Bone Reports 5 (2016) 158–162

Contents lists available at ScienceDirect

Bone Reports

journal homepage: www.elsevier.com/locate/bonr

Effect of four monthly doses of a human monoclonal anti-FGF23 antibody (KRN23) on quality of life in X-linked hypophosphatemia

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ARTICLE INFO

Article history:
Received 7 December 2015
Received in revised form 15 April 2016
Accepted 11 May 2016
Available online 13 May 2016

Keywords:
X-linked hypophosphatemia
KRN23
Health-related quality of life
Fibroblast growth factor 23 (FGF23)
Rickets

ABSTRACT

X-linked hypophosphatemia (XLH) is characterized by lower extremity deformities that lead to bone and/or joint pain that result from decreased renal tubular reabsorption leading to hypophosphatemia caused by elevated levels of fibroblast growth factor 23 (FGF23).

Objective: Validate the use of SF-36v2 Health Survey (SF-36v2) and the Western Ontario and McMaster Osteoarthritis Index (WOMAC) to measure previously unstudied health-related quality of life (HRQoL) in XLH patients and determine the change in HRQoL before and after treatment with KRN23, a human monoclonal anti-FGF23 antibody.

Methods: Twenty-eight adult outpatients with XLH received up to four doses of KRN23 administered subcutaneously every 28 days. General HRQoL was measured with the SF-36v2 and condition-related HRQoL with the WOMAC at baseline and study endpoint as a secondary outcome of a Phase 1/2, open-label, multicenter, dose-escalation trial.

Results: Testing for scale discriminant validity and convergent-divergent validity supported the use of these scales in the assessment of HRQoL in XLH. Both instruments indicated impairment of physical function at baseline with all mean scores showing a trend to improved health at study endpoint compared to baseline. When corrected for multiple comparisons, the score for Role Limitations due to physical health on the SF-36v2 which measures the patient's perception of their own chronic functional impairments due to poor physical health remained significantly improved ($P < 0.05$), increasing to the mean score of US adults. For the WOMAC, Physical Functioning and Stiffness scores were significantly improved ($P < 0.05$).

Conclusion: KRN23 administration was associated with significantly improved patient perception of their Physical Functioning and Stiffness due to their disease. This study demonstrates that the SF-36v2 and WOMAC are valid tools for assessing HRQoL in XLH.

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1. Introduction

X-linked hypophosphatemia (XLH; MIM307800) is a dominant hereditary bone disorder resulting from *PHEX* mutations and characterized by elevated levels of fibroblast growth factor 23 (FGF23) leading to a dual defect in phosphate metabolism with consequent renal phosphate wasting and impaired renal production of 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] (Imel & Econs, 2005; Liu & Quarles, 2007; Carpenter et al., 2011; Lee & Imel, 2013). It is the most common form of heritable rickets, usually presenting with bowing deformities of the legs in childhood (Holm et al., 2003). Adults suffer from bone pain and osteomalacia, increased risk of skeletal insufficiency fractures, joint abnormalities and pain, enthesopathy, osteoarthritis, and dental abscesses (Reid et al., 1989; Tenenhouse & Econs, 2013). Formal assessments of how this

Abbreviations: PRO, patient reported outcomes; HRQoL, health-related quality of life; WOMAC, Western Ontario and McMaster Osteoarthritis Index; MIC, Minimally Important Change.

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http://dx.doi.org/10.1016/j.bonr.2016.05.004
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symptomatology affects patients' quality of life have not been previously reported. It is also not known whether treatment influences quality of life.

The main therapeutic option, oral calcitriol plus phosphate supplements, offers limited efficacy, is inconvenient to administer, and requires regular monitoring for potential toxicities (Carpenter et al., 2011; Costa et al., 1981). KRN23 is a recombinant human IgG1 monoclonal antibody directed at FGF23. In a recent Phase 1 and Phase 1/2, dose-escalation study of repeated subcutaneous doses of KRN23 in adults with XLH, we showed that KRN23 effectively increased the ratio of renal tubular maximum reabsorption of phosphate to glomerular filtration rate (TmP/GFR), and serum inorganic phosphorus (Pi) and $1.25(OH)_2D$ concentrations (Carpenter et al., 2014; Imel et al., 2015). As a secondary objective of the dose escalation study, we sought to assess the psychometric validity of formal health-related quality of life (HRQoL) testing utilizing two well-established Patient Reported Outcome (PRO) instruments: general HRQoL was measured with the Medical Outcomes Study Short Form Health Survey version 2 (SF-36v2) (Maruish, 2011) and condition-related HRQoL with the Western Ontario and McMaster Osteoarthritis Index (WOMAC) (Bellamy et al., 1988). In addition, we also sought to evaluate the effects of KRN23 on HRQoL.

2. Methods

2.1. Overall study design

The primary Phase 1/2 study was an open-label, dose-escalation trial of KRN23 in adults age ≥ 18 years with a documented clinical diagnosis of XLH conducted at six study centers. The primary results of this study have been previously published with the full methods found within that publication (Imel et al., 2015). Briefly, inclusion criteria were: intact serum FGF23 level > 30 pg/ml, TmP/GFR < 2.0 mg/dl, estimated glomerular filtration rate ≥ 60 ml/min, and serum calcium < 10.8 mg/dl. Exclusion criteria included pregnancy or lactation, major surgery, and receipt of live vaccine or monoclonal antibody products within 3 months before screening. Vitamin D (and its analogues), calcium supplements, phosphate supplements and aluminum hydroxide were not permitted within 10 days before screening nor throughout the study. The screening occurred within 30 days prior to baseline dosing day (Day 0). Patients received KRN23 0.05 mg/kg subcutaneously at baseline (Day 0) followed by step-wise dose escalation (0.1 to 0.3 to 0.6 mg/kg subcutaneously) every 4 weeks based on serum Pi levels for a total of four doses.

The clinical study was conducted according to the principles of the Declaration of Helsinki and with Institutional Review Board approval at each study center. Written informed consent was obtained from the participants prior to study inclusion. The study was conducted between 31 October 2011 and 10 April 2013, and was registered at ClinicalTrials.gov (#NCT01340482).

2.2. PRO measures

SF-36v2 (Maruish, 2011) and WOMAC (Bellamy et al., 1988; Bellamy, 2009) were completed by the patients on the day of initial KRN23 dosing (baseline, Day 0) and at study endpoint (Day 120) which occurred 36 days after the last dose of KRN23. The 36-question self-reported SF-36v2 measures eight concepts to evaluate general HRQoL: Physical Functioning, Role Limitations due to Physical Health, Bodily Pain, General Health Perceptions, Vitality, Social Functioning, Role Limitations due to Emotional Problems, and Mental Health. The Role Limitations scales are construct-based measurements that are meant to measure more abstract properties. These measures evaluate the patient's perception of their own chronic functional limitations due either to poor physical health (Role Limitations due to physical health) or poor emotional health (Role Limitations due to emotional health). Norm-based standardized scores are calculated, with scores below 50 being below the mean for the US population. The eight scales are then used to compute Physical Component Summary and Mental Component Summary scores in the same manner as the individual domains to produce standardized scores relative to the general population. The SF-36v2 is widely accepted as a valid measure of disease burden and has been frequently applied across multiple diseases.

The 24-question self-reported WOMAC was originally designed to evaluate the condition of the knee, hip, and other joints in patients with osteoarthritis using three scales: Pain, Stiffness, and Physical Functioning. This study used WOMAC version LK3.1 (Bellamy, 2004) in which responses to all questions are measured on a 5-point Likert scale: none (0), mild (1), moderate (2), severe (3) and extreme (4). Scoring is a simple sum, so Pain scores range from 0 to 20, Stiffness from 0 to 8, and Physical Functioning from 0 to 68, with higher numbers indicating worse condition. Scores are normalized to a 0–100 metric scale for Pain Scores (20 points is 100%), Stiffness (8 points is 100%) and Physical functioning (68 points is 100%), representing the percent of the maximum score. Unlike SF-36v2 scores, WOMAC scores are not norm-based, so they cannot be interpreted directly as a difference from a population mean. However, mean WOMAC scores from a large population-based sample of healthy adults have been published (Bellamy et al., 2011) giving benchmark values for comparison. These are as follows (mean ± SD): Pain 14.1 ± 19.7, Stiffness 20.1 ± 23.6 and Physical Functioning 15.4 ± 20.2.

2.3. PRO analyses

The aims of the PRO analyses were to describe baseline quality of life in XLH, interpret changes in PRO scales over time, and validate PRO analyses implementation in XLH patients. As described below, disease burden was assessed by comparing the scores to those of a cohort of patients with a disease having several similarities to XLH (osteoarthritis) while validation analysis was performed by comparing the scores to those of a cohort of patients affected with a disease having few similarities (asthma). Both PRO instruments have established algorithms for estimating scores with missing data and were used in these analyses. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

2.4. Descriptive and interpretative analyses

Patient demographics and their response frequencies to all individual PRO questions were analyzed descriptively. The paired *t*-test statistical analysis was then applied to determine whether there were any significant changes in mean PRO scales with treatment.

Significance was set at $P < 0.05$. An adjustment for multiplicity was made to control the family-wise error rate below a given α of 0.05. To adjust for multiplicity, a parallel gatekeeping approach was applied using Hommel's adjustment for the non-primary hypotheses (Hommel, 1988). The inclusion of PROs as secondary endpoints was exploratory. For this reason, both the standard *P*-values of tests (labeled *P*) as well as the multiplicity-adjusted *P*-values (labeled P^m) are presented.

Interpretative disease burden analyses were then conducted for SF-36v2 results for the XLH population compared to two age- and sex-matched SF-36v2 comparator datasets (data on file at Optum/QualityMetric, Lincoln, RI): the general United States population ($N = 4040$) and a subsample with osteoarthritis ($N = 583$), who were unselected with respect to their treatment of osteoarthritis. These samples were chosen so that disease burden analyses could be conducted for XLH relative to the population norm and to a known clinical disease that has some symptoms in common with XLH. The change in values was compared to the Minimally Important Change (MIC). MIC is the smallest change over time in an individual patient's score that represents a clinically significant change in their health status. Using a distributional approach with a U.S. general population sample, MIC scores have been established for the SF-36v2 as: Physical Functioning, 3.5; Role Limitations due to Physical Health, 3.2; Bodily Pain, 4.5; General

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