

Role of Alendronate in Therapy for Posttraumatic Complex Regional Pain Syndrome Type I of the Lower Extremity

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Objective. To evaluate the effects of the antiresorptive agent alendronate at a daily oral dose of 40 mg in patients with posttraumatic complex regional pain syndrome type I (CRPS I) of the lower extremity.

Methods. Forty patients were enrolled in this 8-week randomized, double-blind, placebo-controlled study of alendronate therapy for CRPS I, a condition associated with regional osteoclastic overactivity. An optional 8-week open extension of alendronate therapy (weeks 12–20) was available after a 4-week period without therapy. Clinical assessments included joint mobility, edema of the lower extremity, tolerance to pressure in the lower extremity, and levels of spontaneous pain. Urinary levels of type I collagen N-telopeptide (NTX) were assessed by enzyme-linked immunosorbent assay. Patients were examined at weeks 4, 8, 12, 16, 20, and 24. Statistical analysis included two-way factorial analysis of variance.

Results. In contrast to placebo-treated patients ($n = 20$), all of the alendronate-treated patients ($n = 19$) exhibited a marked and sustained improvement in levels of spontaneous pain, pressure tolerance, and joint mobility, as well as a significant reduction in urinary levels of NTX at weeks 4 and 8. The improvement was maintained at week 12. Twelve patients from each

treatment group volunteered for the 8-week open trial, and all of them had a positive response to alendronate.

Conclusion. Our findings support the use of oral alendronate in posttraumatic CRPS I. By reducing local acceleration of bone remodeling, alendronate might relieve pain by effects on nociceptive primary afferents in bone, pain-associated changes in the spinal cord, and possibly also through a central mechanism.

Reflex sympathetic dystrophy, which is now called complex regional pain syndrome type I (CRPS I) according to criteria of the International Association for the Study of Pain (IASP), is a clinical syndrome characterized by pain, allodynia, hyperalgesia, edema, abnormal vasomotor and sudomotor activity, movement disorders, joint stiffness, regional osteopenia, and dystrophic changes in soft tissue (1–7). For many patients, the pain and ensuing loss of function lead to permanent disability. The nature of the inciting event may be quite variable, including visceral lesions, but trauma of an extremity accounts for more than 50% of the cases (2–5,8). It is now believed that this syndrome is, at least in part, a disease of both the central and peripheral nervous systems (6,7). There is indeed experimental evidence that a sustained peripheral injury may change the expression of genes in dorsal root ganglia and central pain-projecting neurons of the dorsal horn, and it is thought that the resulting change in phenotype establishes and maintains sensitization (hyperalgesia and allodynia), neurogenic inflammation, and autonomic dysregulation (9,10). There is also clinical evidence of changes in the central representation of the somatosensory, sympathetic, and somatomotor systems (7).

The natural history of CRPS I usually varies with its location. CRPS I of the upper extremity is reportedly associated with a relatively short-term morbidity. Yet, at

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1 year after Colles' fracture, joint stiffness is still apparent in 50% of cases, whereas up to 20% of patients continue to experience pain, tenderness, vascular instability, and swelling (8), an observation that may account for the 1–2% incidence of CRPS I that has been reported in retrospective studies of Colles' fracture (11). With the exception of the hip, however, CRPS I of the lower extremity has a protracted course that may persist for several years, and chronic sequelae, such as functional impairment and/or debilitating pain, may occur in 20–40% of patients (2).

CRPS I is difficult to treat. It is generally believed that physical therapy and related techniques aimed at restoring function are a prerequisite for improving pain, although too aggressive joint mobilization or invasive physical therapy approaches may worsen the underlying disease process (12,13). However, in practice, the endeavor is often frustrated by the pain itself, and to alleviate this frustration, the therapeutic use of various drugs as well as physical and psychological approaches have been advocated (12–14). In an exhaustive review of the management of CRPS I (15), Forouzanfar et al concluded that there is no convincing evidence for the efficacy of sympathetic nerve blocks, scavenging of radicals, prednisolone administration, manual lymph drainage, and acupuncture. On the other hand, since the disease process involves enhanced bone resorption and turnover, several investigators have examined the effect of osteoclast-blocking agents. Salmon calcitonin has been reported to be effective in some studies and useless in others (5), whereas intravenous administration of bisphosphonates (pamidronate, clodronate, or alendronate) usually results in a significant reduction in pain (16–20).

We therefore decided to conduct a double-blind randomized study to assess the efficacy of oral alendronate versus placebo in patients with posttraumatic CRPS I of the lower extremity. In comparison with intravenous therapy, oral therapy is less expensive and is associated with a placebo effect that is usually less strong. Our study has at least 2 important advantages over previous studies. First, since the etiology was similar in all study patients, we were dealing with a somewhat homogeneous patient group. Second, since the rate of resolution of symptoms in CRPS I of the lower extremity is rather slow, the placebo-treated patients are likely to represent adequate controls.

PATIENTS AND METHODS

Patients. The results of a preliminary study evaluating the effect of placebo (n = 10 patients) and alendronate (n = 10

patients) treatment on pressure tolerance scores, a well-validated test in CRPS I of the upper extremity (8), indicated that the inclusion of 20 patients in each group would be sufficient to attain 95% power to detect a 50% increase in the pressure tolerance score from a baseline value of 0.2 with a significance level of 1% (2-tailed). Accordingly, the present study included 40 other patients who had CRPS I of the lower extremity. Their CRPS I was secondary to a traumatic event, and none had any other condition that would otherwise account for the degree of pain and dysfunction.

All patients included in the present study fulfilled the consensus-based diagnostic criteria published by the IASP (1) as well as the revised diagnostic research criteria proposed by Harden et al (21). They had the following clinical characteristics: 1) symptoms developed after a traumatic event that was not associated with apparent nerve damage; 2) pain was not limited to the distribution of a single peripheral nerve; 3) spontaneous pain was estimated to be >40 mm on a 0–100-mm visual analog scale (VAS); 4) allodynia and hyperalgesia were present in the diseased area; 5) besides joint stiffness, the affected extremity was swollen, and the skin appeared "glassy"; 6) a red-bluish skin discoloration was observed and/or exacerbated by dependency (sitting with the legs hanging down); 7) in all patients, plain radiographs revealed regional osteoporosis (patchy appearance in 17 patients and diffuse in the other 23); and 8) during the 3-phase bone scintigram (22,23), the early static and late images both revealed high uptake of the bone-seeking agent in all patients, but the hemovelocity and blood pool were normal in 35 patients and slightly reduced in 5. No patient had previously received bisphosphonate therapy or sympathetic nerve blocks.

Exclusion criteria included CRPS I of nontraumatic origin, calcitonin therapy (if ineffective) within 1 week prior to study entry, gastroduodenal ulcers, diabetes mellitus, hyperthyroidism, renal and liver dysfunction, cardiovascular diseases, and overt alcohol addiction. Pregnant and/or lactating women were also excluded.

All patients gave written informed consent to participate in the study. The study was performed in accordance with the amended Declaration of Helsinki and was approved by the appropriate local ethics and drug committees.

Study design. This was an 8-week, randomized, double-blind, placebo-controlled study followed by an 8-week open study after a 4-week nontherapeutic period. At screening, patients who presented with CRPS I of a lower extremity and who were candidates for the study completed informed consent and medical history forms and underwent a physical examination, plain radiography, and a 3-phase bone scintigraphy. Blood and urine samples were collected for analysis. During the randomization visit, patients who met all entry criteria were assigned to either the alendronate group or the placebo group, based on a computer-generated blinded randomization schedule. To preserve the double-blind condition of the study, tablets containing 40 mg of alendronate and those containing placebo were identical in appearance. As strongly recommended by the manufacturer (Merck Sharp and Dohme, Whitehouse Station, NJ), the tablets were taken with a full glass of water upon arising for the day (after an overnight fast), and patients were instructed to remain in an upright position for 30 minutes prior to consuming the first food or beverage of the day.

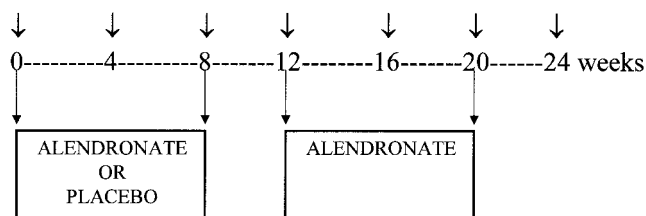


Figure 1. Study protocol. This randomized, double-blind, placebo-controlled study was conducted for 8 weeks, and after a washout period of 4 weeks, the 8-week open-label phase began. Twenty patients with posttraumatic complex regional pain syndrome type I affecting the lower extremity were initially enrolled in each treatment group. Twelve patients from each treatment group elected to receive alendronate for a period of 8 weeks in the open-label phase (weeks 12–20). Arrows across the top indicate the followup visits.

After the first 8-week therapeutic period and a 4-week nontherapeutic period, patients in both treatment groups who wanted to do so received a daily tablet containing 40 mg of alendronate for 8 weeks (i.e., from week 12 to week 20).

Compliance with treatment was estimated by counting the number of tablets used from the pack that was given to the patient at the baseline visit. A value outside the range of 80–100% of the original number was considered a protocol violation.

During the entire study period, patients were encouraged to continue their physical therapy and rehabilitation program on a regular basis.

Schedule of visits and assessments. The visit schedule is illustrated in Figure 1. Besides the randomization visit (week 0), patients enrolled in the double-blind, placebo-controlled study were seen at week 4, week 8, and week 12. Patients included in the open study were seen at week 16, week 20, and week 24. Care was taken to examine each patient between the hours of 9:00 AM and 11:00 AM, the patient having arisen from bed for more than 2 hours at the time of the medical appointment.

At each visit, a 100-mm VAS was used to assess the patient's level of spontaneous pain. As described below, values obtained for tenderness, edema, and joint mobility in the affected limb were divided by the values obtained for the corresponding parameters in the contralateral limb. Although CRPS I might also affect the contralateral limb (6,7), there was no obvious clinical evidence of spreading of the disease process to the contralateral side in our patients.

Tenderness or pressure tolerance threshold was measured with a dolorimeter (8). Using the 1-cm² applicator tip, pressure was applied perpendicular to the skin's surface at a gradual rate of 1 kg/second. For CRPS I of the knee, measurements were made over the dorsal aspect of the midpatellar and midtibial areas of both legs. For CRPS I of the ankle and foot, measurements were made over the dorsal aspect of the midtibial and midtarsal areas of both legs. For each location, measurements were made in triplicate, and the mean value was recorded as the test value. For each of the 2 areas measured, the test value for the affected limb was then divided by the corresponding test value for the unaffected limb, and the 2 ratios were averaged to give the pressure tolerance score

(lower score denotes a more tender leg). With examiner training, the coefficient of variation of this procedure was <8%, and the normal range was 0.9–1.1.

Edema was assessed by measuring the circumference of the knee (midpatellar region), ankle, and foot (midtarsal region) of both legs. The results are expressed as the ratio of the value in the affected joint to the corresponding value in the unaffected contralateral joint. The coefficient of variation was <3%, and the normal range was 0.96–1.04.

Using a goniometer, mobility of the knee, foot, and ankle was assessed. For each movement of flexion and extension of the knee, the angle value obtained for the affected knee was divided by that obtained for the contralateral knee to give the relative test value. Relative test values obtained for flexion and extension were then averaged to give the index of knee mobility. The coefficient of variation was <3%, and the normal range was 0.95–1.05.

For the foot and ankle, dorsal flexion and plantar extension of the ankle as well as subtalar inversion and eversion were measured. For each movement, the angle value obtained for the affected limb was divided by that obtained for the contralateral limb to give the relative test value. Relative test values obtained for each of the 4 movements were then averaged to give the index of foot and ankle mobility. The coefficient of variation was 5%, and the normal range was 0.94–1.06.

Urine samples (second void of the morning; fasting state) were collected at the time of randomization and at week 8. Specimens were immediately frozen at –20°C until analyzed for levels of type I collagen N-telopeptide (NTX) by use of a commercially available enzyme-linked immunosorbent assay (Osteomark; Ostex, Seattle, WA). Results were corrected for urine dilution by urinary creatinine analysis and expressed in nanomoles of bone collagen equivalents (BCE) per liter per millimole of creatinine per liter (ratio reported as nM BCE/mM creatinine).

Statistical analysis. After entering all measured data into a computer database (SigmaStat; Jandel, San Rafael, CA), the treatment randomization was disclosed to allow comparison of the data obtained in the 2 groups of patients. Statistical analysis was performed with analysis of variance (ANOVA): two-way ANOVA with repeated measurements, the independent criteria being treatment and the correlated criteria being time. When needed, Tukey's test was used for multiple comparisons. *P* values less than 0.05 were considered statistically significant.

RESULTS

Demographics and baseline characteristics. The 2 treatment groups were similar with regard to demographics and baseline characteristics of the study patients (Table 1). In both groups, CRPS I of the ankle and foot was more frequent, and the relative percentages of the nature of the initiating traumatic events were similar. In all cases of postsurgical CRPS I of the knee, the nature of the precipitating factor was arthroscopy for meniscal problems.

Table 1. Demographics and baseline characteristics of patients with complex regional pain syndrome type I of the lower limb treated with alendronate or placebo*

Parameter	Alendronate group (n = 20)	Placebo group (n = 20)
Age, mean ± SD years	44.6 ± 12.3	45.2 ± 12.5
No. of men/women	11/9	8/12
Height, mean ± SD cm	169 ± 10	168 ± 11
Body mass index, mean ± SD kg/m ²	26 ± 6	27 ± 6
Disease duration, mean ± SD months	7 ± 2	8 ± 3
Disease site		
Knee	2	8
Foot and ankle	18	12
Inciting injury		
Sprain/strain	10	11
Postsurgery	4	3
Fracture	3	4
Contusion	3	2

* None of the between-group differences were statistically significant.

Before entry into the study, all patients had received various analgesics and nonsteroidal antiinflammatory drugs. Fourteen had received salmon calcitonin. Because of this large variety of medications that had been taken, no attempt was made to correlate the drug treatment with the clinical parameters of disease activity at the baseline visit.

Tolerability and safety. One patient in the alendronate-treated group dropped out after a therapeutic period of 2 weeks because of upper gastrointestinal intolerance. One patient in the placebo-treated group experienced headache, nausea, and heartburn for about 1 hour after ingesting the tablet, but he nevertheless completed the study.

Efficacy during the initial 12-week study period. Obviously, despite various analgesic and antiinflammatory drug regimens that had been administered for an average of 7–8 months, patients included in the study all were severely impaired, as evidenced by their pressure tolerance scores, spontaneous levels of pain, degree of swelling of the affected leg, and levels of joint mobility (Figure 2). ANOVA disclosed that over time, treatment had a statistically significant effect (variation = time × treatment) on the VAS values ($F = 136, P < 0.001$), edema in the affected leg ($F = 5, P = 0.003$), pressure tolerance scores ($F = 63, P < 0.001$), and levels of joint mobility ($F = 28, P < 0.001$).

At study entry, the placebo-treated group and the alendronate-treated group had similar mean VAS scores (Figure 2). In the placebo-treated group, a small, but statistically significant, reduction in the mean VAS score was detected only at week 12 ($P < 0.05$), whereas in the

alendronate-treated group, the mean VAS score was already significantly reduced at week 4. A further significant drop in the score was noted at week 8 and was sustained at week 12. In comparison with the placebo-treated group, patients in the alendronate-treated group exhibited a significant decrease in their mean VAS scores at weeks 4, 8, and 12 ($P < 0.05$). It is noteworthy that at week 12, the mean VAS score in the alendronate-treated group was 33% of that in the placebo-treated group.

Before therapy, the 2 groups exhibited a similar mean score for pressure tolerance (Figure 2). Alendronate caused a sharp increase in the mean pressure tolerance score at week 4 ($P < 0.05$). Although a further significant increase in this score was noted at week 8 ($P < 0.05$) and was sustained at week 12, the score remained below the normal range of values. In contrast, in the placebo-treated group, the mean score remained unaffected for up to week 12, and was thus significantly lower ($P < 0.05$) than that seen in the alendronate-treated group at the 3 time points.

In both groups, the mean score for edema decreased with time (Figure 2). A statistically significant decrease was seen at week 4 in the alendronate-treated group ($P < 0.05$) and only at week 8 in the placebo-treated group ($P < 0.05$). At week 12, the mean edema

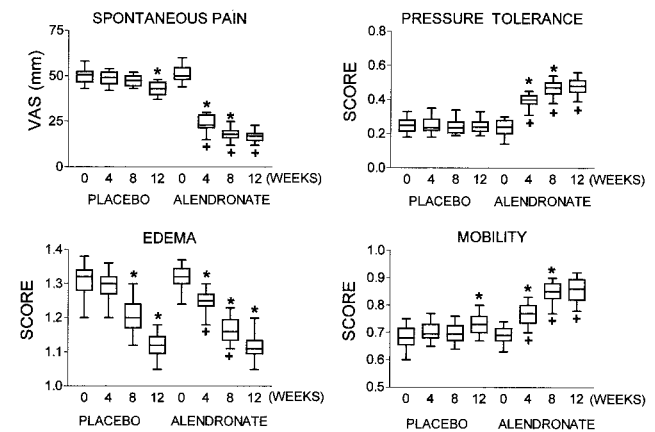


Figure 2. Distribution of visual analog scale (VAS; 0–100-mm scale), pressure tolerance, edema, and mobility scores measured in patients with posttraumatic complex regional pain syndrome type I affecting the lower extremity who were treated with either placebo (n = 20) or alendronate (n = 19) for up to 8 weeks. Data are shown as box plots. The box extends from the 25th percentile to the 75th percentile, with a horizontal line at the median (50th percentile). Whiskers extend down to the lowest value and up to the highest value. * = $P < 0.05$ for the difference between time periods within each group; + = $P < 0.05$ for the difference between groups at a given time point.

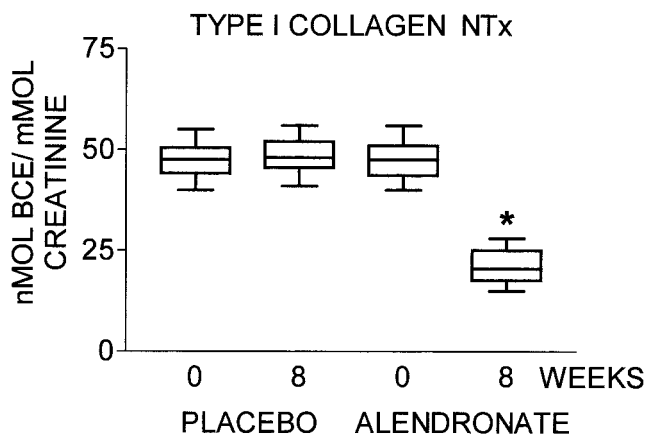


Figure 3. Changes in urinary levels of cross-linked N-telopeptide of type I collagen (NTX) at study entry and at the end of the 8-week therapeutic period in the placebo-treated group and the alendronate-treated group. Data are shown as box plots, where each box represents the 25th to 75th percentiles, whiskers represent the 10th and the 90th percentiles, and lines inside the boxes represent the mean. Values are expressed as bone collagen equivalents (BCE) (see Patients and Methods for derivation). * = $P < 0.001$ versus week 0 in alendronate-treated patients.

score was similar in the 2 groups and remained above the normal range of values.

Before therapy, the 2 groups had a similar mean score for joint mobility (Figure 2). In the alendronate-treated group, the mean score was markedly enhanced ($P < 0.05$) as early as at week 4, increased further at week 8 ($P < 0.05$), and was sustained at week 12. This evolution contrasted sharply with that seen in the placebo-treated group, where the mean score remained unchanged for up to week 8, and increased modestly, but significantly ($P < 0.05$), at week 12. The mean score for joint mobility in the alendronate-treated group was significantly higher ($P < 0.05$) than that in the placebo-treated group at the 3 time points.

As illustrated in Figure 3, after a therapeutic period of 8 weeks, urinary levels of NTX were significantly reduced in the alendronate-treated group ($P < 0.001$), but not in the placebo-treated group.

Efficacy during the 8-week open-label extension study. At week 12 of the double-blind study, 8 of the placebo-treated patients did not want to continue the oral therapy, 4 alendronate-treated patients were unable to pursue the study because of logistical reasons, and 4 other alendronate-treated patients stated that they were sufficiently improved that they did not want to take the oral medication for a longer time period. Therefore, only 12 patients in each group volunteered for the open

trial of alendronate at a daily oral dose of 40 mg for a period of 8 weeks.

As expected, at week 16, which constituted a period of only 4 weeks of alendronate therapy, patients that had previously taken a placebo exhibited a dramatic improvement ($P < 0.05$) in their mean VAS scores for spontaneous pain, their mean pressure tolerance scores, and their mean joint mobility scores (Figure 4). These mean scores showed further improvement at week 20 ($P < 0.05$) and remained unchanged at week 24 (i.e., 4 weeks after stopping alendronate therapy).

In patients that had previously taken alendronate (Figure 4), continued administration of the bisphosphonate during the 8-week therapeutic period was associated with new progressive improvement in the mean scores for spontaneous pain, pressure tolerance, and

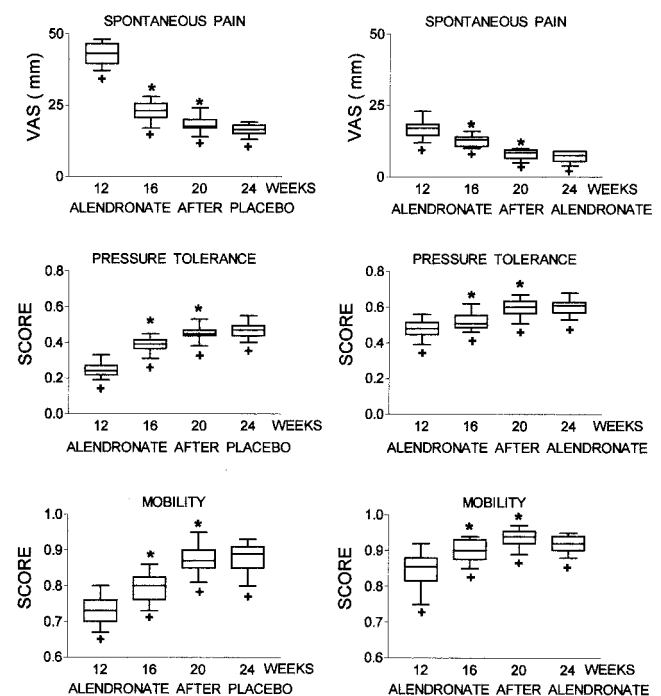


Figure 4. Distribution of visual analog scale (VAS; 0–100-mm scale), pressure tolerance, and mobility scores measured in patients who elected to receive alendronate during the 8-week open-label extension study. After a nontherapeutic period of 4 weeks, 12 patients from the initial placebo group (left panels) and 12 patients from the initial alendronate group (right panels) received alendronate at a daily oral dose of 40 mg for 8 weeks (week 12 to week 20). Data are shown as box plots. The box extends from the 25th percentile to the 75th percentile, with a horizontal line at the median (50th percentile). Whiskers extend down to the lowest value and up to the highest value. * = $P < 0.05$ for the difference between time periods within each group; + = $P < 0.05$ for the difference between groups at a given time point.

joint mobility ($P < 0.05$). This suggests that the previous positive effect of alendronate had not reached a plateau and was not declining after the first 8-week therapeutic period. Furthermore, and as observed after the first therapeutic period, this new improvement was sustained for at least 4 weeks after stopping the drug. Although pressure tolerance scores remained below the normal range at week 20, it is worth noting that at that time, the mobility scores had reached the normal range in half of the patients in this group.

Treatment outcomes could not be associated with the hemovelocity and blood pool values obtained during the 3-phase bone scanning, as assessed at study entry, or with the diffuse or patchy appearance of regional osteoporosis. However, 3 months after the end of the study (week 36), 3 patients in the initial placebo-treated group and 2 patients in the initial alendronate-treated group experienced a relapse. Further followup studies are ongoing.

DISCUSSION

The consensus-based criteria published by the IAPS (1) are adequately sensitive but are not very specific. The inclusion of motor and trophic signs and symptoms in the modified research criteria (21) has improved the specificity without losing much sensitivity. However, there is no clear consensus on how to assess these criteria in daily clinical practice. Patients included in the present study all exhibited the cardinal features of CRPS I that have been clearly formulated by several authors (4,5,8). The semiquantitative approach we used to assess the clinical signs has been well validated in CRPS I of the upper extremity (8,24). Furthermore, the regional osteoporosis seen in disuse conditions can be accurately differentiated from that seen in CRPS I by using the pressure tolerance test (8,24).

Obviously, at a daily dose that corresponds to that recommended for Paget's disease of bone, which amounts to 4 times the daily dose recommended for the treatment of postmenopausal osteoporosis, oral alendronate was very efficacious in the treatment of post-traumatic CRPS I. Although the positive effect of oral alendronate was detected as early as 4 weeks after initiation of treatment, the optimal therapeutic time period remains to be established, since after 16 weeks of alendronate therapy, joint mobility had returned to values within the normal range in half of the patients, whereas tenderness was markedly improved, but still remained below the normal range of values in all patients. In contrast, alendronate apparently had no

effect on edema, since at week 12, both groups exhibited a similar mean score for edema. It is unlikely that the reduction in edema was related to the increase in joint mobility, since this reduction occurred when joint mobility was markedly enhanced in the alendronate-treated group but hardly improved in the placebo-treated group.

Our data help to put into perspective the results of previous studies that have shown a positive effect of intravenous bisphosphonate therapy in patients with CRPS I (16–20). Although the majority of those studies lacked a placebo control group, the drug was shown to relieve pain and enhance the range of motion, and as observed in the present study, the beneficial response to bisphosphonate therapy was rapid and persisted for some time after the end of the therapeutic period. Furthermore, these previous studies have shown that patients with posttraumatic CRPS I responded better than patients with CRPS I associated with other conditions.

The rationale for using bisphosphonates in the treatment of CRPS I relies upon the capacity of the drug to inactivate osteoclasts and to antagonize osteoclastogenesis (25). Indeed, it has been suggested that high levels of markers of bone resorption at baseline have a positive predictive value for bisphosphonate therapy (18). The osteoclastic overactivity and bone marrow edema seen in CRPS I (2,4,5,26) might contribute to the generation and maintenance of chronic pain, since each neuron in the nociceptive pathway has the capacity to change phenotype in the presence of a sustained peripheral injury (6,7,9,10). This contention is further strengthened by the observation that osteoprotegerin (OPG), a potent inhibitor of osteoclast-mediated bone resorption (27), not only halts bone destruction, but also markedly reduces markers of both peripheral and central sensitization in a mouse model of pain associated with cancer of the bone (28,29). Therefore, the possible effect of OPG in CRPS is worth investigating, and alendronate, another potent antiresorptive drug, might have alleviated the pain and tenderness in our study patients by its effects on primary afferent nociceptors in bone and pain-associated changes in the spinal cord. Furthermore, since it has been suggested that, upon stimulation by substance P that is liberated by the activated and sensitized afferent nerve fibers, macrophages start to release proinflammatory cytokines, such as tumor necrosis factor α (TNF α), which in turn, further activate afferent fibers by enhancing sodium influx into the cells (30), it is also tempting to speculate that TNF α inhibitors such as etanercept and infliximab might have therapeutic effects in CRPS.

It is naive, however, to reduce CRPS I to osteoclastic overactivity. The traumatic event triggering CRPS I in our patients might have damaged C fibers and/or A-delta mechanical fibers in soft tissue and nerve, another type of injury believed to establish and maintain central sensitization (6). Obviously, bisphosphonates exhibit antinociceptive properties in a variety of bone and joint disorders (31,32), as well as in other painful situations unrelated to bone and joint diseases (33). Their pain relief properties might be related to their ability to inhibit the production of either proinflammatory cytokines, prostaglandins, lactic acid, and/or various neuropeptides and neuromodulators, all of which are possibly involved in the sensitization of afferent nerve fibers and pain modulation (33,34). The highly water-soluble bisphosphonates might also have a central antinociceptive action, possibly through mechanisms involving ionized calcium (35). Indeed, ionized calcium-channel blockers display antinociceptive properties by inhibiting the influx of calcium that is crucial for the release of neurotransmitters and other substances implicated in nociception and inflammation (36,37). In contrast, liposome-encapsulated bisphosphonates, but not free bisphosphonates, are able to deplete macrophages from an injured nerve and, in so doing, to reduce neuropathic hyperalgesia and Wallerian degeneration (38). This might explain why alendronate was unable to restore the pressure tolerance scores to a normal range.

In conclusion, in this randomized placebo-controlled trial, we observed that oral alendronate taken at a daily dose of 40 mg was well tolerated and appeared to be a very effective tool in the management of CRPS I, a painful and potentially disabling condition.

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REFERENCES

1. Stanton-Hicks M, Janig W, Hassenbusch S, Haddock JD, Boas R, Wilson P. Reflex sympathetic dystrophy: changing concepts and taxonomy. *Pain* 1995;63:127-33.
2. Doury P. Algodystrophy: reflex sympathetic dystrophy syndrome. *Clin Rheumatol* 1988;7:173-80.
3. Veldman PH, Reynen HM, Arntz IE, Goris RJ. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. *Lancet* 1993;342:1012-6.
4. Bonica J. Causalgia and other reflex sympathetic dystrophies. In: Bonica J, editor. *The management of pain*. Philadelphia: Lea & Febiger; 1990. p. 220-43.
5. Kozin F. Reflex sympathetic dystrophy syndrome. *Curr Opin Rheumatol* 1994;6:210-6.
6. Schwartzman RJ, Popescu A. Reflex sympathetic dystrophy. *Curr Rheumatol Rep* 2002;4:165-9.
7. Janig W, Baron R. Complex regional pain syndrome: mystery explained? *Lancet Neurol* 2003;2:687-97.
8. Bickerstaff DR, Kanis JA. Algodystrophy: an under-recognized complication of minor trauma. *Br J Rheumatol* 1994;33:240-8.
9. Hunt SP, Mantyh PW. The molecular dynamics of pain control. *Nat Rev Neurosci* 2001;2:83-91.
10. Schwartzman RJ, Grothusen J, Kiefer TR, Rohr P. Neuropathic central pain: epidemiology, etiology, and treatment options. *Arch Neurol* 2001;58:1547-50.
11. Bacorn RW, Kurtzke JF. Colles' fracture: a study of two thousand cases from the New York State Workmen's Compensation Board. *J Bone Joint Surg Am* 1953;35A:643-58.
12. Bengtson K. Physical modalities for complex regional pain syndrome. *Hand Clin* 1997;13:443-54.
13. Stanton-Hicks M, Baron R, Boas R, Gordh T, Harden N, Hendler N, et al. Complex regional pain syndromes: guidelines for therapy. *Clin J Pain* 1998;14:155-66.
14. Schott GD. Reflex sympathetic dystrophy. *J Neurol Neurosurg Psychiatry* 2001;71:291-5.
15. Forouzanfar T, Koke AJ, van Kleef M, Weber WE. Treatment of complex regional pain syndrome type I. *Eur J Pain* 2002;6:105-22.
16. Devogelaer JP, Dall'Armellina S, Huaux JP, Nagant de Deuxchaisnes C. Dramatic improvement of intractable reflex sympathetic dystrophy syndrome by intravenous infusions of the second generation bisphosphonate APD. *J Bone Miner Res* 1988;3:122.
17. Adami S, Fossaluzza V, Gatti D, Fracassi E, Braga V. Bisphosphonate therapy of reflex sympathetic dystrophy syndrome. *Ann Rheum Dis* 1997;56:201-4.
18. Varenna M, Zucchi F, Ghiringhelli D, Binelli L, Bevilacqua M, Bettica P, et al. Intravenous clodronate in the treatment of reflex sympathetic dystrophy syndrome: a randomized, double blind, placebo controlled study. *J Rheumatol* 2000;27:1477-83.
19. Mailliefert JF, Cortet B, Aho S. Pooled results from 2 trials evaluating bisphosphonates in reflex sympathetic dystrophy [letter]. *J Rheumatol* 1999;26:1856-7.
20. Kubalek I, Fain O, Paries J, Kettaneh A, Thomas M. Treatment of reflex sympathetic dystrophy with pamidronate: 29 cases. *Rheumatology (Oxford)* 2001;40:1394-7.
21. Harden RN, Bruehl S, Galer BS, Saltz S, Bertram M, Backonja M, et al. Complex regional pain syndrome: are the IASP diagnostic criteria valid and sufficiently comprehensive? *Pain* 1999;83:211-9.
22. Demangeat JL, Constantinesco A, Brunot B, Foucher G, Farcot JM. Three-phase bone scanning in reflex sympathetic dystrophy of the hand. *J Nucl Med* 1988;29:26-32.
23. Manicourt DH. L'exploration scintigraphique dans l'algodystrophie sympathique réflexe. *Semin Hop Paris* 1994;33-34:1023-42.
24. Atkins RM, Kanis JA. The use of dolorimetry in the assessment of post-traumatic algodystrophy of the hand. *Br J Rheumatol* 1989;28:404-9.
25. Rodan GA, Reszka AA. Bisphosphonate mechanism of action. *Curr Mol Med* 2002;2:571-7.
26. Basle MF, Rebel A, Renier JC. Bone tissue in reflex sympathetic dystrophy syndrome—Sudeck's atrophy: structural and ultrastructural studies. *Metab Bone Dis Relat Res* 1983;4:305-11.
27. Hofbauer LC, Khosla S, Dunstan CR, Lacey DL, Boyle WJ, Riggs BL. The roles of osteoprotegerin and osteoprotegerin ligand in the paracrine regulation of bone resorption. *J Bone Miner Res* 2000;15:2-12.
28. Honore P, Luger NM, Sabino MA, Schwei MJ, Rogers SD, Mach DB, et al. Osteoprotegerin blocks bone cancer-induced skeletal destruction, skeletal pain and pain-related neurochemical reorganization of the spinal cord. *Nat Med* 2000;6:521-8.

29. Luger NM, Honore P, Sabino MA, Schwei MJ, Rogers SD, Mach DB, et al. Osteoprotegerin diminishes advanced bone cancer pain. *Cancer Res* 2001;61:4038–47.
30. Wasner G, Schattschneider J, Binder A, Baron R. Complex regional pain syndrome — diagnostic, mechanisms, CNS involvement and therapy. *Spinal Cord* 2003;41:61–75.
31. Bonjour JP, Rizzoli R, Ammann P, Chevalley T. Bisphosphonates in clinical medicine. In: Heershe NM, Kanis JK, editors. *Bone and mineral research*. Amsterdam: Elsevier Science; 1994. p. 204–64.
32. Maksymowych WP, Jhangri GS, Fitzgerald AA, LeClercq S, Chiu P, Yan A, et al. A six-month randomized, controlled, double-blind, dose-response comparison of intravenous pamidronate (60 mg versus 10 mg) in the treatment of nonsteroidal antiinflammatory drug-refractory ankylosing spondylitis. *Arthritis Rheum* 2002;46:766–73.
33. Bonabello A, Galmozzi MR, Canaparo R, Serpe L, Zara GP. Long-term analgesic effect of clodronate in rodents. *Bone* 2003;33:567–74.
34. Pennanen N, Lapinjoki S, Urtti A, Monkkonen J. Effect of liposomal and free bisphosphonates on the IL-1 β , IL-6 and TNF α secretion from RAW 264 cells in vitro. *Pharm Res* 1995;12:916–22.
35. Bishop NJ, Ninkovic M, Alexander GJ, Holmes SD, Milligan T, Price C, et al. Changes in calcium homeostasis in patients undergoing liver transplantation: effects of a single infusion of pamidronate administered pre-operatively. *Clin Sci (Lond)* 1999;97:157–63.
36. Carr DB, Goudas LC. Acute pain. *Lancet* 1999;353:2051–8.
37. Sluka KA. Blockade of calcium channels can prevent the onset of secondary hyperalgesia and allodynia induced by intradermal injection of capsaicin in rats. *Pain* 1997;71:157–64.
38. Liu T, van Rooijen N, Tracey DJ. Depletion of macrophages reduces axonal degeneration and hyperalgesia following nerve injury. *Pain* 2000;86:25–32.