Effect of Recombinant Human Parathyroid Hormone (1-84) on Resolution of Active Charcot Neuro-osteoarthropathy in Diabetes: A Randomized, Double-Blind, Placebo-Controlled Study

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OBJECTIVE

Fractures in Charcot neuro-osteoarthropathy (CN) often fail to heal despite prolonged immobilization with below-knee casting. The aim of the study was to assess the efficacy of recombinant human parathyroid hormone (PTH) in reducing time to resolution of CN and healing of fractures.

RESEARCH DESIGN AND METHODS

People with diabetes and acute (active) Charcot foot were randomized (double-blind) to either full-length PTH (1-84) or placebo therapy, both in addition to below-knee casting and calcium and vitamin D3 supplementation. The primary outcome was resolution of CN, defined as a skin foot temperature difference $>2^{\circ}$C at two consecutive monthly visits.

RESULTS

Median time to resolution was 5 months (95% CI 4, 12) in intervention and 6 months (95% CI 2, 9) in control. On univariate mixed Cox and logistic regression, there was no significant difference in time to resolution between the groups ($P = 0.64$) or in the likelihood of resolution ($P = 0.66$). The hazard ratio of resolution was 0.84 (95% CI 0.41, 1.74; $P = 0.64$), and the odds ratio of resolution by 12 months was 0.80 (95% CI 0.3, 2.13; $P = 0.66$) (intervention vs. control). On linear regression analysis, there were no significant differences in the effect of treatment on fracture scores quantitated on MRI scans (coefficient 0.13 [95% CI −0.62, 0.88]; $P = 0.73$) and on foot and ankle X-rays (coefficient 0.30 [95% CI −0.03, 0.63]; $P = 0.07$).

CONCLUSIONS

This double-blind placebo-controlled trial did not reduce time to resolution or enhance fracture healing of CN. There was no added benefit of daily intervention with PTH (1-84) to below-knee casting in achieving earlier resolution of CN.

Charcot neuro-osteoarthropathy (CN), or Charcot foot, is one of the most disabling complications of diabetic neuropathy (1,2). Simple trauma sets off uncontrolled inflammation and pathological fractures, resulting in severe foot deformity with an

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attendant risk of ulcers, infection, and limb loss. At present, the only accepted treatment modality is prolonged immobilization of the foot in a below-knee cast (3). This therapy causes a significant burden to the individual living with an active Charcot foot (4), as well as requiring significant resources for regular replacement of casts and provision of care (5). Yet, despite prolonged off-loading therapy, fracture healing is delayed, and nonunion is common.

Several trials in active CN have assessed the efficacy of adjunctive therapies aiming to diminish bone resorption (bisphosphonates and calcitonin) or curtail the ongoing inflammation and/or osteolysis (methylprednisolone) (6,7). Neither approach has shown clinical benefit to remission and healing.

We hypothesized that therapy with an anabolic agent adjuvant to casting could enhance fracture repair of the acute (active) Charcot foot and reduce time to resolution. The rationale for this approach was based on the anabolic skeletal action of parathyroid hormone (PTH) (8). Preclinical and clinical studies have shown that intermittent administration of either the bioactive fragment of PTH (1-34) or the full-length molecule PTH (1-84) enhances new bone formation on trabecular and cortical bone surfaces, stimulates callus formation, and accelerates fracture healing (9,10). We studied the efficacy of daily intervention with recombinant human PTH (1-84) in comparison with placebo in active CN.

RESEARCH DESIGN AND METHODS

Trial Design and Participants

This was a single-center double-blind placebo-controlled clinical trial performed at the Diabetic Foot Clinic in King's College Hospital NHS Foundation Trust, London, U.K. Consecutive individuals were invited to take part in the study. Participants were 18 years or older and had type 1 or type 2 diabetes, intact feet (absence of a skin breakdown below the malleoli), and a clinically suspected acute (active) Charcot foot. The latter was defined as recent onset of a unilateral hot swollen foot with a skin foot temperature of 2°C or greater than the contralateral foot. Eligible participants were required to have either typical radiological changes (bone fracture, fragmentation, with or without joint subluxation) on standard foot and ankle radiographs or bone marrow edema with or without bone microfracture on MRI in case subjects presenting with normal X-rays. Exclusion criteria were a serum aspartate aminotransferase greater than three times the upper limit, glycated hemoglobin A_{1c} (HbA_{1c}) >12% (108 mmol/mol), and estimated glomerular filtration rate (eGFR) or creatinine clearance <30 mL/min. Subjects were excluded if they had an active foot ulcer and infection or if they were on immunosuppression or corticosteroids.

The trial was conducted in accordance with the Declaration of Helsinki and its amendments, the International Conference on Harmonization Good Clinical Practice guidelines, and all the applicable regulatory requirements. It was approved by the South East Research Ethics Committee (REC reference 09/H1102/113) and registered on clinicaltrialsregister.eu website (EudraCT Number-2009–016873-13). All study participants provided written informed consent.

Intervention

The investigational medicinal product was a full-length recombinant human PTH (1-84). The trade name of the active compound, Preotact, was originally registered by Nycomed (Roskilde, Denmark), which was later acquired by Takeda Pharmaceutical Company Limited (Tokyo, Japan). The active drug contained PTH manufactured using a strain of *Escherichia coli* modified by recombinant DNA technology. Both the active compound and the placebo were supplied in dual-chamber cartridges specifically labeled for the study by WE Pharma Limited (London, U.K.).

Procedures

The study consisted of an initial screening visit, a randomization visit, and monthly follow-up study visits.

Screening and Randomization

Investigations at the screening visit included medical history, foot inspection, and palpation of pulses and standard weight-bearing foot (straight, oblique, and lateral) and ankle (straight and lateral) radiographs. Foot skin temperatures were measured at the metatarsophalangeal joints, tarsometatarsal joints, and medial and lateral malleoli using an infrared thermometer (DermaTemp 1001; Exergen Corporation, Watertown, MA). The temperature difference between the affected and nonaffected foot was calculated, and the maximum temperature difference at each visit was noted. Neuropathy was assessed by measurement of vibration perception threshold with a neurothesiomether on the apex of the hallux (Horwell Neurothesiometer; Scientific Laboratory Supplies, Nottingham, U.K.). Blood samples were obtained by venipuncture. Serum was immediately separated and stored at −80°C for further measurements of carboxyterminal telopeptide of type 1 collagen (CTX), a marker of bone resorption and amino-terminal propeptide of type I procollagen (P1NP), a marker of bone formation. Routine biochemical tests to measure renal and liver function, HbA_{1c}, calcium, phosphate, vitamin D, and PTH were also performed. Below-knee casting (nonremovable off-loading with total contact casts or removable cast walkers) was initiated in all cases.

The randomization visit was scheduled within 2 weeks of screening. Study participants underwent a noncontrast MRI scan of the affected Charcot foot (dedicated foot and ankle coil) (Avanto 1.5T; Siemens Healthineers, Erlangen, Germany), as previously described (11). At this visit, all clinical, biochemical, and radiological data (foot and ankle X-rays and MRI scans) were available, and the inclusion/exclusion criteria were reviewed. If foot and ankle radiographs and/or MRI scans were carried out as part of clinical assessment in eligible participants with suspected CN prior screening, these investigations were considered at baseline to avoid duplication of tests (amendment 1). Individuals were randomized in 1:1 ratio using simple randomization to intervention (daily treatment with 100 μg PTH 1-84) or control (daily treatment with 100 μg placebo). All participants received daily calcium and vitamin D3 supplementation (two tablets of Calceos, equivalent to 1,000 mg elemental calcium and 800 units cholecalciferol). Study participants were taught in the Diabetic Foot Clinic how to administer subcutaneously the investigational medicinal product/placebo using special pens (Preotact Pen).

The computer-generated randomization list was provided by the Biostatistics Unit (King's College Hospital NHS Foundation Trust and Dental Institute,

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King's College London). The intervention label codes were provided by WE Pharma Limited. Access to the unblinded randomization and intervention allocation lists was available only to the Clinical Trials Pharmacists at King's College Hospital. The latter dispensed the investigational medicinal product/placebo as well as Calceos tablets at monthly intervals. Participants and care providers were blinded to the treatment allocation for the whole duration of the study.

Below-knee off-loading was continued and followed standard clinical practice at King's College Hospital (initial cast replacement at 2 weeks and then monthly). Study participants were instructed to limit their physical activity but were allowed to weight bear (11).

Follow-up Visits

All subjects were followed in the Diabetic Foot Clinic at monthly intervals for routine Charcot foot care, including replacement of casts and skin foot temperature. Study participants were treated with PTH (1-84) or placebo until clinical resolution or for 18 months. The proposed 18-month therapy with the investigational medicinal product/placebo was in agreement with data from safety evaluation of PTH therapy. As the average time to resolution of CN was known to be 10 months, the duration of therapy with the investigational medicinal product/placebo was shortened to 12 months (amendment 2), although provision of continuous casting therapy was in place should the Charcot foot not fully heal by 12 months. Clinical resolution of the acute (active) Charcot foot was defined as a skin foot temperature difference of $<2^{\circ}C$ at two consecutive monthly visits.

Routine clinical biochemistry tests and bone turnover markers were measured monthly for the first 3 months and then at 3-month intervals, at clinical resolution, or at 12 months. Foot and ankle radiographs and MRI scans were carried out at baseline and on follow-up (at clinical resolution or at 12 months) and were analyzed at the end of the study by musculoskeletal radiologists who were unaware of the treatment allocation. Proximal phalanges, metatarsals, medial and lateral sesamoids, cuneiforms, navicular, cuboid, talus, calcaneum, distal tibial plafond, and medial and lateral malleoli were scored for bone marrow edema on MRI scans (0, no edema; 1, edema $<50\%$ of bone volume; and 2, edema $>50\%$ of bone volume) and for fracture on MRI and X-rays (0, no fracture; 1, fracture; and 2, collapse/fragmentation). Semiquantitative total MRI bone marrow edema score, total MRI fracture score, and total X-ray fracture score were calculated as the sum of scores of all 22 bones (11). In addition, measures of alignment (calcaneal pitch, Meary's angle, and cuboid height) were assessed on lateral foot radiographs (13). Anatomic involvement was graded on MRI scans based on Sanders and Frykberg's (14) classification (pattern I, metatarsophalangeal joints; pattern II, tarsometatarsal joint; pattern III, tarsal joints; pattern IV, ankle joint; and pattern V, calcaneum).

Treatment-Stopping Rules

Treatment-stopping rules included development of contralateral acute (active) Charcot foot, a fall in eGFR, and/or creatinine clearance <30 mL/min at any time point, severe hepatic impairment defined as a threefold increase in aspartate transaminase of the upper normal limit, an increase in serum corrected calcium >2.7 mmol/L at two consecutive monthly visits (despite a temporary discontinuation of the calcium and vitamin D replacement between these two visits), and in case any study participant developed any uncontrolled illness that, in the opinion of the investigator, might interfere with interpreting the results.

Outcome Measures

Primary outcome measures were time to resolution (months) and a binary indicator of clinical resolution of the active Charcot foot by 12 months. Secondary outcome measures included the effects of treatment on skin foot temperature difference, total MRI bone marrow edema score, total MRI and X-ray fracture scores, and bone turnover markers.

Statistical Analysis

Time to resolution and likelihood of clinical resolution were modeled with Cox and logistic regression analyses, respectively. A multilevel modeling approach was used to account for the within-patient correlations of the repeated measures. In order to adjust for potential confounders, variables that showed univariate significance at a level <0.20 were examined in a multivariate model. The treatment effects on skin foot temperature difference, MRI and X-ray scores, and bone turnover markers were analyzed with linear regressions, adjusted for baseline. Significance for interaction was assessed at 10%. An intention-to-treat analysis was adopted. Missing data analysis, with multiple imputation and sensitivity analysis, was applied to assess the effect of withdrawal on outcome and factors driving withdrawal. Stata v.14 was used for all statistical analyses.

The study was designed to guarantee 80% power, at the 5% significance level, to detect a difference in the median time to resolution of 11 months (in control) versus 4 months (in intervention). This difference corresponds to a hazard ratio of 2.77. Using Schoenfeld's method with equal allocation (15), a total of 30 clinical resolutions were required. The estimated sample size was 42 patients per group (based on an anticipated average length of follow-up of 4.5 months and a dropout rate of 3% per month).

The plan was to recruit 92 patients in total to allow for covariate adjustment and dropouts. Due to slow recruitment and unforeseen shortage of the investigational medicinal product, the original definition of end of study (last patient last visit) was amended, and the end of study was approved as to when the required 30 resolutions for the sample size were achieved (amendment 3).

RESULTS

Between August 2010 to November 2012, 72 patients were screened and 48 were randomly assigned (Fig. 1). The demographic, clinical, off-loading, biochemical, and imaging characteristics (scores and patterns of involvement) at baseline were similar between the two groups, with the only exception being the duration of diabetes, which, on average, was 7 years shorter in the intervention group compared with the control group (Table 1).

Resolution of Acute (Active) CN

Overall, there were 30 resolutions (16 in the control group and 14 in the intervention group) and 13 withdrawals (3 in the control group and 10 in the intervention

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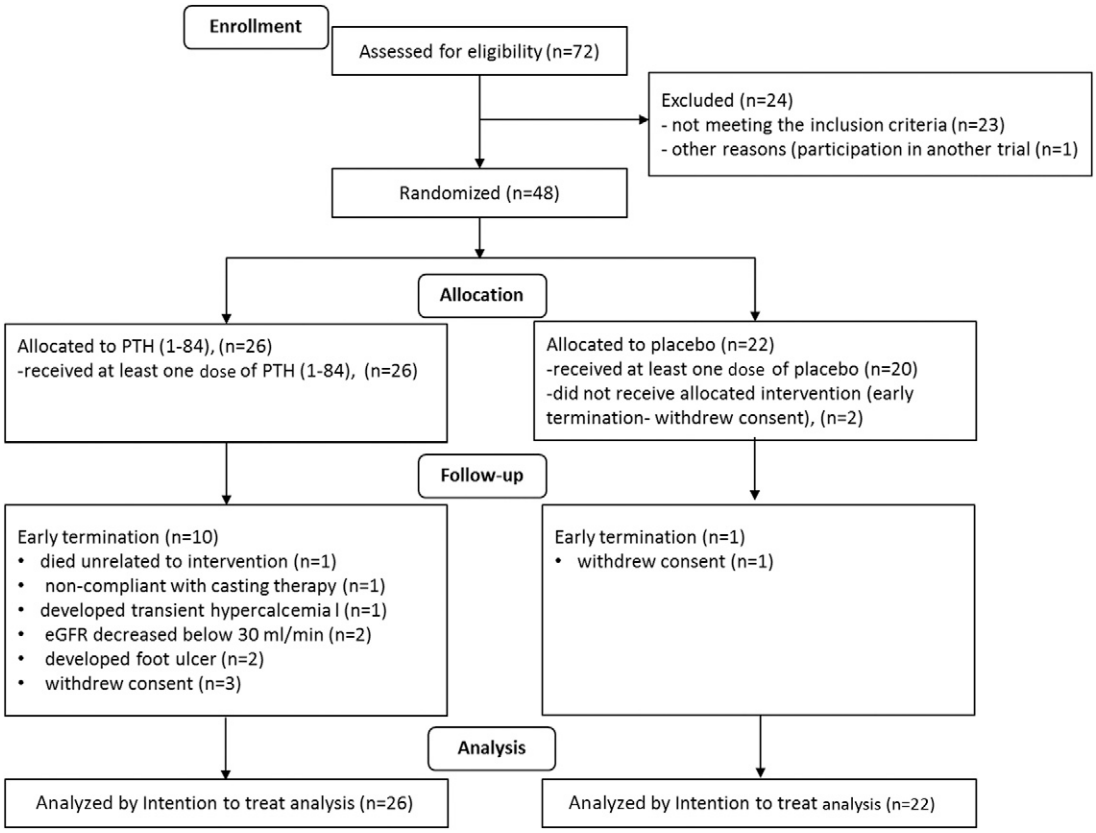

Figure 1—CONSORT diagram showing the patient flow through the clinical trial.

group) (Table 2). By the end of the study period, there were five unresolved Charcot feet (three in the control group and two in the intervention group) (Table 2). The median time to resolution was 6 months (95% CI 2, 9) in the control group and 5 months (95% CI 4, 12) in the intervention group.

Univariate and multivariate models for time to resolution and likelihood of resolution by 12 months are shown in Table 3. The global Schoenfeld residuals supported proportionality of hazards ($P = 0.65$) in the Cox regression, and a good fit was indicated by the Hosmer–Lemeshow test ($P = 0.30$) in the logistic regression. On the univariate Cox regression model, there was no significant difference in time to resolution between the groups ($P = 0.64$). The estimated hazard ratio of clinical resolution of the Charcot foot (intervention versus control) was 0.84 (95% CI 0.41, 1.74; $P = 0.64$). The Kaplan-Meier survival curves showed no significant difference in the proportions of clinical resolution of CN between the groups (log-rank statistic [1 df] was 0.25; $P = 0.61$) (Supplementary Fig. 1).

Baseline variables that showed an association with clinical resolution in the univariate model (skin foot temperature difference, P1NP, CTX, X-ray fracture score, Meary's angle, total MRI bone marrow edema score, and MRI fracture score; all with P values <0.20) were assessed in the multivariate analysis. The variables retained in the final model were skin foot temperature difference (hazard ratio 0.73 [95% CI 0.53, 1.01]; $P = 0.06$) and total MRI fracture score (hazard ratio 0.88 [95% CI 0.80, 0.98]; $P = 0.02$). After adjusting for these variables, the nonsignificant difference of the effect of treatment remained and the hazard ratio for time to resolution was 0.65 (95% CI 0.31, 1.38; $P = 0.26$), and the odds ratio (OR) for clinical resolution by 12 months was 0.69 (95% CI 0.25, 1.9; $P = 0.48$, intervention vs. control) (Table 3).

Skin Foot Temperature Difference

On follow-up (clinical resolution or at 12 months), skin foot temperature difference significantly decreased from baseline at a rate of 0.09°C per month (coefficient −0.09 [95% CI −0.13, −0.04]; $P = 0.0004$). However, the observed reduction was similar between the intervention and control groups ($P = 0.79$). The fall in skin foot temperature difference was significantly associated with the MRI fracture score at presentation (coefficient 0.06 [95% CI 0.01, 0.12]; $P = 0.02$). However, after adjusting for baseline MRI fracture score, the nonsignificant difference in the rate of decrease in skin foot temperature between the groups remained ($P = 0.43$).

MRI and X-ray Scores and Measurements

On linear regression analysis, after adjusting for baseline, there were no statistically significant differences in the effect of treatment on total MRI bone marrow edema score (coefficient 0.36 [95% CI −2.6, 3.3]; $P = 0.81$) and total MRI fracture score (coefficient 0.13 [95% CI −0.62, 0.88]; $P = 0.73$). Similarly, after adjusting for baseline, there were no statistically significant differences in the effect of treatment on total X-ray fracture score (coefficient 0.30 [95% CI −0.03, 0.63]; $P = 0.07$),

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Table 1—Baseline characteristics for the overall cohort and per treatment group

	Overall (*n* = 48)	Control (*n* = 22)	Intervention (*n* = 26)
Demographic features			
Age (years)	55 (51.8, 57.8)	53 (48.5, 58.2)	56 (52, 60)
Men	37 (77)	18 (82)	19 (73)
Women	11 (23)	4 (18)	7 (27)
Duration of diabetes (years)	20 (16.8, 23.8)	24 (19.3, 29.3)	17 (11.9, 21.7)
Type 1 diabetes	16 (33)	10 (45)	6 (24)
Type 2 diabetes	32 (67)	12 (55)	20 (77)
Clinical characteristics			
Left foot involvement	23 (48)	11 (50)	12 (46)
Right foot involvement	25 (52)	11 (50)	14 (56)
VPT of the Charcot foot (volts)	35 (31.1, 39.1)	36 (29.6, 41.8)	32 (24.2, 40.6)
Foot skin temperature difference (°C)	3.4 (3.0, 3.9)	3.3 (2.7, 4.0)	3.5 (2.9, 4.1)
Off-loading			
Nonremovable cast	33 (69)	16 (73)	17 (65)
Removable cast	15 (31)	6 (27)	9 (35)
Biochemistry			
Sodium (mmol/L)	139 (137.6, 140)	139 (137.2, 140.0)	140 (138.8, 141.0)
Potassium (mmol/L)	4.7 (4.6, 4.9)	4.7 (4.5, 5.0)	4.8 (4.5, 5.0)
Creatinine (mol/L)	90 (79.9, 99.1)	85 (74.5, 95.0)	98 (77.0, 119.1)
Alkaline phosphatase (IU/L)	104 (91.7, 116.1)	89 (77.9, 99.8)	115 (86, 142.8)
γ-Glutamyl transferase (IU/L)	62 (31.2, 93.4)	66 (11.1, 121.1)	73 (8.8, 137.3)
Aspartate transaminase (IU/L)	22 (20.1, 24.0)	23 (19.1, 26.6)	22 (18.9, 25.7)
Calcium (mmol/L)	2.34 (2.31, 2.36)	2.36 (2.32, 2.39)	2.32 (2.29, 2.34)
Corrected calcium (mmol/L)	2.28 (2.26, 2.30)	2.28 (2.25, 2.30)	2.28 (2.25, 2.30)
Phosphate (mmol/L)	1.14 (1.09, 1.20)	1.10 (1.02, 1.17)	1.19 (1.07, 1.31)
eGFR (mL/min)	75 (69.6, 80.7)	77 (68.9, 85.3)	71 (59.7, 81.7)
Log-vitamin D (μg/L)	2.5 (2.3, 2.7)	2.5 (2.2, 2.8)	2.6 (2.3, 2.8)
PTH (ng/L)	51 (40.2, 61.1)	47 (35.0, 59.6)	55 (37.7, 72.5)
Glycated HbA_{1c} (%)	8.4 (7.9, 8.8)	8.2 (7.5, 8.9)	8.4 (7.6, 9.1)
Glycated HbA_{1c} (mmol/mol)	68 (63.3, 72.3)	66 (58.7, 74.1)	68 (59.3, 76.4)
Serum bone turnover markers			
Log-P1NP (μg/L)	3.7 (3.6, 3.87)	3.6 (3.4, 3.85)	3.8 (3.65, 3.99)
CTX (μg/L)	0.28 (0.24, 0.32)	0.25 (0.20, 0.31)	0.30 (0.25, 0.36)
X-ray scores			
Calcaneal pitch (°)	17.5 (14.5, 20.6)	17.7 (12.7, 22.7)	17.4 (13.5, 21.4)
Meary's angle (°)	−9.7 (−14.2, −5.3)	−9.6 (−16.3, −2.8)	−9.9 (−16.3, −3.5)
Cuboid height (mm)	8.4 (5.5, 11.3)	7.5 (2.8, 12.1)	9.3 (5.4, 13.2)
Total X-ray fracture score	4.6 (3.3, 5.8)	4.8 (3.0, 6.6)	4.4 (2.5, 6.2)
MRI scores			
Total MRI bone marrow edema score	19 (16.6, 20.8)	19 (15.4, 22.0)	19 (15.7, 21.6)
Total MRI fracture score	6 (4.8, 7.2)	6 (3.74, 7.8)	6 (4.5, 7.9)
Patterns of involvement			
Pattern I present	25 (58)	10 (53)	15 (63)
Pattern II present	44 (92)	22 (100)	22 (85)
Pattern III present	39 (81)	17 (77)	22 (85)
Pattern IV present	12 (27)	7 (35)	5 (20)
Pattern V present	2 (5)	1 (5)	1 (4)

For categorical variables, *n* (%) is presented, and for continuous variables, the mean (95% CI) is presented. The bone turnover marker P1NP and vitamin D exhibited highly skewed distributions, and these variables were log-transformed for the purpose of the analysis. Meary's angle is the angle between the line drawn from the center of the body of the talus bisecting the talar neck and head and the line drawn through the longitudinal axis of the first metatarsal. A negative angle represents arch lowering. Cuboid height is the distance from the most plantar aspect of the cuboid to a horizontal line drawn from the plantar calcaneal tuberosity to the fifth metatarsal head. A smaller number represents arch lowering. Calcaneal pitch is the angle created by a line drawn from the calcaneal tuberosity to the plantar aspect of the distal part of the calcaneus and a horizontal line drawn from the plantar calcaneal tuberosity to the fifth metatarsal head. A smaller angle indicates arch lowering. Almost all participants (45 out of 48) presented with more than one pattern of involvement. There were only two participants who showed abnormality in the calcaneum (pattern V). As this number was very small, there was not enough information to make any statistical inference (pattern V was not included in Table 3). IU, International unit; VPT, vibration perception threshold.

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Table 2—Life table to show clinical resolution and early terminations in the control group and in the intervention group

	Control group (n = 22)				Intervention group (n = 26)			
Time (months)	Active Charcot foot	Clinical resolution	Early termination	Resolution rate* (95% CI)	Active Charcot foot	Clinical resolution	Early termination	Resolution rate* (95% CI)
0–1	22	0	2	0	26	0	0	0
1–2	20	0	0	0	26	0	4	0
2–3	20	6	1	0.30 (0.15, 0.56)	22	3	1	0.14 (0.05, 0.37)
3–4	13	1	0	0.36 (0.19, 0.61)	18	1	0	0.19 (0.07, 0.43)
4–5	12	1	0	0.41 (0.23, 0.66)	17	6	1	0.48 (0.30, 0.71)
5–6	11	1	0	0.47 (0.28, 0.71)	10	1	0	0.53 (0.34, 0.76)
6–7	10	1	0	0.52 (0.32, 0.75)	9	1	1	0.59 (0.39, 0.80)
7–8	9	1	0	0.57 (0.37, 0.79)	7	0	2	0.59 (0.39, 0.80)
8–9	8	2	0	0.68 (0.47, 0.87)	5	1	0	0.67 (0.45, 0.87)
9–10	6	1	0	0.73 (0.53, 0.9)	4	0	0	0.67 (0.45, 0.87)
10–11	5	2	0	0.84 (0.65, 0.96)	4	0	1	0.67 (0.45, 0.87)
11–12	3	0	0	0.84 (0.65, 0.96)	3	1	0	0.84 (0.54, 0.99)

*Resolution rate is the cumulative rate of events (clinical resolution of the Charcot foot).

calcaneal pitch (coefficient −1.5 [95% CI −6.3, 3.4]; $P = 0.55$), Meary's angle (coefficient −0.95 [95% CI −5.1, 3.2]; $P = 0.65$), and cuboid height (coefficient −1.6 [95% CI −4.5, 1.2]; $P = 0.24$).

Bone Markers

From presentation to follow-up (clinical resolution or at 12 months), the serum concentration of the bone resorption marker CTX remained unchanged (coefficient 0.001 [95% CI −0.004, 0.006]; $P = 0.66$). A borderline treatment effect, which was significant at the 10% level ($P = 0.06$), showed that the mean concentration of CTX increased in the intervention group (coefficient 0.305 [95% CI −0.003, 0.13]; $P = 0.001$), while in the control group, this marker remained unchanged. The bone formation marker P1NP significantly decreased from baseline at a rate of 2.2% (95% CI 1, 3.5) per month ($P = 0.001$). However, the rate of this decrease in P1NP was similar between the intervention and control groups ($P = 0.12$).

Missing Data Analysis

The overall withdrawal rate was 27%, with 3 early terminations in the control group and 10 in the intervention group (Table 2). Although withdrawal was more common in women compared with men (OR 6.2 [95% CI 1.7, 23]; $P = 0.01$), on exact logistic regression, it was not related to the variables significantly associated with time to resolution and likelihood of resolution (i.e., skin foot temperature difference at presentation, OR 0.79 [95% CI 0.51, 1.2], $P = 0.28$; and MRI fracture score at presentation, OR 0.88 [95% CI 0.62, 1.30], $P = 0.50$). Therefore, the missing mechanism was classified as missing at random and multiple imputation analysis, with 50 simulations and chained iterations, was used to estimate missing data for resolution for the 13 early terminations and for any other covariate to be used for imputation or to be adjusted for in the final model. Clustering for the repeated measures, a logistic regression was used to impute resolution and linear regression to impute MRI fracture score. After adjusting for the effects of time, baseline skin foot temperature difference at presentation (OR 0.70 [95% CI 0.50, 0.99]; $P = 0.04$), and total MRI fracture score at presentation (OR 0.86 [95% CI 0.76, 0.97]; $P = 0.02$), the nonsignificance and effect size for the likelihood of resolution (OR 0.63 [95% CI 0.26, 1.5]; $P = 0.30$) were consistent with the findings based on the complete-case mixed logistic regression model. In addition, on a sensitivity analysis approach, the likelihood of resolution was assessed, simulating that all 10 early terminations in the intervention group and none in the control group would have had resolution by 12 months. The nonsignificant difference of the treatment effect, found with the complete-case and the imputed-sample analyses, was not reversed by this extreme scenario favoring the intervention (OR 1.5 [95% CI 0.49, 4.5]; $P = 0.49$).

Safety Evaluation

A total of six serious adverse events were reported. There was one death due to ischemic heart disease (which was considered not to be related to the investigational medicinal product). There were five hospital admissions due to respiratory depression caused by fentanyl patch (one), vomiting caused by mild gastritis (one), onset of infected foot ulcer (one), severe pain caused by L3 nerve impingement and trochanteric bursitis (one), and acute liver dysfunction (one). The last three of these serious adverse events resulted in discontinuation of the intervention, one of which was only temporary (liver dysfunction). All five hospital admissions were considered unlikely to be related to the investigational medicinal product. There were no serious adverse reactions or suspected unexpected serious adverse reactions.

CONCLUSIONS

This is the first randomized, placebo-controlled study comparing the effect of anabolic therapy with standard care in patients with active CN. Daily intervention with PTH (1-84) did not reduce time to resolution or enhance likelihood of resolution. Skin foot temperature difference, total bone marrow edema

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Table 3—Mixed-effect Cox and logistic regressions for time to resolution and likelihood of resolution

	Univariate regression models				Multivariate regression models			
	Time to resolution		Likelihood of resolution		Time to resolution		Likelihood of resolution	
	Hazard ratio (95% CI)	*P* value	OR (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	OR (95% CI)	*P* value
Time (months)			1.22 (0.90, 1.67)	0.20			1.37 (0.94; 1.99)	0.10
Age (years)	1.01 (0.97, 1.05)	0.68	1.01 (0.96, 1.06)	0.71				
Sex (men vs. women)	0.89 (0.31, 2.6)	0.83	0.78 (0.20, 3.0)	0.71				
Duration of diabetes (years)	1.00 (0.97, 1.04)	0.84	1.00 (0.96, 1.05)	0.82				
Type of diabetes (type 2 vs. type 1)	1.10 (0.47, 2.6)	0.82	1.21 (0.40, 3.6)	0.74				
Side of Charcot foot involvement (left vs. right)	0.80 (0.39, 1.64)	0.55	0.66 (0.24, 1.81)	0.43				
Skin foot temperature difference (°C)	0.68 (0.50, 0.92)	0.01	0.58 (0.35, 0.97)	0.04	0.73 (0.53, 1.01)	0.06	0.64 (0.38, 1.08)	0.09
VPT of the Charcot foot (volts)	0.99 (0.96, 1.02)	0.41	0.98 (0.94, 1.02)	0.37				
Off-loading (nonremovable cast vs. removable cast)	1.4 (0.63, 3.04)	0.42	1.1 (0.48, 2.5)	0.82				
Sodium (mmol/L)	0.98 (0.84, 1.15)	0.83	0.97 (0.80, 1.18)	0.75				
Potassium (mmol/L)	0.73 (0.34, 1.55)	0.41	0.53 (0.17, 1.72)	0.29				
Creatinine (mol/L)	0.99 (0.98, 1.01)	0.53	0.99 (0.97, 1.01)	0.38				
Alkaline phosphatase (IU/L)	0.99 (0.98, 1.00)	0.21	0.99 (0.97, 1.01)	0.17				
γ-Glutamyl transferase (IU/L)	1.00 (0.99, 1.00)	0.30	1.00 (0.99, 1.00)	0.28				
Aspartate transaminase (IU/L)	1.00 (0.95, 1.06)	0.95	1.01 (0.93, 1.03)	0.84				
Calcium (mmol/L)	0.50 (0.0, 211)	0.82	0.65 (0.0, 305)	0.89				
Corrected calcium (mmol/L)	0.03 (0.0, 14.7)	0.26	0.01 (0.0, 19.4)	0.24				
Phosphate (mmol/L)	0.37 (0.04, 3.10)	0.32	0.23 (0.01, 4.80)	0.34				
eGFR (mL/min)	1.01 (0.98, 1.03)	0.64	1.01 (0.98, 1.05)	0.45				
Log-vitamin D (μg/L)	0.85 (0.49, 1.47)	0.55	0.77 (0.35, 1.72)	0.53				
PTH (ng/L)	1.00 (0.98, 1.00)	0.45	0.99 (0.97, 1.01)	0.39				
Glycated HbA_{1c} (%)	0.93 (0.70, 1.22)	0.62	0.88 (0.61, 1.28)	0.51				
Glycated HbA_{1c} (mmol/mol)	0.99 (0.97, 1.02)	0.61	0.99 (0.96, 1.02)	0.51				
Log-P1NP (μg/L)	0.31 (0.12, 0.78)	0.01	0.13 (0.02, 0.91)	0.04				
CTX (μg/L)	0.03 (0.0, 1.7)	0.09	0.01 (0.0, 2.3)	0.09				
Calcaneal pitch (°)	1.03 (0.98, 1.07)	0.24	1.04 (0.98, 1.11)	0.21				
Meary's angle (°)	1.03 (1.00, 1.06)	0.03	1.05 (1.0, 1.09)	0.05				
Cuboid height (mm)	1.02 (0.98, 1.07)	0.31	1.04 (0.98, 1.10)	0.25				
Total X-ray fracture score	0.93 (0.84, 1.01)	0.09	0.89 (0.76, 1.03)	0.11				
Total bone marrow edema score	0.95 (0.90, 1.0)	0.08	0.94 (0.87, 1.01)	0.09				
Total MRI fracture score	0.86 (0.78, 0.95)	0.004	0.82 (0.69, 0.96)	0.02	0.88 (0.80, 0.98)	0.02	0.83 (0.69, 0.99)	0.04
Pattern I (present vs. absent)	0.91 (0.43, 2.0)	0.82	0.95 (0.43, 2.1)	0.89				
Pattern II (present vs. absent)	1.24 (0.38, 4.1)	0.72	1.01 (0.29, 3.5)	0.98				
Pattern III (present vs. absent)	1.1 (0.44, 2.7)	0.86	0.92 (0.36, 2.4)	0.86				
Pattern IV (present vs. absent)	1.1 (0.53, 2.4)	0.74	1.3 (0.59, 3.0)	0.50				
Treatment (intervention vs. control)	0.84 (0.41, 1.74)	0.64	0.80 (0.3, 2.13)	0.66	0.65 (0.31, 1.38)	0.26	0.69 (0.25, 1.9)	0.48

IU, International unit; VPT, vibration perception threshold.

score, and total MRI and X-ray fracture scores declined similarly in both groups. Bone resorption increased and bone formation decreased with the use of PTH.

It is well established that despite protracted immobilization in a below-knee cast, healing of fractures in the Charcot foot is delayed, and time to resolution is prolonged. We proposed to test whether the addition of an anabolic agent to standard therapy could accelerate remission of the Charcot foot. We observed that daily administration of PTH (1-84), an agent with proven efficacy in enhancing fracture healing and reducing time to healing in non-Charcot factures (9,10,16), shortened time to clinical resolution of active CN by 1 month. However, in our study, the effect of treatment on either time to resolution or resolution by 12

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months was not significant. Moreover, the survival pattern of reaching clinical resolutions and the likelihood of achieving clinical resolution by 12 months were similar between the intervention and control groups.

We anticipated that therapy with PTH (1-84) would augment bone healing and thus moderate the inflammatory response to fracture in CN. Although we observed that skin foot temperature difference fell significantly as the Charcot foot progressed from the acute (active) stage into the chronic (inactive) stage in both groups, this decrease was not significantly different between intervention and control. This is in contrast with findings from a previous preliminary study in active CN, which reported that participants treated with PTH (1-34) ($n = 5$) achieved temperature stabilization more quickly compared with subjects treated with casting alone ($n = 5$) (17).

Although skin foot temperature difference is commonly assessed in daily practice as a surrogate indicator of clinical resolution (18), MRI adjunctive to conventional radiography has been extensively used in the assessment of the Charcot foot. This imaging modality can detect inflammatory osteolysis (bone marrow edema) in CN, as well as microfractures (which are not visible on X-rays) and macrofractures (which are X-ray positive) (19,20). To evaluate the efficacy of PTH to enhance fracture healing, we developed a novel method to quantitate bone marrow edema (MRI) and foot fractures (MRI and X-ray) and scored 22 bones that can be commonly affected by the Charcot process (12). At baseline, the extent of Charcot changes was comparable between the groups, as indicated by nonsignificant differences in MRI scores, X-ray scores, measures of alignment, and patterns of involvement. On follow-up, casting therapy resulted in significant reduction of the total MRI bone marrow edema score and significant reduction in total MRI and X-ray fracture scores in each group. These observations are consistent with previous reports of cohorts with Charcot feet, managed on the basis of MRI (21,22). However, all scores (total MRI bone marrow edema score and total MRI and X-ray fracture scores) declined at a similar rate in intervention and control. Thus, therapy of CN with PTH did not enhance bone repair. This is in contrast to findings from a recent meta-analysis that reported significant clinical value of PTH therapy on healing of non-Charcot factures (23).

To assess the efficacy to PTH therapy, we measured biochemical markers of bone turnover. The bone resorption marker CTX significantly increased in the intervention group, while the bone formation marker P1NP significantly decreased in both groups. This is in contrast to the effect of PTH (1-34) in a cohort with chronic (inactive) Charcot foot for 12 months. This double-blind, placebo-controlled trial reported that P1NP increased with therapy with PTH (1-34), but decreased with placebo, whereas CTX increased in both PTH (1-34) and placebo groups (24). The significance of these systemic biochemical markers, which are commonly used to assess the efficacy of PTH therapy on skeletal tissue in fracture-prevention studies, remains unknown, especially in the localized bone loss of the affected Charcot foot in both active and chronic CN (25).

The study had several limitations. Firstly, annual recruitment was slower than anticipated. Secondly, during the 2nd year of the trial, the research team was made aware of an unprecedented global shortage of the investigational medicinal product. Nevertheless, with the 48 patients recruited, the study achieved the 30 resolutions called by the power requirement to detect the sought hazard ratio of 2.77. Thirdly, withdrawal rate was high. However, missing data analysis indicated the withdrawal mechanism to be "missing at random" since it was not related to skin foot temperature or total MRI fracture score, variables that were significantly associated with the likelihood of clinical resolution by 12 months. Also, findings of the multiple imputation model and the sensitivity analysis were consistent with the findings of the complete-case analysis. This confirms that the high withdrawal rate did not affect the study results.

A further limitation of the study was that only 73% in the control group and 65% in the intervention group were managed in nonremovable casts. Nevertheless, this rate was significantly higher than the previously reported rate of the use of nonremovable off-loading for the acute Charcot foot in the U.K. (35.4%) (26). Also, the type of offloading was similar between the groups and had no significant effect on resolution.

The strengths of this study include information on a new therapeutic approach to CN using an anabolic agent with intensive follow-up and the use of a novel method to quantitate and prospectively analyze reduction of inflammatory bone marrow edema (MRI) and healing of fractures (MRI and X-ray).

In conclusion, we observed no added benefit from PTH (1-84) in achieving earlier resolution of CN as compared with below-knee casting. Daily intervention with PTH (1-84) did not reduce time to resolution or enhance fracture healing of the active Charcot foot. This study used, for the first time, MRI and X-ray scores, in addition to skin foot temperature, to quantitate resolution and fracture healing, and these new efficacy measures should be considered in further clinical trials in CN.

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