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ORIGINAL ARTICLE

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Validation of a Novel Scoring System for Changes in Skeletal Manifestations of Hypophosphatasia in Newborns, Infants, and Children: The Radiographic Global Impression of Change Scale

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ABSTRACT

Hypophosphatasia (HPP) is the heritable metabolic disease characterized by impaired skeletal mineralization due to low activity of the tissue-nonspecific isoenzyme of alkaline phosphatase. Although HPP during growth often manifests with distinctive radiographic skeletal features, no validated method was available to quantify them, including changes over time. We created the Radiographic Global Impression of Change (RGI-C) scale to assess changes in the skeletal burden of pediatric HPP. Site-specific pairs of radiographs of newborns, infants, and children with HPP from three clinical studies of asfotase alfa, an enzyme replacement therapy for HPP, were obtained at baseline and during treatment. Each pair was scored by three pediatric radiologists ("raters"), with nine raters across the three studies. Intrarater and interrater agreement was determined by weighted Kappa coefficients. Interrater reliability was assessed using intraclass correlation coefficients (ICCs) and by two-way random effects analysis of variance (ANOVA) and a mixed-model repeated measures ANOVA. Pearson correlation coefficients evaluated relationships of the RGI-C to the Rickets Severity Scale (RSS), Pediatric Outcomes Data Collection Instrument Global Function Parent Normative Score, Childhood Health Assessment Questionnaire Disability Index, 6-Minute Walk Test percent predicted, and *Z*-score for height in patients aged 6 to 12 years at baseline. Eighty-nine percent (8/9) of raters showed substantial or almost perfect intrarater agreement of sequential RGI-C scores (weighted Kappa coefficients, 0.72 to 0.93) and moderate or substantial interrater agreement (weighted Kappa coefficients, 0.53 to 0.71) in patients aged 0 to 12 years at baseline. Moderate-to-good interrater reliability was observed (ICC, 0.57 to 0.65). RGI-C scores were significantly ($p \leq 0.0065$) correlated with the RSS and with measures of global function, disability, endurance, and growth in the patients aged 6 to 12 years at baseline. Thus, the RGI-C is valid and reliable for detecting clinically important changes in skeletal manifestations of severe HPP in newborns, infants, and children, including during asfotase alfa treatment. © 2018 The Authors. *Journal of Bone and Mineral Research* Published by Wiley Periodicals Inc.

KEY WORDS: HPP; ALKALINE PHOSPHATASE; CALCIFICATION; MINERALIZATION; OSTEOMALACIA; OSTEOPATHY; OSTEOPENIA; RICKETS; SKELETAL DYSPLASIA

Introduction

Hypophosphatasia (HPP) is the rare inborn-error-of-metabolism characterized enzymatically by low activity of the tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP) and caused by loss-of-function mutation(s) in *ALPL* (*TNSALP*), the gene that encodes this cell-surface phosphohydrolase.[1–3] To date, more than 340 such mutations, primarily missense defects, have been identified in patients with HPP.[4] The inheritance pattern may be autosomal recessive or autosomal dominant.[2,5] Consequently, HPP is characterized by remarkably broad-ranging severity and can be lethal in utero or not manifest until late adult life.[5] In HPP, extracellular accumulation of inorganic pyrophosphate, a potent inhibitor of mineralization, often leads to rickets or osteomalacia.[6] In affected newborns, infants, and children, HPP can cause limb deformity, muscle weakness, musculoskeletal

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pain, fractures, poor growth, and premature loss of deciduous teeth.[3,6] When HPP presents during growth, radiography can uncover skeletal features that are pathognomonic.[1,3,7]

In 2000, a Rickets Severity Scale (RSS) was developed to assess radiographic features in the wrists and knees of patients with nutritional rickets.[8] Because assessing radiographic features is also important for patients with skeletal manifestations of HPP, a scale that encompasses the characteristic changes of HPP seemed necessary to best evaluate therapeutic responses.[7]

Herein, we describe and validate the Radiographic Global Impression of Change (RGI-C) scale as a tool for scoring changes over time in key radiographic features of HPP in pediatric patients. Our evaluation of the RGI-C measured agreement and reliability of scores given by multiple raters to select radiographs, and then we determined the correlation of the scores to other outcome measures using data from three recently completed clinical studies of asfotase alfa treatment (Strensiq®; Alexion Pharmaceuticals, Inc., New Haven, CT, USA), an enzyme replacement therapy approved multinationally in 2015, typically for the treatment of pediatric-onset HPP.[9–11]

Materials and Methods

Development of the RGI-C scale

To assess the skeletal burden of pediatric HPP, an author (WHM, an expert concerning the radiologic evaluation of HPP) identified key radiographic features of pediatric HPP in patients ≤5 and ≥5 years of age (Table 1; Fig. 1A and B). The initial version of the RGI-C scale evaluated the changes between time points in irregularity of the provisional zone of calcification; physeal widening; metaphyseal flaring, fraying, radiolucencies, and patchy osteosclerosis; altered ratio of mid-diaphyseal cortex-to-bone thickness; gracile bones; absence of some or all bones; and recent fractures. Then a seven-point RGI-C scale (Fig. 2) was developed by a consensus panel of expert pediatric radiologists chosen by WHM.

RGI-C training

The consensus panel of expert pediatric radiologists ("raters") was trained concerning the identification of the abnormalities of pediatric HPP and the RGI-C by author WHM. Imaging instrumentation representatives (Biomedical Systems, St. Louis, MO, USA) provided additional instruction regarding applicable regulations and guidelines, computer requirements, and proper data reporting. All study personnel involved in data collection and management were given an Imaging Services Review Charter that described the process and procedures for radiographic collection, tracking, data quality assurance, anonymizing data, qualification/training, and independent review procedures.

Data collection for validation

Per protocol, baseline and subsequent radiographs were obtained from patients with HPP aged ≤12 years at study entry for evaluation of asfotase alfa therapy. At baseline, patients were ≤3 years old in study ENB-002-08 with extension ENB-003-08 (NCT00744042, NCT01205152), ≤5 years old in study ENB-010-10 (NCT01176266), and 6 to 12 years old in study ENB-006-09 with extension ENB-008-10 (NCT00952484, NCT01203826). Radiographic assessments for this analysis were performed from March 2013 to December 2014 for Study ENB-002-08/ENB-003-08, from March 2013 to August 2014 for Study ENB-010-10, and from November 2010 to December 2014 for Study ENB-006-09/ENB-008-10. The RGI-C scores compared radiographic findings at baseline with those at treatment weeks 4, 12, 24, 36, 48, 60, 72, 96, 120, 144, 168, 192, 216, and 240 for both the ENB-002-08/ENB-003-08 and ENB-010-10 studies and weeks 6, 12, 24, 36, 48, 60, 72, 96, 120, 144, 168, 192, and 216 for the ENB-006-09/ENB-008-10 study.

Paired radiographs of the chests of patients aged <5 years and hands/wrists and knees of all patients at baseline and during treatment were scored independently by the raters using the RGI-C. Of the six individual raters who were recruited, the same three raters assessed all radiographs from studies ENB-002-08/ENB-003-08 and ENB-010-10, whereas the three other raters assessed radiographs from study ENB-006-09/ENB-008-10. The radiograph pairs from ENB-002-08/ENB-003-08 and ENB-010-10 were read sequentially by the same raters but were not interspersed (ie, raters read all radiographs from ENB-002-08/ENB-003-08 first and then all radiographs from ENB-010-10). The raters were blinded to

Table 1. Radiographic features of HPP evaluated by RGI-C

Patients ≤5 years of age (ENB-002-08/ENB-003-08 and ENB-010-10)	Patients ≥5 years of age (ENB-006-09/ENB-008-10)
Metadiaphyseal patchy focal sclerosis	Metadiaphyseal sclerosis
Apparent physeal widening	Apparent physeal widening
Irregularity of the provisional zone of calcification	Irregularity of the provisional zone of calcification
Metaphyseal radiolucencies ("tongues" or rounded areas)	"Popcorn calcifications" of metadiaphyses (rounded lucencies and patchy sclerosis)
Metaphyseal flaring	Transverse subphyseal band of lucency
Metaphyseal fraying	Osteopenia of short tubular bones (evaluated for hands/wrists)
Thin, gracile bones	Osteopenia (evaluated for knees)
Apparent absence of some or all bones	Metaphyseal radiolucencies (tongues or rounded areas, evaluated for hands/wrists)
Thin ribs	Tongues of radiolucency (evaluated for knees)
Chest deformity	Metaphyseal fraying (evaluated for hands/wrists)
Evidence of recent fractures	Physeal corner defects (evaluated for knees)
	Demineralization of the distal metaphyses (evaluated for hands/wrists)

HPP = hypophosphatasia; RGI-C = Radiographic Global Impression of Change.

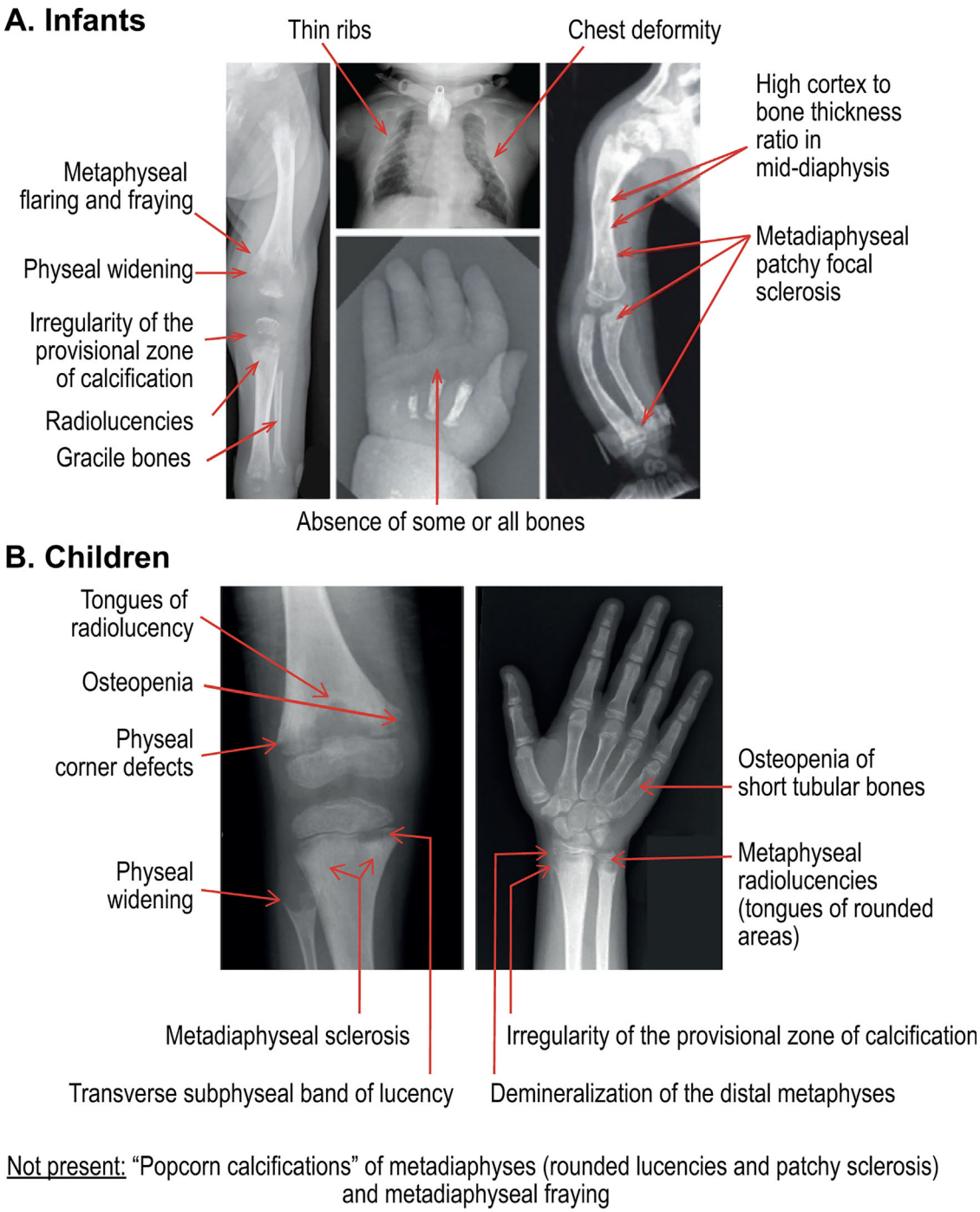

Fig. 1. Skeletal features of HPP evaluated by the RGI-C for infants (*A*) and children (*B*). RGI-C = Radiographic Global Impression of Change; HPP = hypophosphatasia. (Republished with permission from Whyte MP, et al. N Engl J Med. 2012;366:904–13[9] and Whyte MP, et al. JCI Insight. 2016;e85971[12]).

patient identifiers, intervention status, and duration between radiographs.

Intrarater agreement

To determine individual ("intrarater") agreement between repeated assessments, approximately 30 pairs of radiographs were reread in a different session by each rater for each of the three treatment studies (approximately 90 pairs). The percentages of radiograph sets (initial and second assessment) that were given identical scores (exact agreement), and scores within one point for each rater, were calculated. Then, a weighted Kappa coefficient (with quadratic weights following Fleiss and Cohen[13]) was used to estimate intrarater agreement. For the validation, the level of agreement to the weighted Kappa coefficient was categorized as "almost perfect" (1.00 to 0.80),

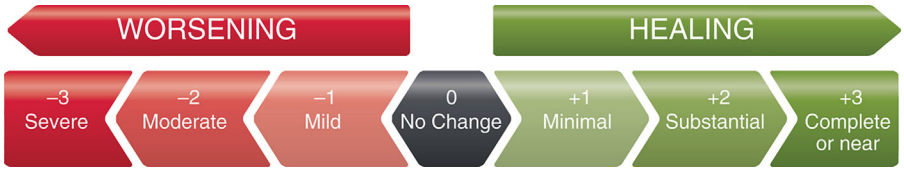

Fig. 2. RGI-C scale (7-point scale) for pediatric HPP. RGI-C = Radiographic Global Impression of Change; HPP = hypophosphatasia.

"substantial" (0.79 to 0.60), "moderate" (0.59 to 0.40), "fair" (0.39 to 0.20), "slight" (0.19 to 0.00), or "poor"(<0.00).[14]

Interrater agreement

To assess group ("interrater") agreement for each of the three studies, percentages of radiograph pairs assigned either identical RGI-C scores between two raters (exact agreement), or scores within one point between two raters, were identified. Then, a weighted Kappa coefficient (with quadratic weights following Fleiss and Cohen[13]) was used to estimate interrater agreement.[14] The level of agreement assigned to the weighted Kappa coefficients was as described in the previous section for the intrarater agreement. Interrater reliability was assessed by calculating intraclass correlation coefficients (ICCs) using a two-way random effects analysis of variance (ANOVA), pooling the similar patient populations of studies ENB-002-08/ENB-003-08 and ENB-010-10, and performing a separate analysis for the older patients in study ENB-006-09/ENB-008-10. The variables for the two-way ANOVA were subject-visit, rater, and interaction between subject-visit and rater. The interrater reliability for the ICC was defined as "excellent" (≥0.75), "good" (0.6 to 7.4), "fair" (0.4 to 0.59), or "poor" (<0.4).[15]

Interrater variability

To assess (i) the sources of variability in rater scores, (ii) whether the level of agreement between them was greater than would be expected by chance, and (iii) differences between raters, we performed a mixed-model repeated measures (MMRM) ANOVA.[16] The dependent variable for the MMRM was RGI-C score, and the independent variables were subject, visit, rater, and interaction between visit and rater.

Correlations of RGI-C to changes in other outcome measures

To assess for validation of the RGI-C, Pearson correlation coefficients were calculated to compare the RGI-C with five other outcome measures: RSS,[8] Pediatric Outcomes Data Collection Instrument (PODCI) Global Function Parent Normative Score,[17] Childhood Health Assessment Questionnaire (CHAQ) Disability Index,[17] 6-Minute Walk Test (6MWT) (% predicted values based on age-, sex-, and height-matched healthy peers),[18] and height *Z*-score.[19]

Results

Expert radiologists

Six expert pediatric radiologists participated as raters across the three studies and evaluated a total of 363 radiographs. Three of the six raters evaluated radiographs from the two studies that focused on severely affected infants and young children (ENB-002-08/ENB-003-08 and ENB-010-10; Table 2).

Intrarater agreement

Among the nine groups of ratings (three raters for each of the three studies), intrarater agreement was considered almost perfect for four raters (44%), substantial for four raters (44%)

Table 2. Intrarater Agreement of Sequential RGI-C Scores

Study/rater	Radiograph sets assessed (*n*)[a]	Identical RGI-C score (%)	RGI-C score within 1 point (%)	Weighted Kappa coefficient (95% confidence limits, LL–UL)[b]
ENB-002-08/ENB-003-08: Newborns, infants, and children ≤3 years of age[9]				
Rater 1	30	77	97	0.90 (0.79–1.00)
Rater 2	30	80	97	0.77 (0.60–0.95)
Rater 3	30	87	97	0.93 (0.84–1.00)
ENB-010-10: Patients ≤5 years of age				
Rater 1	30	53	93	0.58 (0.41–0.75)
Rater 2	27	74	93	0.76 (0.50–1.00)
Rater 3	30	70	90	0.86 (0.73–0.99)
ENB-006-09/ENB-008-10: Children 5 to 12 years of age[12]				
Rater 4	27	48	96	0.78 (0.64–0.91)
Rater 5	27	56	85	0.72 (0.57–0.87)
Rater 6	24	63	96	0.83 (0.70–0.96)

RGI-C = Radiographic Global Impression of Change; LL = lower limit; UL = upper limit.
[a]Includes number of radiograph sets where rater was able to assign a RGI-C score to both sets.
[b]Level of agreement to the weighted Kappa coefficient was categorized as: "almost perfect" (1.00–0.80), "substantial" (0.79–0.60), "moderate" (0.59–0.40), "fair" (0.39–0.20), "slight" (0.19–0.00), or "poor" (<0.00).

Table 3. Interrater Agreement of Sequential RGI-C Scores

Study/rater pair	Radiograph sets assessed (*n*)[a]	Identical RGI-C score (%)	RGI-C score within 1 point (%)	Weighted Kappa coefficient (95% confidence limits, LL−UL)[b]
ENB-002-08/ENB-003-08: Newborns, infants, and children ≤3 years of age[9]				
Rater 1 versus 2	196	54	90	0.38 (0.24–0.53)
Rater 1 versus 3	200	68	92	0.60 (0.45–0.74)
Rater 2 versus 3	196	66	98	0.71 (0.64–0.79)
ENB-010-10: Patients ≤5 years of age				
Rater 1 versus 2	160	61	88	0.53 (0.34–0.71)
Rater 1 versus 3	166	63	89	0.69 (0.60–0.79)
Rater 2 versus 3	159	58	87	0.54 (0.38–0.70)
ENB-006-09/ENB-008-10: Children 5–12 years of age[12]				
Rater 4 versus 5	287	56	97	0.64 (0.57–0.70)
Rater 4 versus 6	287	54	96	0.67 (0.61–0.73)
Rater 5 versus 6	287	53	95	0.59 (0.53–0.66)

RGI-C = Radiographic Global Impression of Change; LL = lower limit; UL = upper limit.
[a]Includes number of radiograph sets where raters were able to assign a RGI-C score to both sets.
[b]Level of agreement to the weighted Kappa coefficient was categorized as: "almost perfect" (1.00–0.80), "substantial" (0.79–0.60), "moderate" (0.59–0.40), "fair" (0.39–0.20), "slight" (0.19–0.00), or "poor" (<0.00).

(weighted Kappa coefficients: 0.83 to 0.93 and 0.72 to 0.78, respectively), and moderate for one rater (11%) (weighted Kappa coefficient: 0.58). Raters assigned identical RGI-C scores 48% to 87% of the time, and assigned scores within one point (of a total of seven points) on their first and second assessments 85% to 97% of the time (Table 2).

Interrater agreement

Among the nine groups of ratings, direct comparisons between raters' RGI-C scores across the three treatment studies showed that interrater agreement was substantial for five raters (56%), moderate for three raters (33%), and fair for one rater (11%) (weighted Kappa coefficients: 0.60 to 0.71, 0.53 to 0.59, and 0.38, respectively). RGI-C scores were identical 53% to 68% of the time, and were within one point 87% to 98% of the time (Table 3).

In an additional assessment for interrater variability, the ICC was 0.65 after pooling the similar patient populations of studies ENB-002-08/ENB-003-08 and ENB-010-10 that involved infants and young children, and 0.57 for study ENB-006-09/ENB-008-10 that involved older children (Table 4*A*), indicating "good-to-fair" reproducibility. To evaluate the sources of variability in RGI-C scores, the ANOVAs (calculated using the MMRM for visit, rater, and influences of both the specific visit and rater) showed statistically significant differences for the visit ($p < 0.0001$ in each study), but not for rater or interaction between visit and rater variables (Table 4*B*).

Correlations to changes in other outcome measures

There was moderate to strong correlation of the RGI-C to change from baseline in the RSS scores ($r = -0.664$; $p < 0.0001$; Fig. 3*A*). The scores from the RGI-C were significantly ($p \leq 0.0065$) and directionally consistent with changes from baseline in the four other outcome measures tested: PODCI Global Function Parent Normative Score ($r = 0.595$; Fig. 3*B*), CHAQ Disability Index ($r = -0.589$; Fig. 3*C*), 6MWT % predicted ($r = 0.284$; Fig. 3*D*), and *Z*-score for height ($r = 0.261$; Fig. 3*E*).

Table 4. Interrater Reliability of RGI-C Scores

(A) Intraclass correlation coefficients

Study	Radiographs analyzed (*n*)	ICC[a]	*p*-value[b]
ENB-002-08/ENB-003-08 and ENB-010-10	227	0.65	<0.0001
ENB-006-09/ENB-008-10	136	0.57	<0.0001

(B) Mixed-model repeated measures analysis of variance

	p-value[b]		
Study	Visit	Rater	Interaction
ENB-002-08/ENB-003-08 and ENB-010-10	<0.0001	0.42	0.17
ENB-006-09/ENB-008-10	<0.0001	0.36	0.88

RGI-C = Radiographic Global Impression of Change; ICC = intraclass correlation coefficient.
[a]Level of agreement for the ICC was defined as "excellent" (≥0.75), "good" (0.6–0.74), "fair" (0.4–0.59), and "poor" (<0.4).

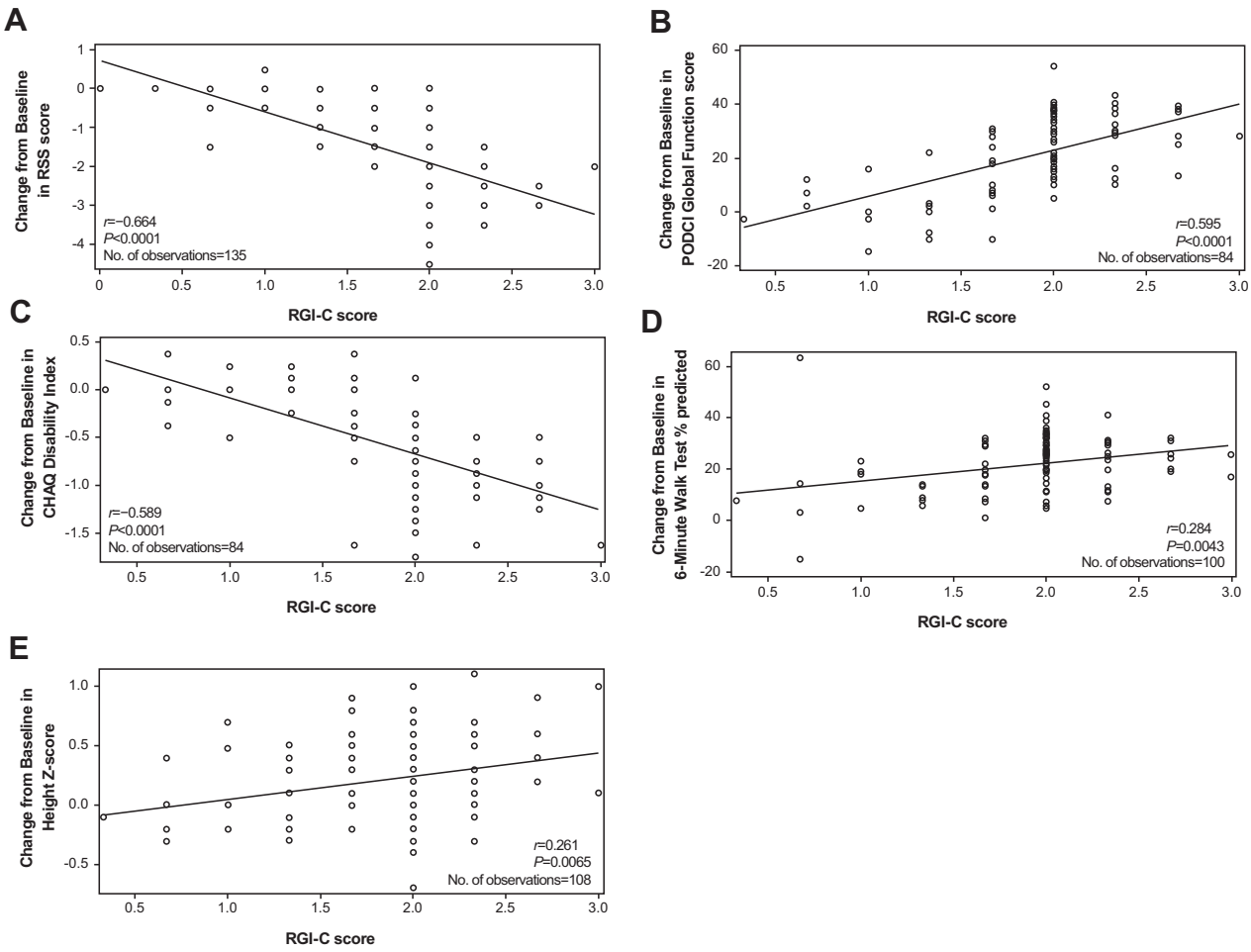

Fig. 3. Correlation of RGI-C scores with RSS scores (*A*), PODCI Global Function Parent Normative Score (*B*), CHAQ Disability Index (*C*), percent predicted 6MWT (*D*), and height *Z*-score (*E*). RGI-C = Radiographic Global Impression of Change; RSS = Rickets Severity Scale; PODCI = Pediatric Outcomes Data Collection Instrument; CHAQ = Child Health Assessment Questionnaire; 6MWT = 6-Minute Walk Test.

Discussion

Based on specified radiographs of affected newborns, infants, and children, we developed the RGI-C scale to address the unmet need to quantify changes in key skeletal manifestations of pediatric HPP. The RGI-C scale was one of the primary outcome measures in our natural history and treatment studies leading to multinational approval in 2015 of asfotase alfa, typically for pediatric-onset HPP.[9,10,12] The current study validates the RGI-C using data from the three pediatric clinical studies of asfotase alfa treatment,[9,12] in which the RGI-C scale was scored by pediatric radiologists (blinded to patient identifiers, intervention status, and duration between radiographs). Good to moderate intrarater and interrater agreement was achieved. The tests then chosen for validation were the RSS (used to radiographically assess nutritional rickets), validated instruments of pediatric global function (PODCI), disability (CHAQ), and endurance (6MWT), as well as *Z*-scores of patient height. All five of these assessments showed significant correlations with the RGI-C scores and thus concurrent validity.

For the three pediatric clinical studies of asfotase alfa, the RGI-C scale was crucial for evaluation of severely affected newborns, infants, and children with HPP.[9,12] It enabled precise assessment of the skeletal complications noninvasively. In fact, other measures to study the skeleton (eg, dual-energy X-ray absorptiometry, computed tomography, bone biopsy) were not feasible in the smallest and initially extremely sick patients.[9] Therefore, the RGI-C became the primary efficacy outcome measure.[9,12] In addition, the RGI-C proved feasible and important for retrospective evaluation of skeletal status in a natural history study of patients with HPP aged 5 to 12 years (NCT02104219). The RGI-C will therefore be useful for future clinical investigations of similarly affected pediatric HPP patients. Furthermore, the RGI-C could be modified to assess the severity of skeletal manifestations of HPP at a single time point, although this was not evaluated in our current analysis. However, the RGI-C scale is limited in HPP because it assesses pediatric patients (ie, those with open growth plates) but not adults. Furthermore, the raters in this study were all academic pediatric radiologists with expertise concerning skeletal disease in infants and children. Therefore, the important intrarater and

interrater agreement observed herein for pediatric HPP may not be generalizable. The RGI-C could be useful for perplexing single cases requiring quantitative data or perhaps be offered by a central facility with a particular interest in pediatric HPP.

Our study validates the RGI-C scale for assessment of changes in the skeletal manifestations of severely affected newborns, infants, and children with HPP. In fact, the RGI-C was subsequently tailored to investigate the effects of the fully human anti–fibroblast growth factor 23 monoclonal antibody burosumab to treat children with X-linked hypophosphatemia.[20] Thus, the RGI-C scale could be similarly useful for other forms of rickets.

Disclosures

MPW was a clinical study investigator and received honoraria, travel support, and research grant support from Alexion Pharmaceuticals, Inc. KPF and SM are employees of and may own stock/options in Alexion Pharmaceuticals, Inc., which sponsored the study. DDT was an employee of Alexion Pharmaceuticals, Inc., when the Radiographic Global Impression of Change (RGI-C) scale was developed; and may have owned stock/options in Alexion Pharmaceuticals, Inc., which sponsored the study. WHM was a clinical study investigator and did not receive any remuneration from Alexion Pharmaceuticals, Inc.

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Authors' roles: All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data. MPW, KPF, SM, DDT, and WHM participated in drafting the manuscript or revising it critically for important intellectual content. MPW, KPF, SM, DDT, and WHM approved the final version of the submitted manuscript. MPW, KPF, SM, DDT, and WHM agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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