The Effect of Zoledronic Acid on the Clinical Resolution of Charcot Neuroarthropathy

A pilot randomized controlled trial

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OBJECTIVE—To investigate the clinical efficacy of zoledronic acid in patients with diabetes and acute Charcot neuroarthropathy.

RESEARCH DESIGN AND METHODS—Thirty-nine consecutive patients were randomly assigned to placebo or three intravenous infusions of 4 mg zoledronic acid. The primary outcome was clinical resolution of acute Charcot neuroarthropathy determined by total immobilization time (casting plus orthosis).

RESULTS—At baseline, there was no significant difference between the randomly assigned groups with respect to Charcot disease activity or other baseline values. In the zoledronic acid group, the median time for total immobilization was 27 weeks (range 10–62), and in the placebo group it was 20 weeks (20–52) ($P = 0.02$).

CONCLUSIONS—Zoledronic acid had no beneficial effect on the clinical resolution of acute Charcot neuroarthropathy in terms of total immobilization time. It is possible that it may prolong the time to clinical resolution of Charcot neuroarthropathy.

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Charcot neuroarthropathy is a rare but devastating complication of diabetes, with an incidence of 0.1–0.3% in patients with diabetes (1,2). The pathogenesis of acute Charcot neuroarthropathy remains unclear. It is hypothesized that the activation of the inflammatory cascade (via receptor activator of nuclear factor κ-B ligand [RANKL] signaling pathway) at the onset of acute Charcot neuroarthropathy leads to the activation of osteoclasts and subsequent bone and joint destruction (3–5). Several pharmacological adjuncts have been reported to be beneficial in acute Charcot neuroarthropathy (6–10). This double-blind, randomized controlled trial investigates the efficacy of zoledronic acid (bisphosphonate) in patients with acute Charcot neuroarthropathy.

RESEARCH DESIGN AND METHODS

The aim of the study was to evaluate whether three intravenous infusions of 4 mg zoledronic acid (Zometa, administered in 1-month intervals) would accelerate clinical resolution of acute Charcot neuroarthropathy in the midfoot. The study protocol was evaluated by the local ethics committee (R01165M), and the study was performed without industrial sponsorship. The trial was conducted in accordance with the Declaration of Helsinki, and all patients gave their written informed consent. Patients with severe renal insufficiency (serum creatinine >400 μmol/L) or previous bisphosphonate treatment were excluded from the study.

The diagnosis of acute midfoot Charcot neuroarthropathy was based on clinical examination and radiological findings. Clinical criteria for acute Charcot neuroarthropathy included the presence of a warm, swollen foot with erythema over the warmest area of the foot. An increase of ≥2°C (infrared thermometer) compared with the same site on the contralateral foot was taken to indicate active Charcot neuroarthropathy. All patients with a suspicion of Charcot neuroarthropathy underwent plain radiographs and magnetic resonance imaging of the affected foot. The main magnetic resonance imaging criteria for Charcot neuroarthropathy were periarticular focal bone marrow odema, absent sinus tracts or soft-tissue fluid collections, and preservation of periarticular subcutaneous fat (11).

Patients initially were treated conservatively with a non–weight-bearing, below-the-knee contact cast. When the skin temperature difference between feet was 1–2°C and no other clinical signs of active Charcot processes were present, partial weight bearing was allowed and a fixed ankle–foot orthosis was applied. The temperature differences and the clinical signs of reactivation of the Charcot process were evaluated in 2–4-week intervals until the resolution stage was reached. The resolution stage was assessed as a temperature difference of <1°C during the last 30-day period with no evidence of erythema or edema. At this point, immobilization was discontinued, and full weight bearing was allowed with accommodative shoe wear (total-contact insoles or custom-made shoes with rocker soles).

A total of 39 consecutive Caucasian patients were recruited into the study. Patients were assessed at baseline and at 2–4-week intervals for the first 3 months and at 6, 9, and 12 months thereafter. Four patients were excluded from the

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final analysis because of a protocol violation (three patients) or the need for surgical procedure (one patient had a below-the-knee amputation) during the immobilization period. Thirty-five patients completed the 1-year follow-up (Supplementary Fig. 1).

Continuous variables are expressed as the median and range. Between-group comparisons of continuous variables at each time point were analyzed with the Mann-Whitney *U* test as a result of skewed distribution. Data were analyzed with use of the χ^2 test and Fisher exact test, as appropriate. Tests were two-tailed, with use of a critical value of 0.05.

RESULTS—At baseline, there was no significant difference between groups (Table 1). In the zoledronic acid group (group Z), the median for total immobilization time was 27 weeks (10–62 weeks), and in the placebo group (group P), the median for total immobilization time was 20 weeks (20–52 weeks) ($P = 0.02$). Feet in group Z were immobilized in a cast for a median of 15 weeks (0–28 weeks) and in group P for 12 weeks (0–20 weeks) ($P = 0.13$). Time of immobilization in orthosis was 15 weeks (7–40 weeks) for group Z and 10 weeks (4–32 weeks) for group P ($P = 0.05$). Total weight bearing with total-contact insoles or custom-made shoes with rocker soles was permitted after a median of 28 weeks (10–64 weeks) for group Z and after a median of 24 weeks (14–52 weeks) for group P ($P = 0.13$). One relapse of Charcot neuroarthropathy was diagnosed in each group during the 12-month follow-up period. No serious adverse events were recorded.

CONCLUSIONS—Previous reports (6–9) have indicated a beneficial effect of bisphosphonates on the reduction in bone turnover markers in Charcot neuroarthropathy, but the clinical efficacy of these drugs remains controversial. However, this study did not suggest any beneficial effect of zoledronic acid on the clinical resolution of acute Charcot neuroarthropathy. To the contrary, patients treated with zoledronic acid required longer immobilization time compared with the placebo group ($P = 0.02$). The main problems of this study are a relatively small sample size (statistically underpowered), a wide variation in immobilization times, and an inability to monitor concordance to the non–weight-bearing protocol.

Fifteen years ago, the first medical trails were performed to investigate whether osteoclast inhibitors (bisphosphonates) had an effect on the Charcot neuroarthropathic disease process (6). Promising results were reported with alendronate and pamidronate, and most recently with calcitonin (nonbisphosphonate osteoclast inhibitor) (6–10). A clear reduction in bone turnover markers was reported in these trials. This is an expected pharmacological effect of these drugs, and the clinical benefit of this remains unclear.

The activation of osteoclasts and bone resorption may represent a late phase of the Charcot neuroarthropathy disease process, and a series of immunoinflammatory reactions is suspected to occur before fragmentation is seen on radiographs (3,4). Recently, understanding of the basic patophysiological cascade responsible for the initiation of Charcot neuroarthropathy has evolved (3), and additional investigation is needed to show whether medications addressing the imbalance of RANKL and osteoprotegerin (i.e., tumor necrosis factor-α inhibitors) could lead to a faster clinical resolution of acute Charcot neuroarthropathy. Until then, the mainstay of the initial management of acute Charcot neuroarthropathy is immobilization and offloading in a plaster cast, with continuous monitoring of the clinical signs of the activity of the Charcot neuroarthropathy disease process (12–14).

Table 1—*Baseline characteristics of the study population* (n = 35)

Characteristics	Zoledronic acid group	Placebo group	*P*
n	18	17	
Age (years)	53.8 ± 9.1	56.0 ± 9.2	0.40§
Sex (female/male)	5/13	1/16	0.18‖
Type 1/type 2 diabetes (*n*)	8/10	5/12	0.49‖
Duration of diabetes (years)	17.3 ± 14.0	16.9 ± 12.4	0.96§
Neuropathy (*n*)	17	15	0.60‖
Retinopathy (*n*)	9	9	1‖
Nephropathy (*n*)	15	9	0.08‖
BMI (kg/m^2)	29.0 ± 6.4	28.4 ± 6.1	0.94§
C-reactive protein (mg/L)	12.7 ± 22.1	3.6 ± 4.1	0.07§
S-ALP (units/L)*	156 ± 90	175 ± 153	0.87§
S-iCa (mmol/L)	1.26 ± 0.04	1.25 ± 0.05	0.87§
S-PiP (mmol/L)	1.07 ± 0.17	1.04 ± 0.21	0.61§
HbA_{1c} (%)	8.2 ± 1.4	7.9 ± 1.6	0.64§
Charcot foot involvement site			
TMT and/or NC joint	14	15	0.66‖
TN and/or CC joint	4	2	
Abnormal foot architecture (*n*)†	11	7	0.32‖
Plantar ulceration (*n*)	2	1	1‖
Initial foot temperature difference (°C)	3.3 ± 1.6	3.2 ± 2.1	0.53§
Distal pedal pulses present‡	17	17	1‖

Data are means ± SD, unless otherwise indicated. S-ALP, serum alkaline phosphatase; S-iCA, serum ionized calcium; S-PiP, serum phosphate; TMT, tarso-metatarsal; NC, naviculocuneiforme; TN, talo-navicular; CC, calcaneo-cuboidal. *One patient in the zoledronic acid group was excluded because of primary biliary cirrhosis (1,250 units/L *S*-ALP at baseline). †Clinical deformation of the medial longitudinal arch of the foot. ‡A. dorsalis pedis and a. tibialis posterior identified. §Mann–Whitney *U* test. ‖Fisher exact test.

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