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Case Report

Enzyme replacement therapy in perinatal hypophosphatasia: Case report of a negative outcome and lessons for clinical practice

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ABSTRACT

Enzyme replacement therapy (ERT) is a newly approved disease-modifying treatment for hypophosphatasia (HPP), a rare metabolic bone disorder. With an orphan drug and ultra-rare disease, sharing information about responders and non-responders is particularly important, as any one centre's familiarity with its use will be limited. Nearly all published data in infants and very young children with life-threatening HPP are from three small clinical trials that have reported generally positive outcomes. We describe in detail a patient with perinatal HPP for whom treatment with ERT was not successful. Lessons learned from this case can inform clinical decision-making and provide topics for the research agenda. We also discuss practical and ethical challenges related to treatment of an ultra-rare disease with an expensive new medication in a publicly funded healthcare system.

1. Introduction

Hypophosphatasia (HPP; MIM#241500) is a rare metabolic disorder characterized by hypophosphatasemia and consequent defective skeletal mineralization [1]. The *ALPL* gene (MIM#171760) encodes the tissue-nonspecific isozyme of alkaline phosphatase (TNSALP), and mutations in *ALPL* are currently the only known cause of HPP [1,2]. The phenotypic spectrum of HPP is divided into six clinical categories, with perinatal HPP being the most severe and odontohypophosphatasia the least debilitating overall [1,3]. Genotype-phenotype correlations exist but are imperfect [4–6]. Historically, perinatal HPP was considered a lethal condition, with most dying soon after birth of restrictive lung disease [7,8].

Until recently, management of all forms of HPP was entirely symptomatic. There are now promising results with a disease-modifying treatment: enzyme replacement therapy (ERT) with recombinant human bone-targeted TNSALP (asfotase alfa, Strensiq®; Alexion Pharmaceuticals, Inc.) [1,9]. Regulatory bodies in Canada, the European Union, the United States, and Japan approved asfotase alfa for treatment of paediatric-onset HPP in 2015. To date, most available data regarding perinatal HPP are from three open-label phase II studies [10–12]. The initial clinical trial publication described treatment outcomes of ten children with perinatal or infantile disease, where all but one required breathing support at baseline [10]. Treatment with a one-time dose of 2 mg/kg IV, followed by 1–3 mg/kg/dose SC three times a week, resulted in radiographic evidence of skeletal healing in nine of ten participants. The sole case fatality in the study period was attributed to sepsis. After 48 weeks, six of nine were breathing ambient air without ventilator support while only one remained on full mechanical ventilation. In a follow-up publication that included additional individuals, 16 of 21 with perinatal or infantile HPP who required ventilator assistance but were treated with asfotase alfa survived for over 1 year [11]. Twelve of these 16 participants were successfully extubated. Similarly positive results have since been reported by a Japanese group, which conducted an open-label single-arm prospective study that included 6 individuals with perinatal HPP (and 13 individuals overall) [12].

To date, factors that influence treatment response and outcome are

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unknown, and when and how to declare treatment non-response is unclear. We report a patient with perinatal HPP for whom treatment with asfotase alfa was not successful. Based on this experience, we identify lessons learned that may help to inform the initiation and monitoring of treatment of affected neonates.

2. Case report

The infant was born to healthy non-consanguineous parents of Palestinian descent. An older sister is healthy, and the family history was non-contributory. The early pregnancy was uncomplicated. A level II fetal ultrasound at approximately 18–20 weeks gestation was reportedly normal, and throughout the pregnancy fetal movements were unremarkable. Another fetal ultrasound was performed at 40 weeks 2 days gestation for an unclear indication, and showed polyhydramnios and short femurs (65 mm; corresponding to 33 weeks 2 days gestation). Labour was induced at a hospital with a level II neonatal intensive care unit (NICU), and a baby girl was born at 40 weeks 3 days gestation by vaginal delivery. Birth weight (3310 g), length (49 cm), and head circumference (34 cm) were all near the 50th centile. There was a nuchal cord. Apgar scores were 7 and 8 at one and 5 min, respectively. She had significant subcostal retractions and poor air entry bilaterally. She required continuous positive airway pressure (CPAP) and fraction of inspired oxygen (FiO_2) up to 0.8 in the immediate neonatal period. The NICU team arrived at 10 min of life. A skeletal dysplasia was suspected on the basis of the chest x-ray and an abnormal physical examination, with depressible skull bones, a large anterior fontanelle, a bell-shaped chest, and the appearance of rhizomelia. Over her first two days of life, she was stable on CPAP with positive end-expiratory pressure (PEEP) 5–8 cm H_2O and FiO_2 0.3–0.4. Her work of breathing decreased and her rate of breathing improved. Serial arterial gases revealed a pH within the normal range and pCO_2 < 50 mmHg. For example, on day 2 the result was pH 7.36, pCO_2 47 mmHg, pO_2 70 mmHg, and bicarbonate 29 mmol/L (on FiO_2 0.42). On day 3, she had increasing oxygen requirements slowly over a period of hours. Her work of breathing worsened, with severe subcostal retractions and tachypnea up to 100–110 breaths per minute. A chest x-ray reportedly showed new severe confluent airspace opacities and ground glass infiltrates. Her arterial blood gas result was pH 7.07, pCO_2 103 mmHg, pO_2 68 mmHg, and bicarbonate 30 mmol/L (on FiO_2 0.98). She was intubated and ventilated for hypoxic hypercarbic respiratory failure, and repeat imaging revealed improved aeration but a persistent ground-glass appearance. She was transferred to our level IV NICU with pressure control tidal volumes between 15 and 20 mL, PEEP 6 cmH_2O, and FiO_2 0.55. The blood gas result at that time was pH 7.44, pCO_2 43 mmHg, pO_2 63 mmHg, and bicarbonate 29 mmol/L.

Initial laboratory investigations at our hospital were notable for an undetectable serum ALP level, with normal serum calcium and phosphate. Urine phosphoethanolamine was markedly elevated at 551 (range 1–63 mmol/mol cre). Plasma pyridoxal-5-phosphate (PLP) was elevated at 2660 (range 20–96 nmol/L). Plasma pyrophosphate (PPi) was not measured, as the assay is not commercially available. Skeletal x-rays on day 4 showed significantly diminished skull ossification, thin poorly mineralized ribs, and flaring and rachitic changes at the ends of the long bone metaphyses (Fig. 1 and Fig S1). No fractures were identified. There were no major findings on brain MRI, echocardiogram, or abdominal ultrasound done in the first week of life. She was diagnosed clinically with perinatal HPP. Later, targeted sequencing of *ALPL* and parental testing confirmed compound heterozygous pathogenic variants in the proband: c.[1171C > T];[1348C > T] / p.[(Arg391Cys)];[(Arg450Cys)] (NM_000478.4). Our patient's genotype is not previously reported. Her specific heterozygous variants were experimentally associated with 10.3% and 4.0% of wild-type enzyme activity, respectively, predicting a severe phenotype [4].

Expert consultation was sought from author C.R-G. The infant was considered a suitable candidate for ERT based on her initial chest x-rays, which showed a degree of pulmonary hypoplasia consistent with some previous treated neonates, and the minimal pressures required for ventilation. However, concerns were raised about cost (including of prolonged NICU care) and resource allocation. Uncertainties surrounding treatment with asfotase alfa were ultimately outweighed by the certainty of the outcome without treatment. The goals of ERT were to prolong life, help to wean from the ventilator, allow for good quality of life, and improve bone quality. A family meeting was held on day 8, and the parents elected to proceed with treatment. Asfotase alfa was initiated at 2 mg/kg/dose SC three times a week on day 13. The dose was sequentially increased to a supraphysiologic level in the absence of signs of clinical improvement, to a maximum of 9 mg/kg/dose on day 67 (Fig. 2). This decision was informed by the facts that the initial lower doses were well tolerated, that there remained no alternative therapies, and that author C.R-G. had prior positive clinical experiences increasing the dose of ERT. Throughout the treatment course, she was weaned from a maximum PEEP of 10 cmH_2O to 7 cmH_2O, but she did not tolerate further attempts at weaning. There were no significant episodes of aspiration pneumonia, severe atelectasis, or infection. Spontaneous breathing trials on days 55 and 56 were unsuccessful, with immediate respiratory distress. A chest x-ray on day 55 (Fig. 1) and additional skeletal x-rays on day 59 (Fig. S1) showed a generalized reduction in bone mineralization affecting almost the entire skeleton, with worsening osteopenia. She required immediate re-intubation after an unplanned extubation on day 69. The resulting chest x-ray showed some improvement in rib ossification compared with two weeks prior (Fig. 1). The ERT was decreased to 3 mg/kg/dose on day 75 because of very high ALP levels (> 12,000 U/L) consistent with drug absorption (Fig. 2).

Irritability was a significant component of her presentation and was managed with opiates. She was more distressed, with an increased oxygen requirement, during nursing interventions. Her disease course was otherwise notable for an absence of seizures. For a period of time, expressed breast milk was supplemented with a calcium-restricted formula because of hypercalcaemia. Later, calcium supplementation was started on day 59 because of hypocalcaemia (Fig. 2) suggestive of “hungry bones”. This has been seen previously in reported patients with infantile HPP early in the course of treatment, when skeletal mineralization starts to occur in response to asfotase alfa [10,12]. There was no evidence of calcium deposition on serial renal imaging and ocular examinations. There was also no evidence of increased intracranial pressure, a potential complication of craniosynostosis, on ocular exam. Feeding intolerance resulted in an uncomplicated gastrostomy tube insertion on day 90. There were no definite drug-related serious adverse events. We did not test for anti-asfotase alfa antibodies.

On day 95, the chest x-ray showed further interval increase in bone formation and ossification, but a persistently small chest size with accompanying suspected pulmonary hypoplasia (Fig. 1). Her ventilator settings and blood gas results had remained grossly unchanged for months. For example, on day 93 she was found to have pH 7.39, pCO2 40 mmHg, pO2 66 mmHg, and bicarbonate 23 mmol/L, in the setting of PEEP 7 cmH_2O, peak inspiratory pressure 21 cmH_2O, mean airway pressure 13 cmH_2O, tidal volume 4.7 mL/kg, and FiO_2 0.21. She was no longer receiving opiates for pain or other sedating medications. Pulmonary function could not be further assessed in the setting of intubation. There was no evidence of pulmonary hypertension on repeat echocardiogram, with an inability to estimate right ventricular systolic pressure due to inadequate tricuspid regurgitation jet, a round septum throughout the cardiac cycle, normal pulmonary vascular resistance (right ventricular ejection time (RVET)/pulmonary artery acceleration time (PAAT) ratio of 2.5), and normal right ventricular systolic function. She remained unable to be placed in the sitting position without associated respiratory distress. The attending physicians were concerned about the potential for progressive damage to her alveoli secondary to prolonged mechanical ventilation, and the likelihood of long-term – if not life-long - ventilator dependence. The parents were