deidentification, pseudonymization, or anonymization (as required by applicable law), and if such disclosure was included in the relevant study informed consent form or similar documentation. Qualified academic investigators may request participant-level clinical data and supporting documents (statistical analysis plan and protocol) pertaining to Alexion-sponsored studies. Further details regarding data availability and instructions for requesting information are available in the Alexion Clinical Trials Disclosure and Transparency Policy at https://www.alexionclinicaltrialtransparency.com/data-requests/.

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