Effect of Single Dose of RANKL Antibody Treatment on Acute Charcot Neuro-osteoarthropathy of the Foot

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Charcot neuro-osteoarthropathy is a rare condition that affects subjects with diabetes with neuropathy (1). Although the underlying pathophysiology is largely unknown, increased receptor activator of nuclear factor κ-B ligand (RANKL) activation in Charcot neuro-osteoarthropathy has been observed (2). As monoclonal RANKL antibody treatment (denosumab, Prolia) reduces osteoporosis-related fractures (3), we studied its effect on fracture resolution time and clinical outcomes in acute Charcot neuro-osteoarthropathy. All patients with diabetes seen at our foot clinic between 2012 and 2016 were categorized by modified Brodsky classification (4) and treated according to a standardized total contact cast (TCC) protocol. This comprises weekly TCC changes and subsequent conventional X-ray imaging every 4 weeks, as well as supplementation daily with calcium 500 mg/cholecalciferol 800 IE to achieve adequate plasma calcium (between 2.2 and 2.5 mmol/L) and vitamin D levels (>30 nmol/L). All subjects with an acute Charcot foot seen between 2012 and 2014 were included as historic control subjects. From 2014 to 2016, subjects were treated with TCC and a single injection of denosumab 60 mg subcutaneously, followed by plasma calcium check 1 week later.

Upon blinding of radiological case data, fracture resolution (improved consolidation of subchondral bone marrow, decreased subchondral lysis, improved lining of the subchondral bone, and a decrease in soft tissue edema) was scored on conventional X-rays of the affected foot (three-way view) by two independent musculoskeletal radiologists (M.M. and F.F.S.). Time to cessation of TCC was based on edema resolution and less than 2°C temperature difference between both feet measured thrice with TempTouch (Xilas Medical). Complication rates (Table 1) were scored by an independent clinician (K.D.) until 1-year follow-up. The study was reviewed and approved by the institutional review board of the Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands.

Although no adverse events or hypocalcemia were observed, fracture resolution was significantly shorter after denosumab (average 109 ± 45 days) compared with the usual-care group (average 174 ± 69 days), with a good correlation (Pearson $r = 0.79$, $P < 0.01$) between the two radiologists (M.M., 119 ± 42 vs. 172 ± 53 days, and F.F.S., 98 ± 48 vs. 176 ± 86 days) (Table 1). Moreover, time to clinical cessation and malalignment in Chopart-Lisfranc joint at end of TCC was also significantly lower with denosumab (123 ± 43 vs. 181 ± 49 days, $P < 0.01$). None of the subjects developed a contralateral Charcot foot during 1-year follow-up. Whereas ulcer recurrence was similar in both groups, there was an (nonsignificant) increased Charcot recurrence and amputation rate in the conventional treatment group during 1-year follow-up.

This single-center observational study has certain limitations including use of historic control subjects and blinding of only the involved radiologists, which limits its generalization of the results to other diabetic foot centers. Also, BMI was increased in the denosumab group due to a higher number of subjects with type 2 diabetes, and more subjects in the usual-care group were treated with bisphosphonates until publication of the review by Richard et al. in 2012 (5). Nevertheless, both confounders tend toward underestimation of denosumab treatment, but efficacy needs to be formally assessed

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Table 1—Baseline characteristics

	Denosumab ($n = 11$)	Usual care ($n = 11$)
Age (years)	59 ± 7	56 ± 16
Sex (men/women)	7/4	3/8
Type 1/type 2 diabetes	1/10	5/6*
Duration of diabetes (years)	16 ± 12	21 ± 8
BMI (kg/m^2)	33 ± 5	26 ± 6*
Alendronate use	0	5
Neuropathy	11	11
Retinopathy	8	9
Albuminuria	7	7
Peripheral arterial occlusive disease	1	1
Systolic blood pressure (mmHg)	132 ± 10	131 ± 10
Diastolic blood pressure (mmHg)	77 ± 10	76 ± 11
Heart rate (bpm)	74 ± 4	76 ± 6
HbA_{1c} (%)	8.1 ± 1.4	8.2 ± 1.2
HbA_{1c} (mmol/mol)	65 ± 15	67 ± 13
Creatinine clearance (mL/min)	117 ± 60	91 ± 27
Calcium (mmol/L)	2.5 ± 0.1	2.4 ± 0.1
Albumin (g/L)	45 ± 3	44 ± 3
25-OH vitamin D (nmol/L)	51 ± 13	38 ± 17
Charcot foot location (left/right)	6/5	7/4
Modified Brodsky		
Type-1	8	6
Type-2	0	0
Type-3A	0	0
Type-3B	0	0
Type-4	2	3
Type-5	1	2
Fracture resolution on imaging (days)	109 ± 45	174 ± 69#
TCC duration (days)	123 ± 43	182 ± 49#
Progressive malalignment of Charcot foot (end of TCC)	2	5
Charcot foot recurrence <12 months	0	2
Ulcer development <12 months	4	5
Amputation <12 months	0	3
Transmetatarsal amputation	0	1
Transtibial amputation	0	2

Data are mean ± SD or *n*. bpm, beats per minute. Peripheral arterial occlusive disease was excluded when both dorsal pedal and posterior tibial artery pulsations were felt or confirmed by a duplex ultrasonography. Differences in clinical variables between the denosumab- and usual-care–treated subjects were tested with unpaired *t* test or Mann-Whitney test based on Gaussian distribution. *$P < 0.05$, #$P < 0.01$.

in a larger, randomized, and appropriately blinded trial.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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