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SYSTEMATIC REVIEW

Treatment of acute Charcot foot with bisphosphonates: a systematic review of the literature

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Abstract
Aim/hypothesis We undertook a systematic review of the literature concerning the efficacy and safety of bisphosphonates in acute Charcot neuropathic osteoarthropathy.
Methods MEDLINE, PubMed, the Cochrane Database of Systematic Reviews, and abstracts presented during the meetings of the American Diabetes Association and the European Association of Diabetes were searched for relevant publications from the period January 1990 to September 2011.
Results A total of ten studies on the treatment of acute Charcot osteoarthropathy with bisphosphonates were identified and included in the analysis. Only four clinical trials were published, three of which were randomised. Bisphosphonates appeared to induce significant reductions in skin temperature and bone turnover markers compared with placebo, without serious adverse events. Nevertheless, bisphosphonates did not shorten the immobilisation time. Moreover, no data were available regarding their long-term effects.
Conclusions/interpretations Bisphosphonates have been shown to be effective for reducing bone turnover markers and skin temperature in some studies. Nevertheless, the long-term efficacy, specifically that regarding the occurrence of deformities and ulcerations, remains to be demonstrated as no follow-up studies have been published. Moreover, some studies have suggested that bisphosphonates may lengthen the resolution phase of the disease. In our opinion, the data are too weak to support the use of bisphosphonates as a routine treatment for acute Charcot neuroarthropathy.

Keywords Bisphosphonates · Charcot neuro-osteoarthropathy · Diabetic foot · Diabetic neuropathy · Osteoprotegerin · RANK-L · Systematic review

Abbreviations

ALP	Alkaline phosphatase
BPP	Bisphosphonate
CNO	Charcot neuropathic osteoarthropathy
OPG	Osteoprotegerin
RANK	Receptor activator of nuclear factor-κB
RANK-L	RANK ligand
uDPD	Urinary deoxypyridinoline crosslink

Introduction

Charcot neuropathic osteoarthropathy (CNO) is a non-infectious destructive process affecting the bone and joint structure that results from significant peripheral neuropathy of almost any aetiology [1, 2]. Nowadays, diabetes mellitus has become by far the most common aetiology of CNO mainly affecting the foot and ankle. It is a devastating limb-threatening condition resulting in dramatic deformities and recurrent ulceration that may ultimately lead to amputation [3]. Moreover, CNO is associated with a high mortality rate [4]. The prevalence of CNO is usually thought to be low, but it is largely underestimated as cases remain undiagnosed by untrained clinicians [5] The pathogenesis of CNO remains a matter of debate and no proven pharmacological treatment is

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currently available [3, 5, 6]. As classic neurotraumatic and neurovascular theories fail to explain all the features of CNO, especially the common asymmetrical damage and self-limiting process, other hypotheses have been put forward: the involvement of the receptor activator of nuclear factor-κB (RANK) ligand (RANK-L)/RANK/osteoprotegerin (OPG) system in the pathogenesis of acute CNO is particularly appealing [3, 6–9], and suggests new pharmacological approaches. Whatever the precise pathophysiological mechanism(s) of CNO, bone resorption and osteoclastic hyperactivity is a major feature of the early acute stage of this condition [8, 10, 11] and makes the use of bone-resorption-inhibiting agents such as bisphosphonates (BPPs) a logical therapeutic approach [12, 13]. In this study we reviewed data from the literature on BPP treatment of acute CNO in terms of efficacy and safety.

Methods

All articles published in the period from January 1990 to September 2011 and relating to the treatment of CNO with BPPs were searched by an investigator (M. Almasri) in MEDLINE and PubMed, Cochrane Database of Systematic Reviews databases and abstracts of presentations from the meetings of the ADA and the European Association for the Study of Diabetes (EASD). The research was expanded by searching websites specialising in clinical trials (www.clinicalstudyresults.org, www.clinicaltrials.gov and http://clinicaltrialsregister.eu/); additional articles were identified from the reference lists of retrieved papers.

A combination of free text and controlled vocabulary search terms was applied, including the following terms: 'Charcot foot', 'Charcot osteoarthropathy', 'bisphosphonates', 'diabetes', 'anti osteoclast', 'RANK-L', 'osteoprotegerin (OPG)', 'treatment of Charcot foot', 'pamidronate' and 'alendronate'.

Studies were included in the analysis if they included people with acute CNO, regardless of aetiology and the number of patients included. We took into account the following outcomes: clinical assessment, changes in bone turnover markers, bone mineral density and radiological assessment.

Results

From 300 articles identified in the initial search, only ten met the criteria for inclusion in the analysis.

Case records and case series reports In 1994 Selby et al. [12] first reported the use of a BPP in the treatment of CNO. They administered 30 mg pamidronate i.v., followed by five infusions of pamidronate 60 mg every 2 weeks for 12 weeks in six patients with diabetes and acute CNO. The treatment was associated with improvement in local pain and a significant reduction in the activity of the CNO as measured by the decrease in the temperature of the affected foot, from 3.4±0.7°C (mean±SE) to 1.0±0.5°C (p=0.05). There was also a significant reduction in bone turnover as judged by alkaline phosphatase (ALP) level, which fell by 25±3% compared with initial values (p<0.001).

An abstract published in 1999 [14] reported a decrease in peak cutaneous blood flow in response to the infusion of 90 mg pamidronate i.v. over 24 h in 20 patients with diabetes and CNO, suggesting a anti-inflammatory action of pamidronate.

In 1999, a case of CNO associated with a hereditary sensory neuropathy was also reported affecting the metatarsophalangeal joints in a non-diabetic patient in whom the use of pamidronate (90 mg i.v. every 4 months for 2 years) was apparently effective [15]. Clinical improvement with a decrease in swelling was observed after 6 months (two infusions). Bone and joint destruction stopped and signs of a reconstructive healing process appeared progressively in the previously affected sites 'with large, strangely shaped osteophytes at joint edges'. This 'cure' was obtained even though the foot was not offloaded [15].

In 1999, Young [16] reported anecdotally two cases of diabetic acute CNO treated with i.v. infusions of pamidronate associated with immobilisation. After 3 months, the clinical outcome was judged favourable with a reduction in clinical signs and an absence of deformity.

Pakarinen et al. in 2002 retrospectively analysed clinical records and X-rays of 36 feet with CNO from 1994 to 2000 [17]. Eighteen patients received BPP treatment (pamidronate 30–60 mg i.v. once a week for 6 weeks) and no complications were registered. There was no statistically significant difference in casting time between patients who received (11 weeks) and patients who did not receive (13 weeks) pamidronate. In this series, pamidronate infusions were used for selected individuals without any striking benefits or disadvantages. The results of the study are, however, difficult to analyse, as off-loading casts were used at different times in the patients for whom they were used. Moreover, 18 patients did not receive any treatment at the initial visit. Finally, the authors did not mention the criteria used for selection of BPP or for removal of casts.

In 2007, Moreno et al. [18] reported seven consecutive cases of CNO recruited during a 4 year period. All were treated according to a standardised protocol including i.v. pamidronate infusion and immobilisation. Recruitment was heterogeneous: CNO was associated with diabetes in four cases, syringomyelia in two and other sensory and autonomic neuropathy in one; the affected joints were located in the foot, ankle, hand and shoulder. Patients received three pamidronate

infusions at 0, 2 and 4 months. The dose was 60 or 90 mg according to patient body weight. Clinical assessment, serum and urine bone turnover markers, X-rays and scintigraphy were performed before and 12 months after the first pamidronate infusion. All patients showed a rapid resolution of clinical symptoms. At the end of the 12 month follow-up, there was a statistically significant reduction of urinary N-terminal telopeptide of type 1 collagen crosslinks and pyridinoline but the decrease in serum level of ALP and bone-specific ALP was not significant. Six of seven patients had radiological healing, and quantitative bone scintigraphy, performed in only three patients, showed a clear reduction in ^{99}Tc uptake. No important side effects were reported.

In 2008, Naqvi et al. [19] reported three cases of diabetic CNO with a fairly long-term clinical response to treatment with i.v. pamidronate. In the first patient, CNO of the midfoot was treated with three i.v. infusions of pamidronate, 90 mg at 2 month intervals. After the first infusion, there was a marked improvement in swelling, pain, erythema and warmth. After the second infusion, the patient was able to bear weight on her foot and after the last infusion she no longer required the use of a cast walker. Radiography of the foot 14 months later showed stabilisation of the radiographic changes. The second patient received a single i.v. infusion of pamidronate (60 mg), a walking cast and physical therapy for CNO of the hindfoot. At 6 and 9 months' follow-up, there were no signs of inflammation, but the foot's natural arch was lost. The patient was able to ambulate with a removable casting device. The last patient was given a single i.v. infusion of 90 mg pamidronate, and this was followed by a significant improvement in the patient's complaints. At 4 weeks' follow-up, she was able to ambulate with a cast, and after 11 months she was asymptomatic and able to ambulate without assistance.

Retrospective case–control study In 2004, Anderson et al. [20] undertook a study in 33 patients with acute CNO, the aetiology of which was not given. Eighteen patients received a single i.v. pamidronate infusion, but five were excluded from the statistical analysis; 15 patients were treated only by traditional off-loading methods but five were apparently excluded from the analysis (control group). The criteria used for choosing BPP infusions were not given. This study showed a statistically significant reduction in the temperature of the limb and the ALP level in the treated group. After pamidronate infusion, the temperature of the affected limb decreased by a mean of 1.6°C at 48 h and 4.0°C after 2 weeks. Two weeks after the infusion, ALP level was also decreased by an average of 53% in the intervention group. The control group showed no reduction in limb temperature at 48 h, and had an average limb temperature decrease of 1.3°C at 2 weeks; the decrease was significantly greater in the treated group at both times. Mean ALP levels declined by only 9% in the control group, and this decline was significantly smaller than in the pamidronate group. In 60% of patients, pamidronate infusion was associated with transient fever and in 36% with mild gastrointestinal upset of short duration.

Randomised controlled studies A 12 month double-blind randomised controlled trial was conducted by Jude et al. (2001) in 39 patients with diabetes and acute CNO [21]. Twenty-one patients were randomised to the active group and were treated by a single i.v. infusion of 90 mg pamidronate; 18 patients were allocated to the placebo group and received an infusion of a normal saline solution (154 mmol/l NaCl). All patients had the affected foot offloaded using appropriate devices. Patients were followed up every 2 weeks for the first 3 months, and then at 6, 9 and 12 months. At entry, the mean skin temperature difference between the affected and the contralateral foot was approximately 3.5°C, with no difference between the two groups. Skin temperature of the affected foot decreased in both groups throughout the study period; the reduction was significantly greater in the active group compared with placebo after 4 weeks but not at all of the other time points. Pain and discomfort improved in both groups at 3 months; it continued improving in the treated group while there was no further improvement in the placebo group. The difference between groups was significant from the third month until the end of the study. Bone-specific ALP and urinary deoxypyridinoline crosslink (uDPD) levels were not different at baseline between the two groups. In the treated group, both markers decreased significantly in the early period of the trial but gradually rose towards baseline value at the end of the study. In the placebo group, no significant changes were observed, and the concentrations of both markers and the concentrations of bone-specific ALP and uDPD were only significantly lower in the active group compared with controls from 4 to 12 weeks and from 4 and 6 weeks post-inclusion, respectively. The only reported side-effect was transient myalgia, which was reported in a single patient treated with pamidronate.

In 2005, Pitocco et al. [22] compared oral alendronate plus off-loading with off-loading alone in an observer-blinded randomised controlled trial. A total of 20 consecutive diabetic patients with a new diagnosis of acute CNO were included. Eleven patients were treated with 70 mg alendronate orally once a week (test group) for 6 months and nine individuals served as controls. In all patients, the affected foot was offloaded using a total-contact cast for the first 2 months followed by a pneumatic walker for the remaining 4 months. Patients were examined twice a week. At the end of the study, pain intensity, assessed by a 10 cm visual analogue scale, improved significantly in the treated group whereas no change was observed in the control group.

Foot temperature decreased significantly after 6 months in both groups with no difference between treated and control patients (−1.7°C and −1.5°C, respectively). Bone mineral density of the total foot improved in the treated group. The level of serum bone ALP, COOH-terminal telopeptide of type 1 collagen and urinary hydroxyproline decreased significantly in BPP-treated patients.

Pakarinen et al. conducted a randomised clinical trial to evaluate the clinical efficacy of zoledronic acid in diabetic acute CNO affecting the midfoot [23]. Of 39 patients, 18 received three i.v. infusions of 4 mg zoledronic acid and 17 received no infusion. Four patients were excluded from the final (per protocol) analysis. All patients were initially treated with a non-weight-bearing total-contact cast and then with a partial weight-bearing device when the condition was judged to be in remission. Full weight bearing was allowed when CNO was considered to have resolved. The endpoint was the duration of off-loading (total and partial), and this was significantly longer in the intervention group (median 27 weeks) compared with the placebo group (20 weeks). No data were given about bone turnover markers, radiological findings or bone mineral density, or regarding side-effects.

A fourth randomised clinical trial was planned in 2006 to compare oral alendronate plus i.v. pamidronate vs placebo in active diabetic CNO (EudraCT registration no. 2006-000900-17 [www.clinicaltrialsregister.eu]; ISRCTN registration no. 86625608, [www.controlled-trials.com]), but the trial was discontinued and the results have not been published.

The main characteristics of the trials included in the analysis are reported in Table 1.

Discussion

Charcot osteoarthropathy was first described over 135 years ago, but it remains both an important cause of morbidity in patients with diabetes and a persistent challenge for clinicians,

Table 1 Characteristics of the clinical trials included

Study	Design	Duration	Agent	Participants	Associated treatment	Outcome
Jude et al. [21]	R, C, DB, ITT	12 months	PMD	A: n=21, 1 i.v. infusion of 90 mg Ct: n=18, 1 i.v. infusion of normal saline solution	Off-loading	Skin temperature: greater reduction at 4 weeks in A (p<0.01) Symptoms (pain and discomfort): greater reduction in A from 3 to 12 months (p<0.001) BSALP: significant reduction in A vs C from 4 to 12 weeks (p<0.03) uDPD: significant reduction in A vs C at 4 and 6 weeks (p<0.03)
Pitocco et al. [22]	R, C, SB	6 months	ALD	A: n=11, 70 mg orally once a week Ct: n=9, no pharmacological treatment	Off-loading	Skin temperature: significant reduction in both groups at 6 months Pain score: at 6 months, improvement in A (p<0.05) but not in C 1CTP and HOPu: significant reduction in A vs C at 6 months (p<0.05) BSALP: not significant reduction in A vs C at 6 months (p=0.06) IGF-1: At 6 months, reduction in A (p<0.05) but not in C
Pakarinen et al. [23]	R, C, OL PP	12 months	ZLD	A: n=20, 3 i.v. infusions of 4 mg at 1 month interval, 2 patients excluded Ct: n=19, no infusion, 2 patients excluded	Off-loading	Total immobilisation time (median): 27 weeks (A) vs 20 weeks (C) (p=0.02)
Anderson et al. [20]	NR, C, OL, PP	2 weeks	PMD	A: n=18, 1 i.v. infusion, 5 patients excluded Ct: n=15, no infusion, 1 patient excluded	Off-loading	Skin temperature: greater reduction in A vs C at 2 days (p<0.008) and at 2 weeks (p<0.001) AP: greater reduction in A vs C at 2 weeks (p<0.001)

A, active (BPP-treated) group; ALD, alendronate; BSALP, serum (bone-specific) ALP; C, controlled trial; Ct, control group; 1CTP, serum COOH-terminal telopeptide of type 1 collagen; DB, double blind; HOPu, urinary hydroxyproline; ITT, intent-to-treat analysis; NR, not randomised; OL, open-label; PMD, pamidronate; PP, per protocol analysis; R, randomised; SB, single blind (observer blinded); ZLD, zoledronate

especially in its acute stage. Pakarinen et al. reported an average delay of 29 weeks between the occurrence of the first symptoms and the diagnosis of CNO in diabetic patients, with a wrong initial diagnosis in 30 of 36 cases. They also showed that inappropriate treatment was associated with poor prognosis and severe deformities [17]. Improvement in the understanding of the underlying pathogenic events provides strong support for an important role of osteoclastic activity and pro-inflammatory cytokines (including IL-1, IL-6 and TNF-α) in the acute phase of the disease [8, 10, 11]. The pro-inflammatory cytokines (including IL-1, IL-6 and TNF-α), by increasing production of RANK-L, play an important role in the activation of osteoclasts [7, 24, 25]. Moreover, recent studies have emphasised the involvement of the RANK-L/RANK/OPG axis as certain genetic variants of the *OPG* (also known as *TNFRSF11B*) polymorphism may predispose diabetic patients to CNO. According to this hypothesis, it would be conceivable that variations in some regions of *OPG* could result in quantitative and/or qualitative alterations of OPG, decreasing the buffering role of OPG against RANK-L [26, 27].

The cornerstone of CNO management is immobilisation and off-loading, which aims to prevent severe deformity, ulceration and, ultimately, amputation [3, 6, 9, 28]. Surgical treatment may be required when this conservative treatment fails. These strategies, however, are not designed to affect the underlying physiological mechanisms that cause bone destruction, Theoretically, pharmacological treatment of CNO by BPPs, which inhibit osteoclastic resorption and may have direct anti-inflammatory properties, might slow or even stop the bony destruction (through its ability to cause macrophage apoptosis) [29].

The review of the literature we carried out showed that several clinicians used BPPs in the treatment of acute CNO, mainly where it occurred as a complication of diabetes. Nevertheless, most of the published articles dealt with case reports, case series or retrospective case–control studies, providing low-level evidence (grade 3–4). Only four clinical trials were published, three of which were controlled and randomised [21–23]. It is difficult to compare these studies, mainly because of heterogeneity in BPP treatment and outcome measures. In the above-mentioned studies, all the patients included received immobilisation and appropriate off-loading. The choice of BPP could have influenced results because the antiresorptive effect differs between preparations. The effect of a BPP on pro-inflammatory cytokines is also thought to depend on the choice of preparation and the dosage [30, 31]. It is worth noting that, in the study by Anderson et al. [20], 60% of pamidronate-treated patients had transient fever just after the infusion, suggesting a pro-inflammatory effect. A second problem associated with the clinical trials reviewed was that they included low numbers of patients and this limited statistical conclusions. Finally, the quality of the methods used in the trials was uneven, as emphasised by Smith et al. [32]. The study by Pakarinen et al. [23], published after the review by Smith et al. has a moderate quality score because it also suffers from a number of shortcomings in its methods.

Clinically, treatment with BPP was associated with a more rapid decrease in skin temperature, but this effect was not sustained [20–22]. Effect on the pain differed among studies, with one showing improvement [22] but another showing none [21]. Regarding the activity of CNO, the studies we analysed showed a reduction of bone turnover markers in the BPP-treated patients. Nevertheless, the most consistent observation was a decrease in serum (bone-specific) ALP level, a marker of osteoblastic rather than osteoclastic activity.

The most important problem of the published studies is the absence of reports of long-term effect. Indeed, the aim of CNO management is to prevent foot deformities, ulceration and amputation, but no data were available regarding these endpoints. Nevertheless, Pakarinen et al. [23] reported that zoledronate did not reduce the duration of immobilisation, and may have increased it. Moreover, the recent audit of acute diabetic CNO in the UK based on a multicentre observational study [33] also showed that the use of BPP was associated with a longer time to resolution. These findings suggest that there is currently no evidence that adding a BPP to immobilisation and off-loading confers long-term benefits.

Finally, the use of BPPs is limited by potential side-effects and contraindications such as chronic kidney disease, which is often associated with CNO in patients with diabetes [34]. On the other hand, the likely role of the cytokine RANK-L/RANK/OPG axis in the pathogenesis of acute CNO opens the way to the use of promising new pharmacological agents such as TNF-α antagonists (monoclonal antibody or circulating receptor fusion protein), human recombinant OPG and RANK-L human monoclonal antibody (denosumab). Calcitonin, which impacts directly on the RANK-L/RANK/OPG axis, may also have a place as an alternative to BPPs in the pharmacological approach of acute CNO. Indeed, in a small randomised controlled trial, Bem et al. showed that intranasal calcitonin treatment (200 U daily) with calcium supplementation in patients with acute CNO significantly decreased bone turnover compared with calcium supplementation only [35]. In addition, as opposed to BPP, calcitonin has the advantage that it can be used in patients with renal insufficiency.

Conclusion

The improvement in the knowledge and understanding of the pathogenesis of acute CNO has provided hope that new

pharmaceutical approaches may improve the outcome of this debilitating condition. On theoretical grounds, BPPs may have clinical benefit, but the results of published studies are inconclusive. On balance, treatment with BPPs appears rather ineffective and even deleterious for the resolution time of the acute stage [22, 33]; moreover, data on long-term outcomes are not available. There is, therefore, currently little evidence to support the use of BPPs as part of the routine management of patients with diabetes complicated by acute CNO. This is in agreement with the ADA consensus report [6] that suggests that off-loading and immobilisation remain the mainstay of treatment.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

References

1. Stanley JC, Collier AM (2008) Charcot osteo-arthropathy. Curr Orthop 22:428–433
2. Sanders LJ, Frykberg RG (2007) The Charcot foot (Pied de Charcot). In: Bowker JH, Pfeifer MA (eds) Levin and O'Neal's the diabetic foot. Mosby Elsevier, Philadelphia, pp 257–283
3. Wukich DK, Sung W (2009) Charcot arthropathy of the foot and ankle: modern concepts and management review. J Diabetes Complications 23:409–426
4. van Baal J, Hubbard R, Game F, Jeffcoate W (2010) Mortality associated with acute Charcot foot and neuropathic foot ulceration. Diabetes Care 33:1086–1089
5. Rajbhandari RC, Jenkins CD, Tesfaye S (2002) Charcot neuroarthropathy in diabetes mellitus. Diabetologia 45:1085–1096
6. Rogers LC, Frykberg RG, Armstrong DG et al (2011) The Charcot foot in diabetes. Diabetes Care 34:2123–2129
7. Jeffcoate WJ, Game F, Cavanagh PR (2005) The role of proinflammatory cytokines in the cause of neuropathic osteoarthropathy (acute Charcot foot) in diabetes. Lancet 366:2058–2061
8. Jeffcoate WJ (2008) Charcot neuro-osteoarthropathy. Diabetes Metab Res Rev 24:62–65
9. Molines L, Darmon P, Raccah D (2010) Charcot's foot: newest findings on its pathophysiology, diagnosis and treatment. Diabetes Metab 36:251–255
10. Gough A, Abraha H, Li F et al (1997) Measurement of markers of osteoclast and osteoblast activity in patients with acute and chronic Charcot neuroarthropathy. Diabet Med 7:527–531
11. Mabilleau G, Petrova NL, Edmonds ME, Sabokbar A (2008) Increased osteoclastic activity in acute Charcot's osteoarthropathy: the role of receptor activator of nuclear factor-κB ligand. Diabetologia 51:1035–1040
12. Selby PL, Young MJ, Boulton AJ (1994) Bisphosphonates: a new treatment for diabetic Charcot neuroarthropathy? Diabet Med 11:28–31
13. Lyn TA, Greenstein A, Jarrett S, McGonagle D (2005) Acute neuropathic joint disease. A medical emergency? Diabetes Care 28:2962–2964
14. Stansberry KB, Moss QE, Peppard HR, McNitt PM, Vinik AI (1999) Intravenous bisphosphonate rapidly reverses the paradoxical increase in blood flow to the foot in Charcot neuroarthropathy. Diabetes 48:A92
15. Guis S, Pellissier JF, Arniaud D et al (1999) Healing of Charcot's joint by pamidronate infusion. J Rheumatol 26:1843–1845
16. Young MT (1999) The management of neurogenic arthropathy: a tale of two Charcots. Diabetes Metab Res Rev 15:59–64
17. Pakarinen T-K, Laine H-J, Honkonnen SE, Peltonen J, Oksala H, Lahtela J (2002) Charcot arthropathy of diabetic foot: current concepts and review of 36 cases. Scand J Surg 9:195–201
18. Moreno M, Gratacós J, Casado E, Galisteo C, Orellana C, Larrosa M (2007) Utilidad del pamidronato en el tratamiento de la artropatía de Charcot (Usefulness of pamidronate in the treatment of Charcot's arthropathy). Reumatol Clin 3:257–261, article in Spanish
19. Naqvi A, Cuchacovich R, Saketkoo L, Espinoza LR (2008) Acute Charcot arthropathy successfully treated with Pamidronate: long-term follow-up. Am J Med Sci 335:145–148
20. Anderson JJ, Woelffer KE, Holtzman JJ, Jacobs AM (2004) Bisphophonates for the treatment of Charcot neuroarthropathy. J Foot Ankle Surg 43:2285–2289
21. Jude EB, Selby PL, Burgess J, Lilleystone P, Mawer EB et al (2001) Bisphosphonates in the treatment of Charcot neuroarthropathy: a double-blind randomised controlled trial. Diabetologia 44:2032–2037
22. Pitocco D, Ruotolo V, Caputo S et al (2005) Six-month treatment with Alendronate in acute Charcot neuroarthropathy. Diabetes Care 28:1214–1215
23. Pakarinen T-K, Laine H-J, Mäenpää H, Mattila P, Lahtela J (2011) The effect of zoledronic acid on the clinical resolution of Charcot neuroarthropathy. A pilot randomized controlled trial. Diabetes Care 34:1514–1516
24. Vega D, Maalouf NM, Sakhaee K (2007) The role of receptor activator of nuclear factor-κB (RANK)/RANK ligand/osteoprotegerin: clinical implications. J Clin Endocrinol Metab 92:4514–4521
25. Uccioli L, Sinistro A, Almerighi C et al (2010) Proinflammatory modulation of the surface and cytokine phenotype of monocytes in patients with acute Charcot foot. Diabetes Care 33:350–355
26. Pitocco D, Zelano G, Gioffré G et al (2009) Association between osteoprotegerin G1181C and T245G polymorphisms and diabetic Charcot neuroarthropathy. A case–control study. Diabetes Care 32:1694–1697
27. Korzon-Burakowska A, Jakóbkiewicz-Banecka J, Fiedosiuk A et al (2011) Osteoprotegerin gene polymorphism in diabetic Charcot neuroarthropathy. Diabet Med. doi:10.1111/j.1464-5491.2011.03442.x
28. Pinzur MS, Lio T, Posner M (2006) Treatment of Eichenholtz stage 1 Charcot foot arthropathy with a weightbearing total contact cast. Foot Ankle Int 27:324–329
29. Frith JC, Mönkkönen J, Auriola S, Mönkkönen H, Rogers MJ (2001) The molecular mechanism of action of the antiresorptive and anti-inflammatory drug clodronate: evidence for the formation in vivo of a metabolite that inhibits bone resorption and causes osteoclast and macrophage apoptosis. Arthritis Rheum 44:2201–2210
30. Russell RGG, Watts NB, Ebetino FH, Rogers MJ (2008) Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. Osteoporos Int 19:733–759
31. Maksymowych WP (2002) Bisphosphonates—anti-inflammatory properties. Curr Med Chem Anti Inflamm Anti Allergy Agents 1:15–28

32. Smith C, Kumar S, Causby R (2007) The effectiveness of non-surgical interventions in the treatment of Charcot foot. Int J Evid Based Healthc 5:437–449
33. Game FL, Catlow R, Jones GR, Edmonds ME, Jude EB, Rayman G, Jeffcoate WJ (2012) Audit of acute Charcot's disease in the UK: the CDUK study. Diabetologia 55:32–35
34. Drake MT, Clarke BL, Khosla S (2008) Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clin Proc 83:1032–1045
35. Bem R, Jirkovská A, Fejfarová V, Skibová J, Jude EB (2006) Intranasal calcitonin in the treatment of acute Charcot neuroosteoarthropathy. A randomized clinical trial. Diabetes Care 29:1392–1394