

Case Report

Impact of discontinuing 5 years of enzyme replacement treatment in a cohort of 6 adults with hypophosphatasia: A case series

Cheryl Rockman-Greenberg^{a,*}, Robert Josse^b, Mira Francis^c, Aziz Mhanni^a^a University of Manitoba, Winnipeg, Manitoba R3E 3P4, Canada^b St. Michael's Hospital, Toronto, Ontario M5B 1W8, Canada^c Alexion, AstraZeneca Rare Disease, Vaughan, Ontario L4K 0G6, Canada

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ABSTRACT

Asfotase alfa is a human recombinant enzyme replacement therapy for hypophosphatasia. We describe 6 adults who were treated with asfotase alfa for 61–68 months in a clinical trial (NCT01163149), after which asfotase alfa was discontinued for 15–48 months. The patients experienced clinical deterioration and, when treatment was restarted, showed improvement. Patients with hypophosphatasia should be closely monitored if asfotase alfa is stopped as clinical decline is likely. Clinical practice guidelines are needed.

1. Introduction

Hypophosphatasia (HPP) is a rare, inherited inborn-error-of-metabolism caused by pathogenic variants (heterozygous/homozygous) of the tissue-nonspecific alkaline phosphatase (TNSALP) gene, *ALPL* (Conti et al., 2017; Weiss et al., 1988; Whyte, 2017). Low TNSALP activity results in extracellular accumulation of the TNSALP substrates inorganic pyrophosphate (PPi), pyridoxal 5'-phosphate (PLP), and phosphethanolamine (Conti et al., 2017). Accumulation of PPi leads to inhibition of bone mineralization and causes rickets in children and osteomalacia in adults; accumulation of PLP can also cause vitamin B₆-dependent seizures in children (Conti et al., 2017; Balasubramaniam et al., 2010). Onset of HPP can occur at any time from in utero and infancy through adulthood, with presentation varying within and between families (Conti et al., 2017; Mornet, 2007) and clinical manifestations varying with age at the time of onset. These manifestations can include skeletal deformities, dental problems, musculoskeletal pain, muscle weakness, impaired mobility, and disability (Whyte, 2017). Because of this wide range of manifestations involving many body systems, HPP is associated with a significant burden of disease, including hindered physical function, anxiety, and depression, for perinatal/infantile- and juvenile-onset disease (Durrrough et al., 2021).

Asfotase alfa (Strensiq®, Alexion, AstraZeneca Rare Disease, Boston, MA, USA) is a human recombinant TNSALP enzyme replacement therapy (ERT) approved for the treatment of perinatal/infantile- and

juvenile-onset HPP (Strensiq [package insert], 2020). Two clinical studies have shown that adults and adolescents with pediatric-onset HPP had reductions in both PPi and PLP concentrations, as well as improved physical function, during up to 5 years of asfotase alfa treatment; asfotase alfa was also well tolerated (Kishnani et al., 2019; Seefried et al., 2021). A separate retrospective analysis of real-world data in adults with pediatric-onset HPP treated with asfotase alfa for at least 12 months confirmed these results, showing improved physical function and health-related quality of life from baseline through 3, 6, and 12 months of treatment (Genest et al., 2020).

Although prior studies provide valuable insight into the role of asfotase alfa in treating patients with HPP, there remains a need to better characterize adults in this population (Seefried et al., 2020). Data on the long-term motor and overall functioning of adults with HPP are lacking and require refinement based on clinical evidence (Durrrough et al., 2021). Clearer, more specific treatment guidance and diagnostic criteria in adults are needed to improve disease management and patient care.

In addition, HPP is a lifelong disease, and it is unknown whether lifelong treatment with ERT in children and adults is needed (Huggins et al., 2020). Based on our knowledge of the pathogenesis of HPP, one might anticipate deterioration and reemergence of clinical, biochemical, and radiologic manifestations of HPP if ERT is withdrawn. Indeed, limited clinical evidence suggests that long-term interruptions in asfotase alfa treatment in young patients can lead to a dangerous rebound of HPP (Rockman-Greenberg, 2019). However, such data are lacking in

* Corresponding author at: University of Manitoba and Children's Hospital Research Institute of Manitoba, Room 511 - 715 McDermot Avenue, Winnipeg, Manitoba R3E 3P4, Canada.

E-mail address: cgreenberg@hsc.mb.ca (C. Rockman-Greenberg).

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adults.

This report details a case series of 6 adult patients with HPP who received ERT as part of a cohort of 19 patients who had participated in a phase 2 clinical trial (NCT01163149; Study 009) (Kishnani et al., 2019). Asfotase alfa treatment was discontinued in these 6 patients after completion of the trial but was later reinitiated. The main objective of this report is to provide insight into the natural history of HPP, the impact of discontinuing ERT in adults with HPP who had received ERT for up to 5 years, and the clinical course after reinitiation of ERT with asfotase alfa.

2. Cases

Among the 6 adult patients with HPP who discontinued and then reinitiated asfotase alfa treatment, 1 patient decided to discontinue ERT 1 year before the end of the clinical trial and then received asfotase alfa through compassionate use under the Global Access to Medicines Program (time off therapy was 48 months). The remaining 5 patients restarted ERT 15–17 months after stopping asfotase alfa at the end of the trial. Demographics and details of the individual treatment histories of these 6 patients are summarized in Table 1. Clinical characteristics are summarized in Fig. 1 and Table 2.

Overall, during the clinical trial, functional improvement was evident in the results of the 6-Minute Walk Test, reductions in pain medication, and improvements in quality of life. All patients were taking analgesics at baseline, and scores on the pain domain of the 36-item Short Form Health Survey (SF-36) were available for 5 patients after study discontinuation. Pain worsened in 4 of the 5 patients after discontinuation of asfotase alfa and improved 6 months after reinitiation (Fig. 1A). However, patients rated pain as having a greater impact on quality of life after reinitiation of ERT. Alkaline phosphatase concentrations returned to pretreatment levels in all patients after discontinuation of asfotase alfa and improved after reinitiation (Fig. 2A). Other biomarkers, including calcium, and 25-hydroxy vitamin D remained within normal limits (Fig. 2). Vitamin B₆ levels, available for some patients, decreased substantially after reinitiating asfotase alfa. Scores on

the physical function domain of the SF-36 indicated improvement in quality of life after reinitiation of asfotase alfa (Fig. 1B). A brief overview of each individual case follows.

2.1. Patient 1

This patient first presented with signs and symptoms of confirmed HPP at 1 month of age. This patient is a compound heterozygote for pathogenic *ALPL* missense variants (c.550C>T and c.571G>A). During childhood, she manifested an abnormally shaped head, bowing of legs, delayed walking with an unusual gait, and numerous poorly healing fractures. During adulthood, she had a history of no fewer than 9 major long bone fractures, as well as pseudofractures requiring numerous related surgeries; severe osteoarthritis with recurrent joint swelling, chronic joint pain, muscle pain, and muscle weakness; and severe limitations in activities of daily living. Treatment with asfotase alfa began in August 2010 at age 56 years and continued until the end of study in 2016. Baseline transiliac bone biopsy at study enrollment showed typical features of increased osteoid and mineralization lag typical of HPP, with follow-up biopsy showing improvement in the osteoid indices. When medication was discontinued, all the gains experienced during the 5 years of the clinical trial were lost and the patient again experienced more significant pain, had repeated fractures, and required more assistive devices for ambulation (Table 2). After restarting asfotase alfa, pain scores associated with normal work and sleep improved; however, the pain domain of the SF-36 indicated a worse impact of pain on overall quality of life following reinitiation of ERT.

2.2. Patient 2

This patient was a compound heterozygote for 2 pathogenic *ALPL* missense variants (c.571G>A and c.1001G>A). The patient's first signs and symptoms of HPP were bowed legs, chest wall deformity (pectus carinatum), leg pain, joint pain, premature loss of deciduous teeth, and rickets. Other HPP-specific medical history included unusual gait; pain severe enough to limit activity and require pain medication; history of

Table 1
Summary of demographics and treatment course.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Demographics						
Sex	Female	Male	Male	Male	Female	Female
Race	White	White	White	White	White	White
Height/weight/BMI	145 cm/ 56.8 kg/ 27.0 kg/m ²	174 cm/ 90.7 kg/ 30 kg/m ²	172 cm/ 96.4 kg/ 32.6 kg/m ²	164 cm/ 88.6 kg/ 32.9 kg/m ²	174 cm/ 68.4 kg/ 22.6 kg/m ²	164 cm/ 69.0 kg/ 25.7 kg/m ²
<i>ALPL</i> mutation	Compound heterozygous: c.550C>T and c.571G>A	Compound heterozygous: c.571G>A and c.1001G>A	Compound heterozygous: c.571G>A and c.1001G>A	Heterozygous: c.551G>A	Heterozygous: c.1001G>A	Compound heterozygous: c.550C>T and c.571G>A
Treatment course						
Age at study entry, years	56	64	26	57	44	55
Age at onset of symptoms	1 mo	Unknown	2 y	2 y	36 y	2 y
Duration from disease onset to treatment initiation, years	56	Unknown	24	55	8	53
Date of treatment initiation	8-11-2010	10-13-2010	10-20-2010	11-3-2010	3-21-2011	3-16-2011
Date of last overall visit in trial	2-18-2016	4-21-2016	11-15-2015 (Week 264)	5-17-2016	4-12-2016	4-16-2016
Treatment end date	5-5-2016	4-20-2016	11-15-2015	5-18-2016	4-13-2016	5-5-2016
Duration off treatment, months	15	17	48	15	16	15
Date of treatment reinitiation	8-2017	8-2017	12-2019	8-2017	8-2017	8-2017

BMI, body mass index.

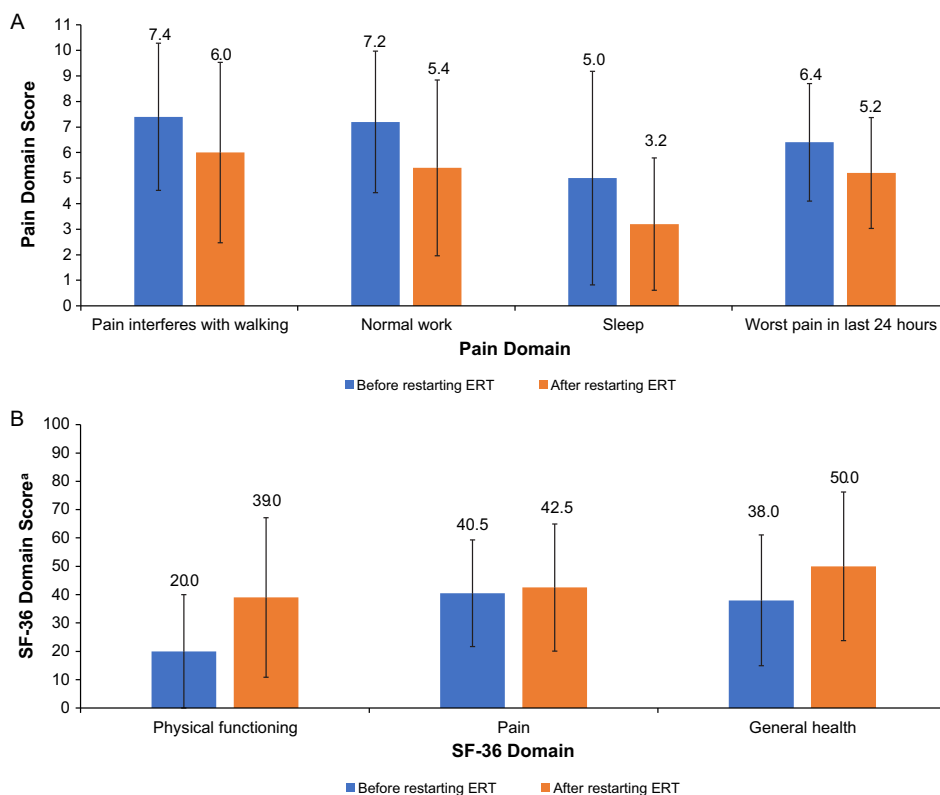


Fig. 1. Mean (SD) changes in pain and quality of life after reinitiation of asfotase alfa ($n = 5$). A. Pain. B. SF-36. ERT, enzyme replacement therapy; SF-36, 36-item Short Form Health Survey.

^aScores for each domain range from 0 to 100, with a higher score defining a more favorable health state (Ware and Sherbourne, 1992).

multiple poorly healing fractures, pseudofractures, joint swelling, decreased range of motion in elbows (limited by pain), muscle pain and weakness, gout, and kidney stones; and loss of adult teeth leading to use of upper and lower dentures. At the time of study entry at age 64 years, this patient had advanced disease and numerous comorbidities. He started treatment with asfotase alfa in October 2010 and discontinued in April 2016, when the patient again suffered severe limitations in activities of daily living with reduced mobility and increased pain. These manifestations were ameliorated when the drug was reinitiated. Vitamin B₆ levels decreased from 509 nmol/L when off treatment to 10 nmol/L after treatment reinitiation. The patient developed multiple myeloma in 2021 and died.

2.3. Patient 3

This patient was diagnosed with HPP following premature tooth loss at age 2 years; he was found to be a compound heterozygote for pathogenic *ALPL* missense variants (c.571G>A and c.1001G>A). He had a history of 6 fractures in childhood and early adulthood requiring open reduction and internal fixation with plates and screws or titanium rods. He also underwent 2 craniectomies for craniosynostosis and had excessive cavities requiring root canal surgery and other dental issues. He has a history of nephrocalcinosis and kidney stones. Pain medication was required daily as were vitamin and dietary supplements. At enrollment into the asfotase alfa clinical trial at age 26 years, baseline strength measurements were markedly below normal and the patient required assistive devices to ambulate. Strength greatly improved during treatment with asfotase alfa but deteriorated significantly after treatment was stopped. When treatment was reinitiated, the patient's functional status and quality of life improved significantly, leading to a reduction in pain medication. Vitamin B₆ levels decreased from 641 nmol/L when off treatment to 50 nmol/L after treatment reinitiation.

2.4. Patient 4

This patient is known to have a dominant form of HPP (heterozygous pathogenic *ALPL* missense variant c.551G>A). The patient's first signs and symptoms of HPP were loss of baby teeth at age 2 years, followed by tooth decay and multiple root canals during adolescence and adulthood. Additional HPP-related medical history included unusual gait, knock knees, long bone fractures, pseudofractures, joint pain and swelling, muscle pain and weakness, bone pain severe enough to limit activity and require pain medications, gout, pneumonia, kidney stones, excessive cavities, and loss of adult teeth. He started asfotase alfa treatment in November 2010 at age 57 years and discontinued in May 2016. After the medication was discontinued, the patient suffered more significant pain, recurrent stress fractures, and limited mobility. However, pain scores and scores on the pain domain of SF-36 continued to worsen after restarting asfotase alfa and had not yet returned to baseline values at the end of the clinical trial. Vitamin B₆ levels decreased from 186 nmol/L when off treatment to 12 nmol/L after treatment reinitiation.

2.5. Patient 5

Patient 5 was found to be a manifesting HPP carrier (heterozygous for a known missense pathogenic variant in the *ALPL*, c.1001G>A) following an incidental finding of low alkaline phosphatase at age 36 years. Her HPP-related medical history included several stress fractures and a finger fracture, as well as joint pain, muscle pain and weakness, and severe bone pain. Bone biopsy confirmed the mineralization defect typical of HPP. The patient-initiated treatment with asfotase alfa in March 2011 at age 44 years, after which scores on all SF-36 domains improved. Treatment with asfotase alfa was discontinued in April 2016, at which time, the patient suffered more significant pain and repeated stress fractures, which was associated with worse quality of life. After

Table 2
Clinical characteristics of adult patients with HPP On and Off ERT.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Pain						
Study baseline	Moderate pain: Knee, shoulder, foot pain	Moderate to severe pain (score of 8 at baseline): Hand, wrist, neck, upper back, bilateral arm pain	Mild to moderate pain; scores ranged from 1 to 5 Right rotator cuff pain	Mild to moderate pain (score of 6 at baseline)	No pain at baseline	Moderate pain: Joint pain, hip pain, bone pain
Study completion	Sustained moderate levels of pain throughout the study, with scores ranging from 4 to 6	Sustained moderate to severe pain through Week 96, with some improvement observed at Week 120 (score of 3)	Sustained mild to moderate levels of pain throughout the study; scores ranged from 1 to 5	Mild to moderate pain (score of 3 at Week 24, 6 at Week 96)	No pain through Week 12 (score of 0) and mild pain at later time points, with mean pain scores increasing from Week 24 (mean score of 1) through Week 96 (mean score of 3)	Moderate pain at Week 24 (mean score of 6), mild pain (score of 1 to 3) at the time of the other assessments
Concomitant medications						
Study baseline	Acetaminophen, amoxicillin, codeine, menthol with methyl salicylate cream, methylprednisolone, morphine, oxycodone	Acetaminophen, codeine, gabapentin, ibuprofen, methocarbamol, mineral supplements, naproxen, prednisone, tramadol	Ibuprofen, naproxen	Acetaminophen, amitriptyline, codeine, diclofenac, ibuprofen, morphine, naproxen	Acetaminophen, ibuprofen, naproxen, propionic acid derivatives	Acetaminophen, codeine, ibuprofen, methylprednisolone, naproxen
Last registry visit	Acetaminophen, methocarbamol	Not available	Not available	Acetaminophen, codeine, diclofenac, ketorolac tromethamine, naproxen	Acetaminophen, codeine, ibuprofen, naproxen	Not available
Use of assistive devices						
Prior to restarting ERT	Cane, walker, modification to bath/shower, long-handled appliances	Not available	Cane, special or built-up chair, modification to toilet/bath/shower, long-handled appliances	None used	Orthotic shoes, jar opener	Cane, table, props, modification to bath/shower
Most recent follow-up	Walker, cane, modification to bath/shower, jar opener, long-handled appliances	Not available	Cane, special or built-up chair, modification to toilet/bath/shower, long-handled appliances	None used	Orthotic shoes, left-hand splint, jar opener	Jar opener

ERT, enzyme replacement therapy.

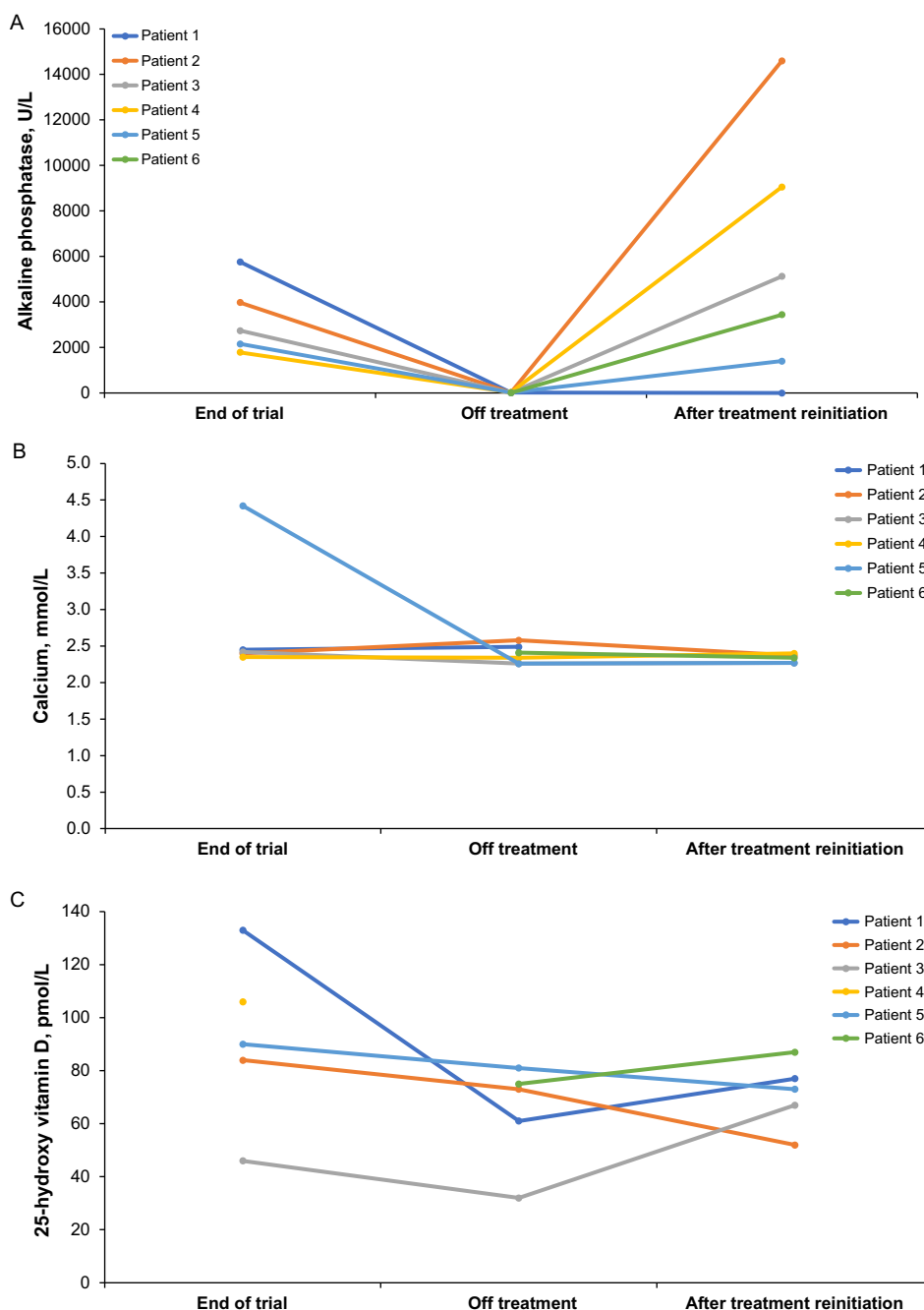


Fig. 2. Plasma concentrations of key metabolites at the end of treatment in the clinical trial, after treatment discontinuation, and approximately 1 year after reinitiation of asfotase alfa. A. Alkaline phosphatase. B. Calcium. C. 25-hydroxy vitamin D.

restarting ERT, most pain measures improved, but the SF-36 pain domain scores indicated a worsened impact of pain on quality of life, which had not returned to baseline at end of the clinical trial. Vitamin B₆ levels decreased from 245 nmol/L when off treatment to 61 nmol/L after treatment reinitiation.

2.6. Patient 6

This patient had a confirmed HPP diagnosis after early loss of teeth at the age of 2 years in the context of a known positive family history. This patient is a compound heterozygote for pathogenic *ALPL* missense variants (c.550C>T and c.571G>A). Other HPP-related medical history included an unusual gait and recurrent fractures in early adulthood requiring multiple surgeries, joint pain, muscle pain and weakness, and

severe bone pain requiring chronic pain medication and impacting activities of daily living. She initiated asfotase alfa as part of the clinical trial at age 55 years. At baseline, prior to entry into the clinical trial, the patient used bilateral foot orthotics. After discontinuation of asfotase alfa at the end of the clinical trial, the patient experienced significant clinical deterioration. She needed to resume use of assistive devices, including a walker for ambulation, and experienced significant pain and recurrent fractures. Pain scores, functional status, and quality of life scores on the SF-36 also deteriorated following ERT discontinuation but significantly improved once asfotase alfa was reinitiated.

3. Discussion

To our knowledge, our case series is the first to provide real-world

evidence of the impact of both asfotase alfa treatment interruption and reinitiation in adults with HPP. The 6 adults in our case series were aged 26–64 years at the time of study entry and had disease onset from ages 1 month to 36 years. During the trial, improvements were documented in clinical signs and symptoms for the population as a whole, as shown by results on the 6-Minute Walk Test, alkaline phosphatase activity and other biochemical markers, and scores on the SF-36 pain domain (Kishnani et al., 2019). Conversely, discontinuation of ERT was accompanied by negative clinical sequelae, as anticipated given the pathogenesis of HPP. Four of the 5 patients for whom pain data were available after trial completion experienced worsening pain while off treatment. All of these patients had improved pain 6 months after restarting treatment with asfotase alfa. The improved pain scores were accompanied by an overall reduction in use of analgesics. However, 3 of 5 patients who completed the SF-36 reported a greater impact of pain on quality of life after restarting ERT; the reason for this contradiction is not clear. Four of these 5 patients also reported improvements in physical functioning after restarting asfotase alfa.

Regulatory approval of asfotase alfa was based on data from 99 patients with perinatal/infantile- or juvenile-onset HPP (Strensiq [package insert], 2020). Minimal real-world experience describing ERT for HPP in adults has been documented since approval (Magdaleno et al., 2019; Klidas et al., 2018). Additionally, there have been few reports of the impact of discontinuing asfotase alfa treatment in this population. Our search of the literature identified 3 case reports of patients who discontinued treatment (Rockman-Greenberg, 2019; Bowden and Adler, 2018; Mohseni et al., 2017). In the first case, a child with infantile-onset HPP who began treatment with asfotase alfa at age 4 months was considered a good responder for 6 years but developed hypercalcemia, as well as severe nausea, vomiting, and lethargy, after 12 weeks without the ERT; the child's condition deteriorated rapidly, and she died 4 days after developing hypercalcemia (Rockman-Greenberg, 2019). In the second case, a reappearance of hypomineralized bone was noted in an adolescent with childhood HPP who had been nonadherent to treatment for 1 year (Bowden and Adler, 2018). Finally, another adolescent patient with infantile HPP experienced deterioration of physical function and bone mineral density within months of discontinuing treatment because of injection-site lipohypertrophy (Mohseni et al., 2017). She subsequently resumed asfotase alfa treatment, resulting in less pain, increased bone mineral density, and increased physical endurance (Mohseni et al., 2017). Taken together with our case series, these results demonstrate the importance of continued treatment in children, adolescents, and adults with HPP, warranting intervention with asfotase alfa. Indeed, in at least 1 case, discontinuation resulted in a fatal outcome.

The results of this case series should be cautiously interpreted because of potential limitations. This retrospective analysis included a small number of cases, and data for all measures of interest were not collected consistently after the initial discontinuation of asfotase alfa as part of the clinical trial. However, objective results for measures of pain and quality of life after discontinuation of asfotase alfa are available for 5 of the 6 patients. Importantly, vitamin B₆ levels before and after discontinuation of asfotase alfa suggest that patients responded as expected after asfotase alfa was reintroduced. Alkaline phosphatase decreased to pretreatment levels as predicted after treatment with asfotase alfa was discontinued and then increased when treatment was reintroduced. Other biomarkers on and off asfotase alfa treatment, including calcium and 25-hydroxy vitamin D, did not fluctuate. Notably, serum calcium remained normal and is of particular importance because of the case of the 1 child who discontinued asfotase alfa and subsequently developed hypercalcemia and died (Rockman-Greenberg, 2019).

Although the results of this case series suggest that asfotase alfa discontinuation leads to unfavorable outcomes, such a conclusion remains uncertain and requires further study. If asfotase alfa is discontinued, it should be done with caution and the patient should be closely monitored for development of negative sequelae.

4. Conclusions

Discontinuing ERT in adults with HPP treated with asfotase alfa for prolonged periods was associated with varying degrees of clinical, radiologic, and biochemical deterioration, and reinitiating ERT was associated with clinical improvement. Our results suggest that abrupt cessation of ERT with asfotase alfa in adults who have received ERT for prolonged periods should not be recommended because clinical deterioration is likely to occur. The risks associated with treatment discontinuation are highlighted by a nonuniform improvement after reinitiation of asfotase alfa. Whether deterioration would occur in adults with HPP who were treated for shorter periods or in adults with HPP manifesting predominantly pain and fibromyalgia type symptoms is unknown. Given the potential dangers of treatment discontinuation, the decision to initiate ERT in adults with HPP must be carefully considered. Better clinical practice guidelines are needed to aid in identifying appropriate candidates for asfotase alfa treatment and the subsequent management of the disease. Given the complexity and heterogeneity of HPP, diagnostic criteria are an essential first step in developing treatment guidelines and will help inform indications for ERT in adults with HPP; these are currently in development.

Data sharing statement

Alexion, AstraZeneca Rare Disease will consider requests for disclosure of clinical study participant-level data provided that participant privacy is ensured through methods like data de-identification, 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, AstraZeneca Rare Disease Clinical Trials Disclosure and Transparency Policy at <https://alexion.com/our-research/research-and-development>.

(Link to Data Request Form: <https://alexion.com/contact-alexion/medical-information>).

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CRediT authorship contribution statement

Cheryl Rockman-Greenberg: Conceptualization, data curation, format analysis, investigation, methodology, project administration, writing – original draft, review, and editing.

Robert Josse: Conceptualization, data curation, format analysis, investigation, methodology, project administration, writing – original draft, review, and editing.

Mira Francis: Conceptualization, format analysis, investigation, methodology, project administration, writing – original draft, review, and editing.

Aziz Mhanni: Conceptualization, data curation, format analysis, investigation, methodology, project administration, writing – original draft, review, and editing.

Conflicts of interest

C. Rockman-Greenberg is a consultant for and has received research funding and honoraria from Alexion, AstraZeneca Rare Disease.

R Josse has participated on advisory boards and received honoraria from Alexion, AstraZeneca Rare Disease; Amgen Inc.; and Ultragenyx Pharmaceutical Inc.

M Francis is an employee of Alexion, AstraZeneca Rare Disease and may own stock/stock options in that company.

A Mhanni has participated on advisory boards and received honoraria from Alexion, AstraZeneca Rare Disease.

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