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Commentary

Clinical Outcome Assessments: Use of Normative Data in a Pediatric Rare Disease

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ABSTRACT

Pediatric rare diseases present unique challenges in clinical trial design and in selection of clinical outcome assessments (COAs) used to support claims in medical product labeling. COAs that discriminate level of function relative to a normative sample are particularly important in the pediatric rare disease setting because the literature is often void of natural history data. Pediatric rare disease clinical trials will often include a wide age distribution. Gross and fine motor skills, communication, cognition, and independence in activities of daily living vary by age, and it may be difficult to distinguish between treatment effect and change due to developmental maturation. Asfotase alfa was granted breakthrough therapy designation and subsequently approved for the treatment of hypophosphatasia (HPP; a genetic metabolic musculoskeletal disorder) and is used in this discussion to illustrate COA selection in a pediatric rare disease. Multiple COAs with normative data in HPP clinical trials for asfotase alfa are presented. The assessment instruments included the Bayley Scales of Infant and Toddler Development-Third Edition, the Bruininks-Oseretsky Test of Motor Proficiency, Second Edition, the Childhood Health Assessment Questionnaire, the Pediatric Outcomes Data Collection Instrument, handheld dynamometry, the 6-minute walk test, and the Modified Performance-Oriented Mobility Assessment-Gait scale. Multiple end points were required to adequately capture the impact of asfotase alfa treatment on the multiple systems affected in HPP. These data illustrate the importance of using multiple COAs that provide normative data and to use COAs early in the drug development process for rare pediatric disease.

Keywords: asfotase alfa, clinical outcomes, hypophosphatasia, rare disease.

Introduction

Clinical design in pediatric rare disease research often requires complicated end point models with multiple clinical outcome assessments (COAs) to capture the constructs. This commentary will focus on the use of existing standardized instruments that consider development by age and classify function relative to normative values. In this discussion, hypophosphatasia (HPP) is used to illustrate COA selection in a pediatric rare disease. HPP, a genetic metabolic musculoskeletal disorder, is caused by mutations in the tissue-nonspecific alkaline phosphatase gene [1]. Heterogeneous manifestations can include rickets, fractures, muscle weakness, limb deformities, pain, and respiratory compromise, which result in delayed acquisition of age-appropriate developmental skills, gait impairments, and decreased functional independence in activities of daily living (ADL) [1]. The disease has a particularly high burden in children and is associated with high mortality rates in infants [2].

Use of Existing Standardized Developmental Assessments

Rare disease studies often have a small sample size that is insufficient to divide by group-level differences in age and function. Normative data can define function in a heterogeneous sample and be used to characterize the disease presentation in the natural history and treatment groups. Rare diseases often present with multisystem impairments that limit ability to capture the direct impact of disease-defining concepts.

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Comprehensive developmental COAs can be used to characterize the disease impact on age-appropriate markers across multiple domains, examine the relationship between domains, and guide selection or development of additional disease-specific measures.

Pediatric rare disease clinical trials often enroll a wide age distribution. Gross and fine motor skills, communication, cognition, and independence in ADL vary by age, and it may be difficult to distinguish between treatment effects and change due to developmental maturation. Identical function may be age-appropriate for a younger child and considered atypical or delayed in an older child. Variability in typical function by age requires that multiple age versions be developed for disease-specific validated patient-reported outcomes. Comparisons with a normative sample in an existing tool can provide age-appropriate developmental expectations.

Existing standardized developmental assessments can provide a range of values to measure treatment benefits including, but not limited to, standard scores (including scale scores), percentile rank, age-equivalent (AE) scores, and developmental quotients (DQs) [3]. Different values may be used to interpret treatment benefit in infantile and juvenile disease phenotypes. The infantile form of the rare disease may include progressive loss of developmental skills and high mortality, and treatment benefit may be defined by the acquisition of a developmental skill that exceeds function observed in the natural history study. The rate of skill acquisition in response to a treatment may be slower than in the normative sample and improvement may be reflected only as an increase in AE scores. Standard scores can be insensitive to change in low-functioning children because either the children fall below the test floor or the rate of change is slower than in typically developing children in the normative sample, and standard scores either plateau or decline [3]. In a progressive condition in which treatment is focused on arresting deterioration, a treatment response may be indicated only by stable AE values because a subsequent decline in standard scores will result with increased age. DQ (AE/chronological age × 100) can be sensitive to age as a determinant of disease progression in children with low function and can be used to compare the rate of change between disease natural history and intervention groups [3].

Application to HPP

The US Food and Drug Administration approved asfotase alfa (Strensiq®, Alexion Pharmaceuticals Inc., Cheshire, CT, USA) in 2015 as the first approved drug for perinatal, infantile, and juvenile HPP, after development with orphan drug designation. The clinical development plan included multiple studies to evaluate safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy. The end point model included HPP-related rickets as a primary end point and a combination of secondary/exploratory variables to provide a comprehensive picture of function, disability, pain, and health-related quality of life Fig. 1. Heterogeneity in functional presentation and a wide range of ages necessitated the use of COAs that characterize function relative to normative values. The results highlighted herein focus on the use of COAs with normative values and are presented in Table 1.

Bayley Scales of Infant and Toddler Development-Third Edition

The five developmental domains of the Bayley Scales of Infant and Toddler Development-Third Edition (Bayley-III) (i.e., cognition, language, motor skills, social-emotional behavior, and adaptive behavior) were developed (normed and validated) for use in impaired and healthy children aged between 1 and 42 months [4]. The Bayley-III is regarded as the best practice tool, and is thus most widely used in clinical practice [5]. In an open-label, retrospective study, 11 patients were assessed using Bayley-III at baseline and at 24 and 48 weeks after initiation of asfotase alfa for treatment of HPP [1,2]. All patients had fine motor, gross motor, and cognitive delays at baseline, and 87.5% of

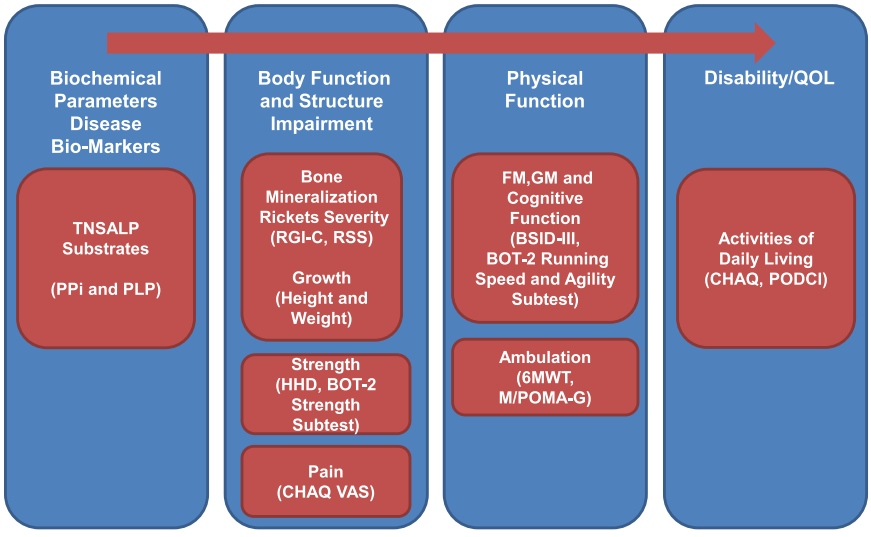

Fig. 1 – Biomarkers and clinical outcome assessments for HPP. 6MWT, 6-minute walk test; BOT-2, Bruininks-Oseretsky Test of Motor Proficiency-Second Edition; BSID-III, Bayley Scales of Infant Development-Third Edition; CHAQ, Childhood Health Assessment Questionnaire; FM, fine motor; GM, gross motor; HHD, handheld dynamometry; HPP, hypophosphatasia; MPOMA-G, Modified Performance-Orientated Mobility Assessment-Gait; PLP, pyridoxal 5'-phosphate; PODCI, Pediatric Outcomes Data Collection Instrument; Ppi, inorganic pyrophosphate; QOL, quality of life; RGI-C, Radiographic Global Impression of Change; RSS, Rickets Severity Scale; TNSALP, tissue-nonspecific alkaline phosphatase; VAS, visual analogue scale.[1,14,19]