Management of Tracheobronchomalacia During Asfotase Alfa Treatment in Infants With Perinatal-Onset Hypophosphatasia: A Case Series

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INTRODUCTION

- Hypophosphatasia (HPP), a rare and inherited metabolic disease resulting in hypophosphatemia of bone, is caused by loss-of-function mutations in the ALPL gene, which encodes bone-specific alkaline phosphatase (TNSALP).
- Perinatal HPP is characterized by respiratory failure secondary to poor skeletal mineralization, restrictive chest, and pulmonary hypoplasia.
- Tracheobronchomalacia (TBM) may contribute to respiratory failure in infants with HPP. TBM is characterized by weakness of the tracheal and bronchial walls caused by hypotonia of myoeelastic elements and softening of the supporting cartilage. The primary form of TBM is congenital and is caused by increased intrathoracic pressure (i.e., during forced expiration, coughing, or the Valsalva maneuver), which results in collapse during tidal expiration.

OBJECTIVE

- To characterize TBM in infants with HPP treated with asfotase alfa.

METHODS

Patients

- HPP diagnosis was confirmed in 4 patients by physical examination, skeletal survey, and serum biochemistry analysis (i.e., ALP, pyridoxal phosphate, and/or phosphoethanolamine levels) supplemented by genetic testing.
- TBM was identified by direct laryngotracheobronchoscopy or flexible bronchoscopy.

RESULTS

Respiratory Status

- Respiratory support requirements were documented and are defined as:
  - Mechanical ventilation via intubation or tracheostomy
  - Ventilation by continuous positive airway pressure (CPAP) or bilevel positive pressure support (bilevel PS)

Asfotase Alfa Administration

- Asfotase alfa was administered as a subcutaneous injection at an initial dose of 2 mg/kg 3 times per week (with dose adjustment as clinically indicated).

Genetic Analyses

- ALPL gene mutations were found in all 4 patients (Table 1): Patients 2 and 3 have compound heterozygous gene mutations, and Patients 1 and 4 have homozygous mutations.
- All mutations except the L53H, E57K,G239A,S247F mutation in Patient 2 have been previously reported.

Table 1. Baseline clinical characteristics at birth

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Birth weight</td>
<td>2.99 kg</td>
<td>3.56 kg</td>
<td>3.44 kg</td>
<td>3.19 kg</td>
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<tr>
<td>NELA genotype</td>
<td>[Glu744X, Del586X]</td>
<td>[Glu744X, Del586X]</td>
<td>[Glu744X, Del586X]</td>
<td>[Glu744X, Del586X]</td>
</tr>
<tr>
<td>ALPL activity</td>
<td>0.00%</td>
<td>0.00%</td>
<td>0.00%</td>
<td>0.00%</td>
</tr>
<tr>
<td>Respiratory status post-birth</td>
<td>Sub-glottic stenosis, intubation, ventilation starting at 2 wk</td>
<td>Sub-glottic stenosis, intubation, ventilation starting at 2 wk</td>
<td>Sub-glottic stenosis, intubation, ventilation starting at 2 wk</td>
<td>Sub-glottic stenosis, intubation, ventilation starting at 2 wk</td>
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Treatment and Patient Outcomes (Table 2)

- All patients required ventilatory support and subglottic tracheotomy for long-term ventilation with continuous positive expiratory pressure (PEEP, up to 12 cm H2O).
- TBM was confirmed within 4 months of birth in 4 infants, and intubation was initiated in 1 patient from the DNB-010 trial at an early age.
- All infants had frequent episodes of profound desaturations and bradycardias, and 3 infants had 4 experienced cardiac arrhythmias.
- Current Status (Table 2)
  - TBM completely resolved in Patients 1 and 4, and ventilator support has been discontinued.
  - TBM improved in Patient 2, the need for ventilator support persists, although the patient is weaning from PEEP and has brief ventilator-free periods during the day.
  - Patient 3 was discharged to home at age 15 months, but flexible bronchoscopy revealed significant TBM tracheomalacia with ventilator support remaining in place at age 23 months.

SUMMARY

- Infants with HPP who are treated with asfotase alfa require prolonged respiratory support with high PEEP to maintain intubation and ongoing CPAP to prevent collapse of airways.
- It is difficult to determine whether the improvements in TBM can be attributed to treatment with asfotase alfa or to gradual improvements in normal anatomy and airway patency that may occur naturally with age.

CONCLUSIONS

- Infants diagnosed with HPP during the perinatal period should be screened for TBM using direct laryngotracheobronchoscopy or flexible bronchoscopy if they require intubation or PEEP to maintain ventilation.
- Three of the infants with TBM who were treated with asfotase alfa had a survival rate of 95% at 1 year, in contrast, only 43% of historical controls who were untreated survived to age 1 year.

REFERENCES


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DISCLOSURES

FP and ENR have no conflicts of interest. ENB-010 (the clinical trial) was funded by Alexion Pharmaceuticals, Inc., the licensor of asfotase alfa, a therapeutic product. The clinical trial was registered at ClinicalTrials.gov (NCT01176266; EudraCT:2010-019850-42).