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Treatment of complex regional pain syndrome type I with neridronate: a randomized, double-blind, placebo-controlled study

Massimo Varenna[1], Silvano Adami[2], Maurizio Rossini[2], Davide Gatti[2], Luca Idolazzi[2], Francesca Zucchi[1], Nazzarena Malavolta[3] and Luigi Sinigaglia[1]

Abstract

Objective. Complex regional pain syndrome type I (CRPS-I) is a severely disabling pain syndrome for which no definite treatment has been established. The aim of this multi-centre, randomized, double-blind placebo-controlled trial was to test the efficacy of the amino-bisphosphonate neridronate in patients with CRP-I.

Methods. Eighty-two patients with CRP-I at either hand or foot were randomly assigned to i.v. infusion of 100 mg neridronate given four times over 10 days or placebo. After 50 days the former placebo patients were given open label the same regimen of neridronate.

Results. Within the first 20 days, visual analogue scale (VAS) score decreased significantly more in the neridronate group. In the following 20 days, VAS remained unchanged in the placebo group and further decreased in the active group by 46.5 mm (95% CI −52.5, −40.5) *vs* 22.6 mm (95% CI −28.8, −16.3) for placebo group ($P < 0.0001$). Significant improvements *vs* placebo were observed also for a number of other indices of pain and quality of life. During the open-extension phase in the formerly placebo group the results of treatment were superimposable on those seen during the blind phase in the active group. A year later none of the patients was referring symptoms linked to CRPS-I.

Conclusion. In patients with acute CRPS-I, four i.v. infusions of neridronate 100 mg are associated with clinically relevant and persistent benefits. These results provide conclusive evidence that the use of bisphosphonates, at appropriate doses, is the treatment of choice for CRPS-I.

Trial registration: EU Clinical Trials Register, https://www.clinicaltrialsregister.eu/, 2007-003372-18.

Key words: complex regional pain syndrome type I, neridronate, randomized clinical trial, bisphosphonates, algodystrophic syndrome.

Introduction

Complex regional pain syndrome type I (CRPS-I) is a severely disabling pain syndrome characterized by sensory and vasomotor disturbance, oedema and functional impairment [1] that in most cases develop following a trauma or surgery [2]. No specific test is currently available to diagnose CRPS-I and the recently updated Budapest Criteria are widely accepted to make a clinical diagnosis due to their sensitivity and specificity [3, 4]. To date, the treatment of CRPS-I remains a medical challenge and no definite treatment has been established. A number of therapeutic approaches have been proposed with varying success. The limited number of randomized controlled trials [5], the heterogeneity of the proposed treatments and the methodological limitations in terms of homogeneity and size of the study samples preclude any definitive conclusion about the efficacy of these different therapeutic modalities [6]. Among pharmacological treatments, bisphosphonates appear to offer clear benefits as documented by the results of four randomized controlled trials,

[1]Rheumatology Unit, Ospedale G. Pini, Milan, [2]Rheumatology Unit, Department of Medicine, University of Verona, Verona and [3]Rheumatology Unit, Ospedale Malpighi, Bologna, Italy.

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Correspondence to: Silvano Adami, Rheumatology Unit, Policlinico GB Rossi, Piazzale Scuro, 37121 Verona, Italy.
E-mail: silvano.adami@univr.it

all of them showing positive results in controlling pain, oedema and functional impairment [7]. However, none of these trials provided sufficient data to make the use of a bisphosphonate formally indicated for the treatment of CRPS-I.

Neridronate is an amino-bisphosphonate structurally similar to alendronate and pamidronate, differing only in the number of methyl groups of the side chain: five for neridronate, three for alendronate and two for pamidronate. It has been shown to be effective and then registered for the treatment of Paget's disease of bone and osteogenesis imperfecta [8, 9]. In this study we evaluated the efficacy of neridronate administered by i.v. infusion in patients with CRPS-I by a prospective, double-blind, placebo-controlled study.

Methods

Patients

Patients were included over 20 months from the outpatient services of six Italian rheumatology centres. All patients included in the study fulfilled the Budapest criteria for research purposes [3]. Only patients with involvement of the hands or feet were included. Additional inclusion criteria were age of at least 18 years, disease duration no longer than 4 months, spontaneous pain intensity in the affected limb of at least 50 mm on a visual analogue scale (VAS) ranging from 0 (no pain) to 100 mm (maximal pain) [10]. In all patients, a three-phase bone scintigraphy was obtained before study entry and an abnormal uptake of the bone-seeking agent in both early and late phases [11] was an indispensable prerequisite for being included in the study. Women of childbearing potential were required to have a negative pregnancy test before entering the study. Exclusion criteria were hepatic, renal, endocrine, haematological, cardiac, pulmonary or neurological diseases or routine laboratory abnormalities and prior treatment with bisphosphonates. The study complied with the amended Declaration of Helsinki and was approved by each local ethics committee (Comitato Etico, Ospedale G. Pini, Milan; Comitato Etico Provinciale, Ospedale Regionale, Lecce; Comitato Etico, Ospedale O Molinette, Torino; Comitato Etico, Ospedale Forlanini, Roma; Comitato Etico Ospedale S Orsola-Malpighi, Bologna). All patients gave written informed consent to participate in the study.

Study design

A centrally computer-generated table of random numbers was used for the treatment assignment. Patients were treated with either neridronate (Abiogen Pharma, Pisa, Italy) 100 mg/8 ml i.v. ampoules or placebo with an identical appearance in a 1:1 ratio. Both neridronate and placebo were diluted in a 500 ml saline isotonic solution and infused in the morning over 2 h.

Neither patients nor investigators knew whether assignment would be to the placebo or neridronate group. The treatment was administered every third day four times, starting from day 1 (first infusion) and ending on day 10 (fourth infusion). After 40 days from the first infusion, the last blind assessment of clinical results was immediately sent to the coordinating centre. The results were reviewed and locked and eventually the codes were unblinded. The patients who had been receiving neridonate exited the study, while 10 days after the last assessment, those who had been on placebo were given neridronate following the same regimen (four 100-mg infusions over 10 days) and a follow-up obtained at 40 days.

Measures

Outcome measures were assessed before randomization and before the first infusion (day 1). Further assessments were obtained at the end of treatment (day 10) and after 20 and 40 days. During the open phase the same procedure was repeated in the former control patients switched to neridronate treatment. The primary efficacy measure was the comparative changes in the VAS 40 days after the first infusion of neridronate in the double-blind phase of the study. A decrease from the baseline value of at least 50% was considered clinically significant and qualified the patient as a responder [12].

By analysing the data from previous clinical trials [13, 14] it was decided not to assess sweating (present only in a minority of the patients) and to assess changes in joint volume or local oedema only by scores (0 = none, 1 = mild, 2 = moderate, 3 = severe) based on observations like the ability to normally wear socks, shoes or gloves.

Additional clinical assessment included (i) pain evoked by passive motion (ankle for foot involvement and wrist and finger joints for hand involvement) rated as 0 = none, 1 = mild, 2 = moderate, 3 = severe; (ii) allodynia (pain to light stroking with a small brush) and hyperalgesia (pain evoked by a pinprick at the affected site but not at the unaffected side), both rated as a dichotomous variable (present/absent); (iii) McGill Pain Questionnaire and 36-Item Short Form Health Survey (SF-36) questionnaire to assess functional status; (iv) a count of the number of NSAID or paracetamol tablets taken weekly.

These outcome parameters, together with the treatment outcomes after the open-label treatment, were considered as secondary end points. In each participating centre the clinical evaluation was independently performed by two investigators; in case of discordance, assessment was repeated by a third investigator.

In order to verify the long-term treatment efficacy, all patients were asked to participate in one or two follow-up visits a few months after the completion of the controlled study. This was considered a separate study and might include a control of bone scintigraphy or MRI.

Adverse events

All patients were informed about a possible acute-phase reaction (polyarthralgia and/or fever) [15] occurring after i.v. amino-bisphosphonate administration. Physicians at the study sites reported adverse events (AEs) and serious adverse events that were coded as preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA)

system. According to investigator judgement, a drug-related AE was defined as definitely, probably or possibly related to study treatment. A non-drug-related AE was defined as unlikely or not related.

Statistical analysis

Sample size calculation was performed assuming a two-tailed probability of type I error equal to 0.05. The planned total sample size of 80 subjects, randomized in a 1:1 ratio for neridronate and placebo, achieves a 90% power to detect a proportion of 50% of patients in the neridronate group showing $\geqslant$50% VAS score reduction when a 35% difference is expected *vs* placebo.

The statistical analysis was carried out according to the intention-to-treat principle, including all randomized patients who received at least one dose of the study medication. Baseline characteristics were compared with the use of Student's *t*-test for quantitative variables and Fisher's exact test for binary ones. VAS score changes were evaluated using an analysis of covariance (ANCOVA) model for repeated measures using the change from baseline as the dependent variable; treatment, visit, centre and the treatment-by-visit interaction as factors and baseline as covariates. Differences between treatments were reported as least-square mean estimates together with associated two-sided 95% confidence limits. The proportion of responders (VAS reduction $\geqslant$ 50%) as well as dichotomous variables (allodynia and hyperalgesia) were compared with Fisher's exact test while results were reported as risk difference together with associated two-sided 95% confidence limits. The results of the McGill Pain Questionnaire and SF-36 questionnaire were analysed using repeated-measure analysis of variance (ANOVA) models. The comparison of clinical parameters evaluated by means of rating scales were performed using the Wilcoxon rank sum test. Multivariate regression analysis was performed to assess the potential influence of baseline variables on treatment effect [site of disease: (upper/lower limb), disease duration and precipitating event (none/trauma, surgery)]. The statistical analysis was performed using SAS (version 9.2; SAS Institute, Cary, NC, USA). Significance was taken at two-tailed $P < 0.05$.

Results

Between January 2008 and May 2010, 84 patients were screened and 82 were recruited from six Italian rheumatology units from Milan, Verona, Bologna, Lecce, Rome and Turin. Most patients (71) were coming from the two centres operating in a hospital devoted to bone and joint diseases: Hospital G. Pini (Milan) and Orthopaedic Rehabilitation of Valeggio (Verona). In these centres, the patients were almost invariably referred to the rheumatology centres immediately at the onset of the symptoms. One screening failure was due to previous bisphosphonate treatment for osteoporosis and one to refusal to participate in a randomization including a placebo arm. No other exclusion criteria were applied. Participating patients were randomized to treatment or placebo in two equal ($n = 41$) groups. The two groups were well balanced for demographic and clinical characteristics (Table 1).

Table 1 Demographic and clinical characteristics of patients with CRPS-I treated with neridronate or placebo

Characteristic	Neridronate ($n = 41$)	Placebo ($n = 41$)	*P* value
Age, mean (S.D.), years	58.2 (12.7)	57.0 (10.3)	0.6
Gender, M/F, *n*	16/25	13/28	0.6
Disease duration, mean (S.D.), weeks	4.7 (4.1)	5.0 (4.6)	0.7
Precipitating event, *n* (%)			
Fracture	11 (26.8)	17 (41.4)	0.2
Trauma	10 (24.4)	7 (17.1)	0.5
Surgery	5 (12.2)	4 (9.8)	0.9
Unknown	15 (36.6)	13 (31.7)	0.8
Site, *n* (%)			
Upper limb	8 (19.5)	12 (29.3)	0.4
Lower limb	33 (80.5)	29 (70.7)	

The flow chart illustrating the disposition of patients is presented in Fig. 1. Six patients dropped out during the double-blind phase: one patient in the neridronate group and five in the placebo group; the main reasons were consent withdrawal (three patients in the placebo group), AE occurrence (one patient in each arm) and lack of efficacy for one placebo-treated patient. One of these patients in the placebo group did not have any post-baseline assessment available for a primary efficacy measure. Seventy-six patients, 40 (98%) and 36 (88%) in the neridronate group and placebo group, respectively, completed the double-blind phase. Among the 36 completers of the placebo group who started the open phase, 34 completed the extension study: one patient dropped out for AE and the other for consent withdrawal.

Efficacy in double-blind phase

The time course of VAS score is shown in Fig. 2. At study entry (day 1) the neridronate-treated group and the placebo-treated group had similar VAS score [mean (S.D.) 71.6 (11.8) and 70.4 (8.3), respectively; $P = 0.59$]. Within the first 20 days of follow-up the pain score decreased in both groups, but a significant treatment-by-visit interaction ($P < 0.0001$) was observed, with the difference becoming significant at day 20 ($P = 0.043$). During the following 20 days no further improvements were observed in the placebo group, while VAS values continued to decrease linearly in the neridronate group. At the end of the double-blind phase, estimates for changes from baseline were −47.0 mm (95% CI −53.7, −40.3) for the neridronate group and −22.6 mm (95% CI −29.5, −15.6) for the placebo group, with a highly significant difference ($P < 0.0001$). A $\geqslant$ 50% VAS score decrease was obtained in 30 neridronate-treated patients (73.2%) *vs* 13 controls

FIG. 1 Flow chart illustrating the study protocol and the disposition of patients.

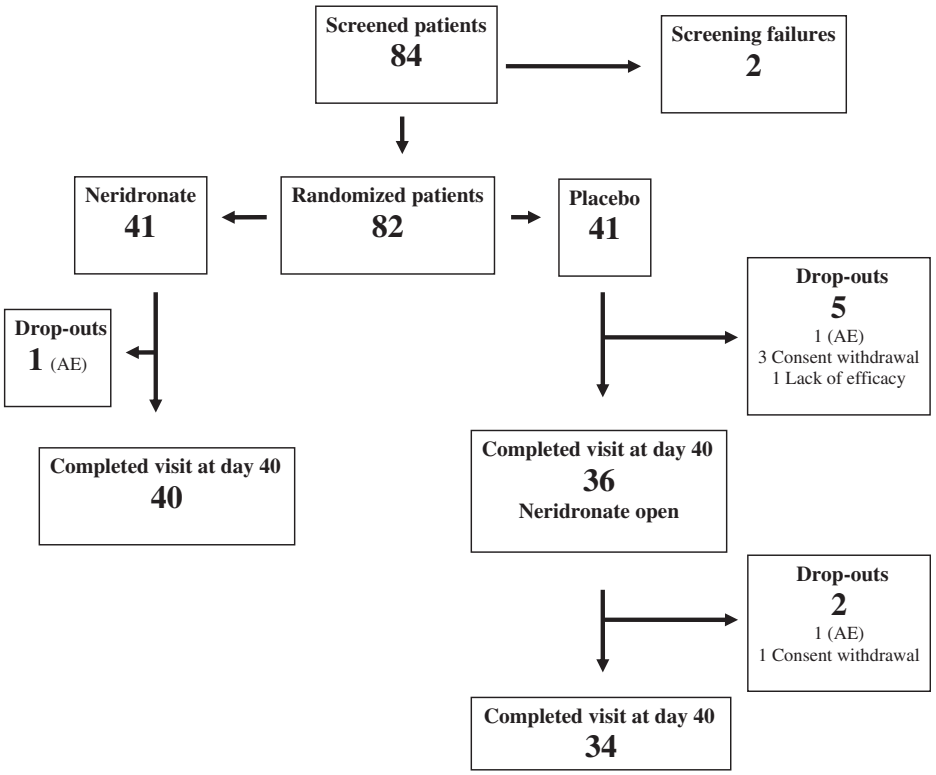
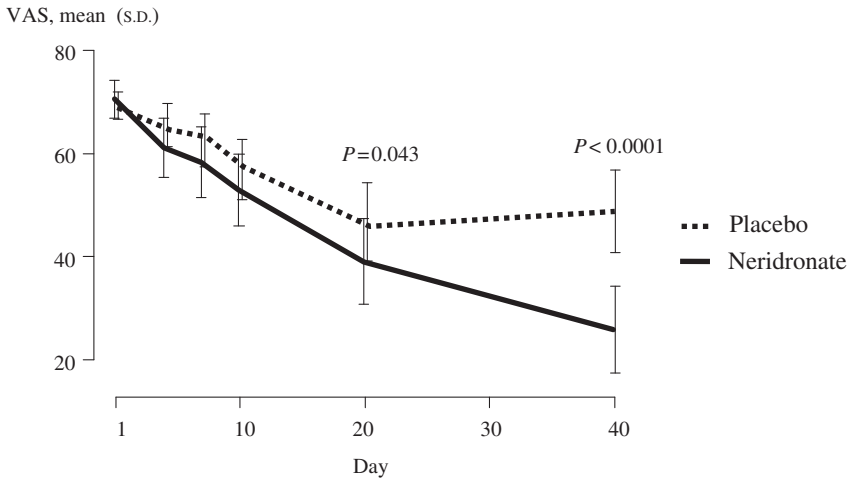


FIG. 2 Double-blind phase.



VAS trends from baseline to day 40 in patients with CRPS-I treated with neridronate or placebo.

(32.5%), with a 40.7% (95% CI 20.8%, 60.5%; $P = 0.0003$) treatment difference. For the McGill Pain Questionnaire significant differences between groups for sensory items (−5.47; 95% CI −8.28, −2.65; $P = 0.0002$) and affective items (−2.45; 95% CI −3.40, −1.51; $P < 0.0001$) were observed at day 40.

The results of the SF-36 questionnaire showed at day 40 significant differences for all items except for role limitations due to emotional problems, vitality and general health (Table 2).

Oedema and pain evoked by passive motion significantly improved in the neridronate group compared

TABLE 2 SF-36: treatment difference estimates from baseline to day 40 in patients with CRPS-I treated with neridronate or placebo

Domains and components	Difference between neridronate and placebo		
	Estimate	95% CI	*P* value
Physical functioning	13.2	4.7, 21.8	0.003
Role limitations due to physical health	19.1	4.3, 33.9	0.012
Role limitations due to emotional problems	13.3	−2.9, 29.5	0.107
Energy/fatigue (vitality)	3.5	−3.1, 10.2	0.295
Emotional well-being (mental health)	13.6	6.7, 20.5	0.0002
Social functioning	9.9	0.5, 19.3	0.039
Pain	9.8	2.1, 17.4	0.013
General health	1.2	−4.6, 7.1	0.683
Physical component scale	3.7	0.9, 6.5	0.009
Mental component scale	4.9	1.2, 8.6	0.010

Data are expressed as least-square mean estimates with associated 95% confidence interval.

with the placebo group. At day 40, the oedema score fell from a baseline value of 1.66 to 0.53 in the neridronate group in comparison with a decrease from 1.63 to 1.11 in the placebo group ($P = 0.0009$). Pain at passive motion fell from 2.32 to 0.78 in the neridronate group and from 2.18 to 1.70 in the placebo group ($P < 0.0001$ for between-group changes).

At baseline, allodynia was detected in 25 patients in the neridronate group and in 26 patients in the placebo group. At day 40, allodynia was present in 6 neridronate-treated patients and in 18 placebo patients, a 34% difference (95% CI −53,−14; $P = 0.0027$). Hyperalgesia was present at baseline in 31 patients in the neridronate group and in 34 in the placebo group. At day 40, hyperalgesia was detected in 5 patients in the neridronate group and in 22 patients in the placebo group, with a 47% difference (95% CI −66, −28; $P < 0.0001$). At study entry, 68 patients were taking either NSAIDs or paracetamol. All patients on neridronate and 45% on placebo discontinued the symptomatic drugs within 2 weeks (results not shown). In multivariate regression analysis, neither baseline variables except treatment assignment nor the occurrence of the acute-phase reaction appeared to influence outcome measures.

Open-extension phase

The results of the open-extension phase in the patients previously receiving placebo are listed in Table 3. The mean (S.D.) VAS value decreased from 55.4 (24.2) at the start of the infusion course to 13.9 (15.8) 40 days later ($P < 0.0001$), with a trend similar to that observed in the neridronate group during the double-blind phase (Fig. 3). In 28 of the patients (82.3%) VAS score decreased by >50%. Neridronate treatment also improved the pain rating index of the McGill Pain Questionnaire ($P < 0.0001$ for both sensory and affective items). The oedema score fell to zero in 32 patients (94.1%) and pain at passive motion significantly improved ($P < 0.0001$) and fell to zero in 20 patients (58.8%). Allodynia and hyperalgesia disappeared in all patients. Functional assessment (SF-36) improved significantly for all domains except for the mental component scale.

At an investigator global assessment, the disease was considered resolved in all patients, with the remaining symptoms (pain or stiffness) not attributed to CRPS-I. At the last visit only two patients were still taking NSAIDs for problems unrelated to CRPS-I.

Seventy-eight of the patients agreed to participate in the long-term follow-up. In all patients the clinical improvements achieved at the end of the study remained unchanged or improved further. A bone scintigraphy control was obtained in 36 of the patients and a complete normalization of the abnormal uptake was reported. In 12 patients the disappearance of localized bone oedema was observed at an RMI control.

Safety evaluation

Twenty-one patients in the neridronate group and 12 patients in the placebo group complained of at least one AE during the double-blind phase. Reports of drug-related AEs concerned musculoskeletal disorders (mainly polyarthralgia) graded as mild to moderate, with an incidence of 12 patients (29.3%) for neridronate and 5 patients (12.2%) for placebo. Fever was reported by nine patients (21.9%) for neridronate and one patient (2.4%) for placebo. Fever never exceeded 38°C and disappeared within 3 days after the first infusion in all patients. Fourteen patients (38.9%) out of the 36 participating in the open-phase treatment reported drug-related AEs (polyarthralgia and/or fever with the same features as in the double-blind phase). No serious drug-related AEs were reported during the study.

Discussion

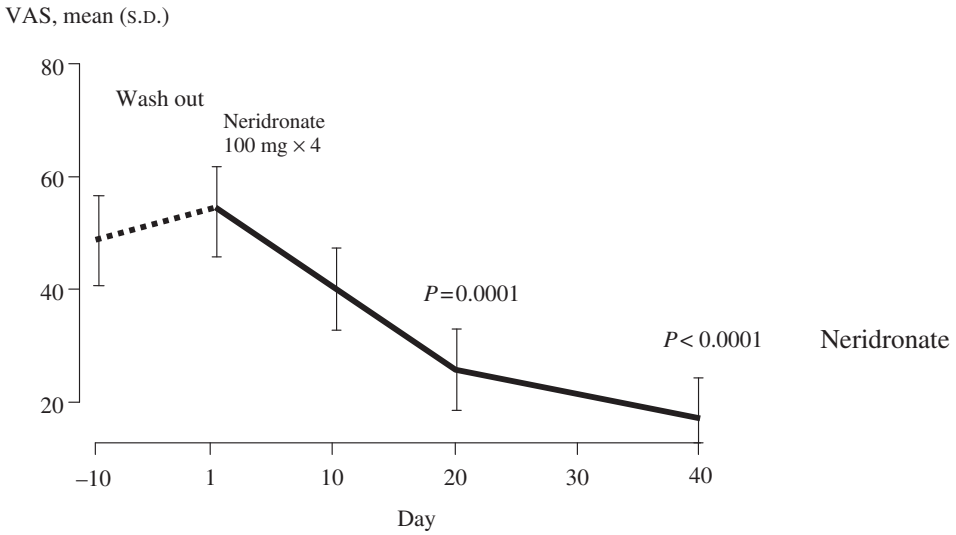
This randomized controlled study provides evidence that a course of i.v. neridronate reduces pain intensity and improves clinical signs and functional status in patients with CRPS-I at either the hand or foot. The age distribution, male-to-female ratio and prevalence of precipitating

Table 3 Changes in VAS and proportion of responders during the open-label extension phase of the study in patients with CRPS-I treated with neridronate

Assessments	Start of open phase ($n = 36$)	Day 40 ($n = 34$)	*P* value
Pain assessment			
Pain assessed on VAS (mm), mean (S.D.)	55.4 (24.2)	13.9 (15.8)	<0.0001
Responders (pain decrease > 50%), *n* (%)	12 (33.3)[a]	28 (82.3)[b]	0.0015
Other clinical signs and symptoms			
Oedema (present[c]), *n* (%)	29 (80.6)	2 (5.9)	<0.0001
Pain at motion (present[c]), *n* (%)	34 (94.4)	14 (41.2)	<0.0001
Allodynia (present), *n* (%)	19 (52.8)	0 (0.0)	<0.0001
Hyperalgesia (present), *n* (%)	22 (61.1)	0 (0.0)	<0.0001
SF-36			
Physical functioning, mean (S.D.)	52.6 (29.7)	71.5 (19.3)	<0.0001
Role limitations due to physical health, mean (S.D.)	38.2 (44.9)	58.8 (43.5)	0.0073
Role limitations due to emotional problems, mean (S.D.)	51.9 (44.7)	68.6 (39.3)	0.043
Energy/fatigue (vitality), mean (S.D.)	50.1 (22.5)	58.7 (14.5)	0.024
Emotional well-being (mental health), mean (S.D.)	54.9 (20.6)	63.6 (16.2)	0.011
Social functioning, mean (S.D.)	52.8 (26.6)	69.5 (20.9)	0.0001
Pain, mean (S.D.)	36.9 (15.8)	61.4 (21.8)	<0.0001
General health, mean (S.D.)	45.4 (18.4)	54.1 (17.0)	0.006
Physical component scale, mean (S.D.)	35.5 (9.0)	43.3 (9.0)	<0.0001
Mental component scale, mean (S.D.)	42.5 (11.1)	46.2 (9.0)	0.121
McGill Pain Questionnaire			
Sensory items, mean (S.D.)	11.5 (6.7)	3.8 (4.1)	<0.0001
Affective items, mean (S.D.)	3.8 (3.4)	1.0 (1.3)	<0.0001

[a]In comparison with baseline values. [b]In comparison with start of the open phase. [c]Of any degree (mild, moderate or severe).

Fig. 3 VAS values at the end of the follow-up period of the double-blind phase (day −10) and after the treatment course with i.v. neridronate in patients with CRPS-I.



events in the study population was similar to that reported in the largest epidemiological survey carried out in the Netherlands [2], suggesting a lack of referral bias.

In this study, most patients were recruited at a very early stage of the disease. This was made possible by the operating conditions of the main rheumatology centres, sited in orthopaedic hospitals. The inclusion of patients with an early diagnosis is likely to better simulate the operating condition when i.v. bisphosphonate will be formally registered for the treatment of CRPS-I.

Of interest is the remarkable reduction in pain intensity observed in patients treated with placebo and reported also by others [16]. This further emphasizes the need for well-randomized, double-blind studies while testing new therapies for CRPS-I. However, in this study the placebo effect was limited to the first 3 weeks of observation, with a clear diverging of the two arms during the following weeks. In patients who experienced an acute-phase reaction, possibly revealing the treatment they were given, the response rate was similar. We could not identify other baseline factors influencing the outcome measures to neridronate treatment as well as the high positive response rate we observed. The previously reported difference in clinical improvement between hand and foot CRPS-I using ibandronate was probably due to the small sample size of that study [17].

For registrative purposes the primary end point of this study was subjective pain but the evidence of efficacy is supported also by objective assessments obtained 7–14 months later, such as the observation of the absence of bone oedema at the RMI examination (12 patients) and normalization of abnormal uptake at the bone scintigraphy in 36 patients. Remarkable also is the observation that in all patients interviewed months after completion of the study, the signs and symptoms of the disease did not relapse and they actually improved.

Positive results have also been reported in four randomized clinical trials using a single i.v. infusion of 7.5 mg alendronate [13], i.v. clodronate (300 mg for 10 days) [14], i.v. pamidronate (60 mg once) [18] and 40 mg daily oral alendronate for 12–16 weeks [19]. However, none of these studies provided conclusive evidence of efficacy mainly because of their limited size, with 10–20 treated patients per study.

A comparative analysis of the results is made difficult by the variety of drugs used and bio-equivalent doses. However, while designing the present study, in order to identify the most appropriate dose we had to rely on the analysis of previous studies and on previous open-label data accumulated in two of the centres participating in the study. By assuming a potency ratio of 1:10:10:40 for clodronate, neridronate, pamidronate and alendronate, respectively, and a 0.7% intestinal absorption rate for oral alendronate [20], the cumulative neridronate equivalent doses in the four previous studies were 900 mg [13], 300 mg [14], 60 mg [18] and 76 mg [19]. In the studies with i.v. alendronate [13] and clodronate [14], bio-equivalent doses of bisphosphonates close to those used in this study (400 mg neridronate) were used and a complete remission of disease was reported in most patients, even though a long-term follow-up was not available. In the study with oral alendronate [19], a single treatment course with oral alendronate was not associated with the full resolution of the symptoms and signs of the disease in most patients, and in the few patients who had a second treatment course further subjective and objective improvements were obtained. In the study with pamidronate [18], with the smallest bio-equivalent doses, the treatment was associated with only a partial remission of the symptoms. This analysis of previous studies permitted a rough estimate that the dose of i.v. neridronate to be tested in a phase 3 trial had to be somewhat higher than the 200 mg dose registered for the treatment of Paget's disease of bone [8]. Smaller doses (200 and 300 mg i.v. neridronate) had been previously tested in 37 patients with CRPS-1 in two of the centres participating in this study [21]. In 20 of 37 patients, complete remission could not be obtained and symptoms partially relapsed within 1–3 months. These preliminary results and the analysis of previous clinical trials with bisphosphonates provided the rational for selecting the dose of 100 mg i.v. neridronate given four times over 10 days. It appears reasonable to assume that other bisphosphonates should be associated with comparable results, provided that equivalent i.v. doses are used. Our results suggest that for the treatment of CRPS-I the dose of bisphosphonate associated with long-term remission of the disease is somewhat higher than that generally recommended for the treatment of moderate Paget's disease. Thus, in countries where neridronate is not available, the dose of pamidronate that should be recommended for the treatment of CRPS-I is an i.v. dose of 90 mg given four times over 4–10 days.

The mechanism of action responsible for the brilliant results observed with bisphosphonates for the treatment of CRPS-I remains conjectural, mainly because the exact pathophysiology of the disease is still unknown. The most obvious action of bisphosphonate in bone is its capacity to inactivate osteoclast formation and activity [22], and high levels of markers of bone resorption at baseline have been observed to be predictive of a positive response to bisphosphonate therapy [14]. Local high bone turnover translates in the MRI findings of bone marrow oedema seen in CRPS-I [2, 23] and possibly in the generation and maintenance of chronic pain [19]. Intriguing also is our observation that treatment with bisphosphonates is associated with permanent remission of the disease. CRPS-I tends to spontaneously clear over several months in most cases; the longer the disease duration, the higher the risk of suffering permanent rigidity and loss of function [2]. It is therefore conceivable that bisphosphonates, by suppressing locally increased bone turnover, switch off an unknown vicious circle responsible for the maintenance of high bone turnover. This favours the acceleration of the healing process, with positive results on the clinical sequels of the disease.

A possible limitation of our study is the inclusion only of patients with a disease duration no longer than 4 months, since the general opinion is that the longer the disease duration, the worse the treatment outcome [24].

In addition to the action of bisphosphonates on local bone turnover, an alternative mechanism of action might include a direct effect of locally accumulated drug [25] on metabolic aspects linked with inflammation and pain. These include decreased local lactate concentration and acidosis [26], since low pH is a recognized factor that induces the local release of peptides related with plasma

extravasation, swelling, hyperhidrosis and pain [27, 28]. Bisphosphonates might also locally affect macrophage activities [29] involved in the expression of nerve growth factor, probably associated with the onset of neurogenic inflammation [30]. In conclusion, this randomized, placebo-controlled trial has shown significant, clinically relevant and persistent benefit to patients with acute CRPS-I following an i.v. neridronate course, providing in our opinion conclusive evidence that the use of bisphosphonate, at appropriate doses, is the treatment of choice for CRPS-I.

Rheumatology key messages

- No treatments are available for CRPS-I, a disabling pain syndrome.
- i.v. infusion of the bisphosphonate neridronate is associated with CRPS-I persistent remission.
- Bisphosphonates should be considered the first choice of treatment for CRPS-I.

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