

An Open-label Pilot Trial of Ibandronate for Complex Regional Pain Syndrome

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Objective: Complex regional pain syndrome (CRPS) type I, also known as reflex sympathetic dystrophy, usually develops after trauma or immobilization, is characterized by focal pain and autonomic dysregulation, and sometimes focal trophic changes such as osteoporosis. The pathophysiology is unknown and there have been few controlled treatment trials. The purpose of this study was to obtain pilot data on the safety and efficacy of a highly potent bisphosphonate, ibandronate, for the treatment of CRPS, which might be responsive to bisphosphonates' inhibition of osteoclast and anti-inflammatory activity.

Methods: An open-label trial (n = 10) of 6 mg ibandronate infusions was administered on each of 3 days. The infusions were preceded by a 2-week baseline period, and followed by a 4-week follow-up period.

Results: One participant dropped out after the first infusion because of a decreased glomerular filtration rate. Otherwise, aside from transitory flu-like symptoms characteristic of bisphosphonate treatments, the drug was well tolerated. Significant post-intervention improvements were observed in average and worst pain ratings; the neuropathic pain qualities of "unpleasant," "sensitive," "deep," "intense," "surface," "hot," "cold," "sharp," and "dull"; and hyperalgesia and allodynia. Participants with hand CRPS improved significantly more than those with foot CRPS in average and worst pain, as well as in the following neuropathic pain qualities: "dull," "intense," "deep," and "time."

Discussion: These data justify a randomized, double-blind, placebo-controlled trial of ibandronate that should perhaps be limited to patients with hand CRPS.

Key Words: complex regional pain syndrome, CRPS, reflex sympathetic dystrophy, RSD, pilot trial, ibandronate, bisphosphonates

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There are 2 forms of complex regional pain syndrome (CRPS), CRPS I and CRPS II. CRPS I replaces the term reflex sympathetic dystrophy (RSD). According to the International Association for the Study of Pain, the diagnosis of CRPS I requires (1) continuing pain, allodynia, or hyperalgesia disproportionate to the injury; (2) evidence at some time of changes in skin blood flow, edema, or abnormal sudomotor activity in the region of pain; and (3) no other conditions that would otherwise account for the degree of dysfunction and pain.¹ The affected site is usually the distal aspect of an extremity. Symptoms of CRPS may begin gradually in the days or weeks after an injury or within a few hours. CRPS II (formerly causalgia) is the same syndrome with the addition of peripheral nerve injury.²

Although the incidence of CRPS may be underestimated because of misdiagnoses attributable to the poor correlation between the intensity of the pain and the initiating trauma (which may not always be identified), reported rates range from 5 to 26/100,000 person-years.^{3,4} The prevalence of CRPS 6 months after total knee arthroplasty is 13%,⁵ and estimated incidence rates are 1% to 2% after fracture, 12% after brain lesions, 1% to 5% after peripheral nerve injury, and 5% after myocardial infarction.⁶ Females are affected at least 3 times more often than males. The upper extremity is affected more frequently than the lower extremity and a fracture is the most common precipitating event. In approximately 10% of cases, chronic forms can occur accompanied by severe pain and serious disability.⁷

There is no consensus as to what constitutes appropriate treatment for CRPS. Although most patients undergo a trial of sympathetic blockade, its overall efficacy is unknown.⁸ Among the pharmacotherapies that have been studied for CRPS, there is empirical support for bisphosphonates, such as alendronate and pamidronate.^{7,9–11} The findings of localized osteoporosis in the affected limb and the frequently positive 3-phase bone scan of the CRPS affected limb strongly suggest that osteoclasts are involved in the CRPS syndrome. The association between osteoclasts and inflammatory cytokines strengthens this hypothesis.¹² In vitro and in vivo studies show that certain bisphosphonates inhibit the synthesis of these cytokines, and thus their analgesic effects may be attributable to their anti-inflammatory effects.^{13–17} As ibandronate, a third-generation aminobisphosphonate,¹⁸ may be a more potent treatment for

CRPS than alendronate and pamidronate, we conducted a small open-label trial of this bisphosphonate in patients with CRPS.

MATERIALS AND METHODS

The study and its informed consent form were approved by the Institutional Review Board of Beth Israel Medical Center. Participants were recruited via advertisements on the radio, in New York City buses, in hospital lobbies, and from physician referrals. To maximize specificity, inclusion in the study was based on the criteria of Sandroni et al,⁴ as adapted by Bruehl et al.¹⁹ In addition, participants had to be at least 21 years of age and had to have a diagnosis of CRPS of a limb for 1 month or longer. Exclusion criteria were having: (1) a history of hypocalcemia, or significant cardiac, renal, hepatic, metabolic, endocrinologic, or neurologic disease, (2) an allergy to bisphosphonates, (3) CRPS with irreversible tissue damage, or (4) renal impairment, as evidenced by a creatinine level greater than 1.4 mg/dL or a glomerular filtration rate (GFR) that is less than 80.²⁰ Because of recent concern regarding the association between prolonged bisphosphonate treatment and osteonecrosis of the jaw, we excluded individuals who, according to these reports, seemed to be at an increased risk of osteonecrosis of the jaw.^{21–31} Participants who had a vitamin D deficiency received supplements to normalize their levels before administering any infusion.

From the 2-week baseline period through the end of the follow-up period 4 weeks after the last infusion, the research coordinator called participants 3 times weekly to administer the Brief Pain Inventory (BPI)^{32,33} and the Neuropathic Pain Scale,³⁴ and to gather information about usage of rescue analgesics and adverse events. Except for the neuropathic pain quality (NPQ) “time,” both instruments use a 0 to 10 numeric rating scale, where 0 indicates absence of the pain or pain quality, and 10 indicates that the pain or pain quality is at the worst possible level. We rated “time,” on a 1 to 3 ordinal scale, with lower scores reflecting a more severe status. Participants also self-administered the BPI daily. To remain eligible, during the 6 baseline telephone calls, participants had to have an average score of at least 4 for the 4 highest worst pain scores, or an average score of 4 or more on any of the items included in the Neuropathic Pain Scale that are rated on a 0 to 10 scale.³⁴

Baseline and final physical examinations included a range of motion and neurologic assessment. At baseline, immediately after each infusion and 5 to 7 days after the last infusion, each participant had comprehensive laboratory tests, including assays of blood urea nitrogen/creatinine, and electrolytes (including calcium, magnesium, and phosphates). Participants also had a baseline 3-phase nuclear bone scan to determine whether the uptake of the bone scan tracer, technetium-99m-methylene diphosphate, is predictive of responsiveness to ibandronate, as diphosphonates fall into the same drug classification as ibandronate; that is, they are both bisphosphonates.

Calcium and vitamin D supplements were administered from 1 week before the infusion through study completion. A 6-mg ibandronate infusion was administered over a 2-hour period on each of 3 consecutive days. An electrocardiogram preceded each infusion. To lower the likelihood and intensity of an acute phase reaction, each participant was prescribed acetaminophen to be taken 2 to 3 times daily, starting from the day of the first infusion and through the third day after the final infusion. The participant's overall evaluation of the treatment was assessed with the Patient Global Impression of Change Scale,³⁵ which is a single-item rating of improvement with treatment on a 7-point scale ranging from “very much improved” to “very much worse” with “no change” as the midpoint. A similar scale was used to rate the change in the participant's activity level.

Statistical Analyses

The Student *t* test, the Wilcoxon test, or a paired *t* test was used for univariate analysis of ordinal data, and the χ^2 test for categorical data. The Mixed procedure (SAS, version 9.0; SAS institute, Cary, NC) was used for analysis of variance with repeated measures. For changes in BPI pain levels and NPQ, we averaged the scores of each outcome variable over the 2-week baseline period, and referred to those scores as preintervention scores. Similarly, we averaged the scores of the final 3 weeks of follow-up, and referred to the resulting averages as postintervention scores. The analyses did not include the week that the last infusion was administered, nor the following week, as acute phase reactions (ie, a rise in body temperature accompanying flu-like symptoms) associated with bisphosphonate treatment could have confounded our results.^{36–40} Our protocol included all the recommended measurements for pain clinical trials that are encompassed in the IMMPACT^{41,42}; that is, pain, physical functioning, emotional functioning, participant ratings of improvement and satisfaction with treatment, and detailed information regarding participant recruitment and progress through the trial.

RESULTS

Six participants heard of the study through an advertisement (3 from radio advertisement and 3 from posters placed in hospital lobbies), and 4 were physician referrals. Nine participants were female; the mean age was 42.1 ± 7.5 years. Eight described themselves as Whites/not-Hispanic, 1 as Hispanic, and 1 as African American. The reported duration of limb pain was 4.3 ± 3.1 years. Figure 1 is a flowchart of the study. Participants had undergone the following procedures: MRI ($n = 8$), radiography, including flexion-extension views ($n = 5$); oblique view radiography ($n = 4$); CT scan, bone scintigraphy ($n = 3$ for each); and dual energy x-ray absorptiometry ($n = 2$). They had received the following treatments: physical therapy ($n = 8$), opioid agents, antiepileptic drugs ($n = 7$ for each); antidepressants, nonsteroidal anti-inflammatory drugs ($n = 6$ for each); sympathetic block ($n = 4$); trigger point injections, transcutaneous

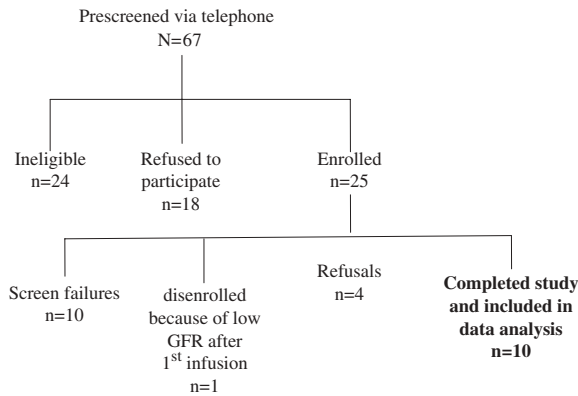


FIGURE 1. Flowchart of study participants.

electrical stimulation (n = 3 for each); and spinal cord stimulation (n = 1).

The drug was well tolerated except for the following: 8 of the 10 participants who completed the study had an acute phase reaction, that is, flu-like symptoms, within a few days of 1 of the 3 infusions. During the time around the infusion, 2 participants also reported pain in the chest wall. An eleventh participant dropped out of the study after the first infusion because the GFR went down to a value of 59. It returned to normal within a week after the infusion, however. Upon a review of additional possible contributing factors to the GFR decline, we learned that the participant increased use of over-the-counter analgesics (approximately 2 g of naproxen sodium a day) taken for a few days before the infusion, and a dose of diclofenac sodium/misoprostol combination the night before the infusion. Because of the small sample size, however, the 95% confidence interval of the incidence of this adverse event is wide, and because only 1 person experienced it, the interval includes 0.

Using the Patient Global Impression of Change, 4 participants reported that after the drug treatment their overall status was much improved, and 6 reported it was minimally improved. Regarding activity level, 3 participants reported very much improvement, 5 reported minimal improvement, and 2 reported no change. Postintervention BPI average and worst pain levels as reported during the telephone calls placed by the research coordinator improved significantly by 0.8 and 0.9 points, respectively. Similar pain changes and statistical significance levels were found for the participants' daily BPI diary entries. Table 1 shows the 9 of the 10 NPQ for which there was significant improvement.³⁴

BPI pain reports were unrelated to the difference in the amount of uptake of the bone scan tracer between the affected and unaffected limbs. Hyperalgesia to pinprick stimuli and allodynia to touch/brush, as determined by baseline and final physical examination, and rated on a 0 to 10 numeric rating scale, each showed a statistically significant improvement of 2.0 points. We collected data on the following classes of medications used for pain: opioids, nonsteroidal anti-inflammatory drugs, tramadol, acetaminophen, anticonvulsants, antidepressants, muscle relaxants, and combinations of opioids and acetaminophen. There was no statistically significant changes in the amounts of pain medications, whether we analyzed each class individually or as a variable that reflected all pain medication types taken.

Compared to those with CRPS of the foot, hand CRPS participants had statistically significant better improvements in the BPI items worst and average pain (both $P \leq 0.001$), and in the NPQ of "dull" ($P \leq 0.05$), "intense" ($P \leq 0.01$), "deep" and "time" (both $P \leq 0.001$). The differences between the groups in these improvements ranged from 1.7 to 3.3 points. Although there were only 2 participants with hand CRPS (and these were the only 2 with bilateral CRPS), for the above items each of these 2 participants had greater improvements than any of the 8 participants with foot CRPS. Figure 2 illustrates the differences in the mean changes in BPI items from baseline to postintervention between the hand and foot CRPS participants. Plotting the data for the above NPQ items produces a graph of similar appearance.

DISCUSSION

In this open-label trial, there were transitory flu-like symptoms. In addition 1 participant was disenrolled because of a decrease in GFR to below 80. The significance of this event, however, is problematic because of the small study sample size, the fact that only 1 participant experienced this event, and because shortly before the day of the first infusion the participant had increased the use of medications that could have contributed to the GFR change. Otherwise, ibandronate was well tolerated and was associated with improvements in many aspects of CRPS, that is, in average and worst pain ratings, hyperalgesia and allodynia, and the NPQ of "unpleasant," "sensitive," "deep," "intense," "surface," "hot," "cold," "sharp," and "dull". Of special interest, compared to those with foot CRPS, those with hand CRPS showed much greater improvement in BPI and NPQ ratings. Although the impressive statistical findings are surprising in light of the fact that only 2 of the 10

TABLE 1. Statistically Significant Changes in Scores for Neuropathic Pain Qualities From Baseline to Postintervention (for all $P \leq 0.05$)

Neuropathic Pain Quality	Dull	Sharp	Cold	Surface	Intense	Hot	Unpleasant	Deep	Sensitive
Estimate (standard error)	-1.06 (0.40)	-0.67 (0.24)	-0.80 (0.28)	-0.77 (0.24)	-0.89 (0.26)	-1.66 (0.47)	-0.92 (0.25)	-1.13 (0.31)	-1.63 (0.40)

Estimate = (average of the weekly averages for weeks 5-7) - (average of the weekly averages for weeks 1-2).

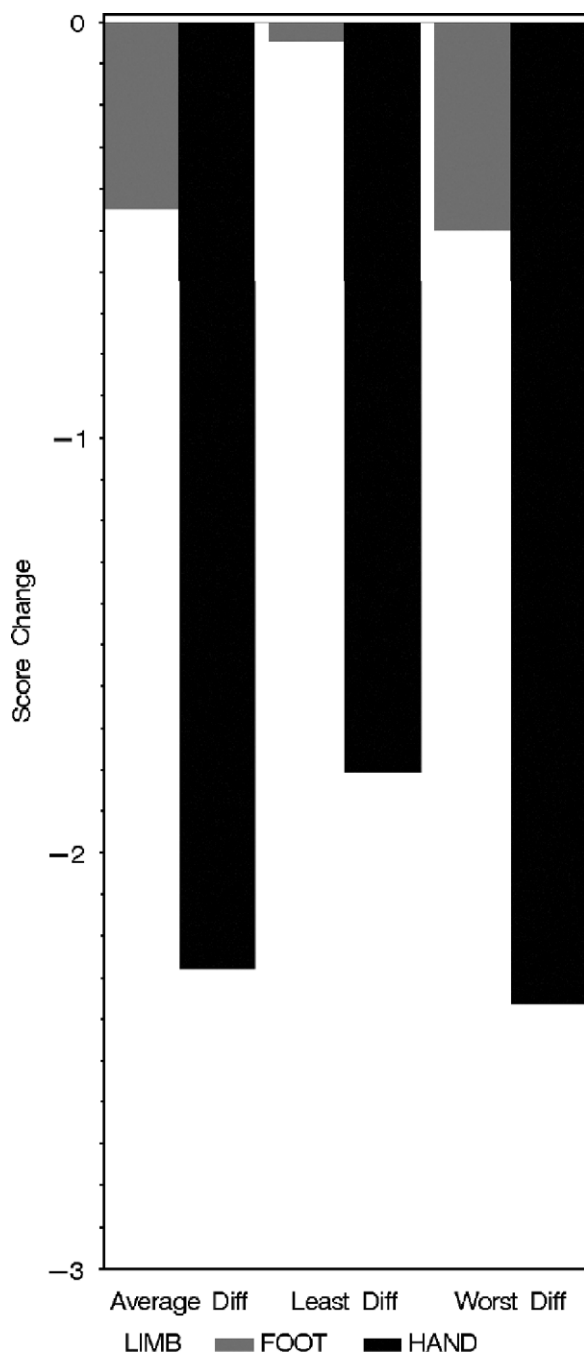


FIGURE 2. Comparison of the “hand” complex regional pain syndrome (CRPS) participants ($n=2$) to the “foot” CRPS participants ($n=8$) with respect to mean changes (postintervention – preintervention) in average, least, and worst BPI ratings. Average diff indicates mean difference (change from baseline) in BPI average pain scores; least diff, mean difference (change from baseline) in BPI least pain scores; worst diff, mean difference (change from baseline) in BPI worst pain scores.

participants had hand CRPS, credibility is supported by the dramatic improvements in *each* of the participants with hand CRPS compared with much less impressive

improvements in *each* of the foot CRPS participants for many of the items in these scales. The greater responsiveness of hand CRPS to treatment was also found with electrical nerve stimulation.³ One might speculate that the difference between hand and foot responsiveness to treatment may be attributable to the greater mass of the foot, which might imply a “dilution” of the treatment in the foot compared with the hand. Although the lack of a placebo group in our trial precludes definitive conclusions, the differences noted between hand and foot CRPS suggest that our findings are real, as (1) there is no apparent reason for a placebo effect to be so dramatically greater for the hand than the foot, and (2) the better outcomes in hand CRPS in our trial is consistent with the reports of others.

When we embarked upon this study, we recognized that its limitations included the small sample size and the lack of a placebo group. The possibility of the specific placebo effect of regression to the mean, however, was minimized by our 2-week baseline period, and the requirement that painful symptoms be maintained throughout this period. The surprising finding of the difference in treatment responsiveness between hand and foot CRPS compounded the small sample size limitation. Given the costs and challenges associated with a large trial in this condition we conducted this pilot trial, as we hoped that despite its apparent limitations, it could assess the feasibility of study procedures, the within-group variability, and whether there is appropriate evidence regarding the safety and efficacy of the drug that would justify a larger, placebo-controlled trial.

As the treatment of CRPS is a difficult one, our findings of a possible treatment that is effective in even a minority of patients is useful. Our data support the justification of a randomized, double-blind, placebo-controlled trial of ibandronate that should allow for a definitive determination of analgesic efficacy, and that closely monitors possible adverse renal effects. Because of the dramatic results seen with hand CRPS participants in our study, the consistency of our findings of better treatment outcomes of the hand with those of others, and the greater prevalence of hand CRPS as compared with foot CRPS, it seems that the likelihood of finding clinically significant improvement would be greatest for a trial limited to those with hand CRPS.

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