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Original Research Article

Predictors of Responsiveness to Bisphosphonate Treatment in Patients with Complex Regional Pain Syndrome Type I: A Retrospective Chart Analysis

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Abstract

Objective. The aim of this study was to assess whether the effectiveness of bisphosphonate infusion in patients with complex regional pain syndrome type I (CRPS-I) is influenced by variables related to patient and/or disease characteristics.

Methods. This is a retrospective analysis of patients referred in the last five years to our rheumatologic tertiary care center, all fulfilling the Budapest CRPS-I diagnostic criteria and treated with three different bisphosphonate schedules (clodronate, pamidronate, and neridronate). For every subject, demographic and clinical variables were retrieved and retrospectively analyzed. We identified variables that independently influenced the therapeutic outcome of patients by a logistic regression analysis. For exploratory purposes, the effectiveness of the different bisphosphonate treatments employed was compared.

Results. Among the 194 patients included in the analysis, the overall therapeutic response rate was 71.6%. Logistic regression analysis showed that the independent predictive variables for therapeutic effectiveness were disease duration (odds ratio [OR] = 0.83, 95% confidence interval [CI] = 0.72–0.96 for a one-month increment), fracture as a predisposing event (OR = 3.23, 95% CI = 1.29–8.03), and "warm" disease subtype (OR = 4.88, 95% CI = 1.57–15.20). These variables were found to influence the odds of responsiveness when analyzed together with age at onset, gender, and disease localization. No significant difference in therapeutic effectiveness was found by comparing the three different bisphosphonate schedules employed.

Conclusion. Early disease, fracture as a predisposing event, and "warm" disease subtype are predictors of responsiveness to bisphosphonate treatment in patients with CRPS-I.

Key Words. CRPS; Reflex Sympathetic Dystrophy; Treatment; Bisphosphonate; Outcome

Introduction

Complex regional pain syndrome type I (CRPS-I) is a severe disabling disease in which long-lasting pain is the cardinal feature, together with other hallmarks of this disease including swelling, vasomotor instability, and abnormal sensory findings. The rate of patients showing a progression over time toward a permanent functional impairment rather than those who spontaneously resolve remains an issue still debated [1]. In recent years, although the understanding of the different pathogenic mechanisms of CRPS-I has improved and a multitude of interventions have been proposed and are in use,

there has been limited evidence for the effectiveness of any therapeutic modality, no strong consensus exists regarding the optimal management of the syndrome, and a shared therapeutic algorithm has yet to be established. Current treatment interventions include analgesics and anti-inflammatory drugs, opioids, calcitonin, anticonvulsants, antidepressants, local and intravenous (i.v.) anesthetics, transcutaneous electrical nerve stimulation (TENS), occupational therapy, physiotherapy, rehabilitation medicine, and psychological therapies. Several guidelines for the management of CRPS have been published [2–5], but the critical lack of high-quality evidence for the effectiveness of most therapies for CRPS limits the development of an evidence-based approach in managing the condition [2].

Over the past two decades, bisphosphonate administration appears to be a therapeutic strategy that has collected convincing evidence, with five randomized controlled trials (RCTs) all showing good results in controlling pain, local inflammation, and functional disability [6–10], improving the quality of life of patients with CRPS-I. Nevertheless, as reported in some meta-analyses, reviews, and institutional guidelines, there are still concerns about widespread use of these drugs, partly justified by some issues that remain unresolved. For example, these trials employed four different drugs (alendronate, clodronate, pamidronate, and neridronate) using two different routes of administration (oral or i.v.); all but one included only patients with early disease and bone involvement, such as a local osteoporosis demonstrated by x-rays or an increased uptake showed by bone scan [6,7,9,10]. Also, the fear of adverse events associated with bisphosphonate administration (e.g., osteonecrosis of the jaw, atypical fractures) possibly contributes to their underuse.

Thus, even if combining the results of these studies suggests good evidence for the efficacy of bisphosphonates in CRPS-I, some questions remain. For example, whether there are subgroups of patients who may better respond to bisphosphonate treatment has yet to be established.

As a contribution toward answering these questions, we retrospectively collected and analyzed the data of patients with CRPS-I treated with i.v. infusions of various bisphosphonates during the last five years at a tertiary rheumatology care center in order to evaluate if variables related to patient and/or disease and the type of drug employed can influence the treatment outcome.

Methods

Study Design

We performed a retrospective data analysis of patients with a diagnosis of CRPS-I referred to our unit in the last five years for treatment with bisphosphonate infusions.

Patients

All patients referred to the day hospital of our institute for treatment with a course of bisphosphonate infusion from January 2009 to December 2013 were identified from the hospital database that collects administrative information. The results were matched with diagnostic code or free-text data indicating a potential diagnosis of CRPS-I, and medical records of the patients were retrieved. All patients came from the orthopedic and rheumatology outpatient services and the emergency department of our hospital, a tertiary care center devoted to bone and joint diseases.

All medical records of patients were reviewed by two of the authors (MM and FR), who had not been involved in the clinical management of the patients, and data were extracted following a predefined data extraction form. The first step (Figure 1) was to exclude patients with diseases that were possibly not CRPS-I, such as regional migratory osteoporosis, post-traumatic bone marrow edema, postarthroscopic bone marrow edema, etc. Among the remaining subjects, patients were included in this study only if: 1) their medical records confirmed that all symptoms and signs included in the Budapest 2007 criteria (now also known as the new International Association for the Study of Pain [IASP] criteria for CRPS) [11] had been assessed and checked before

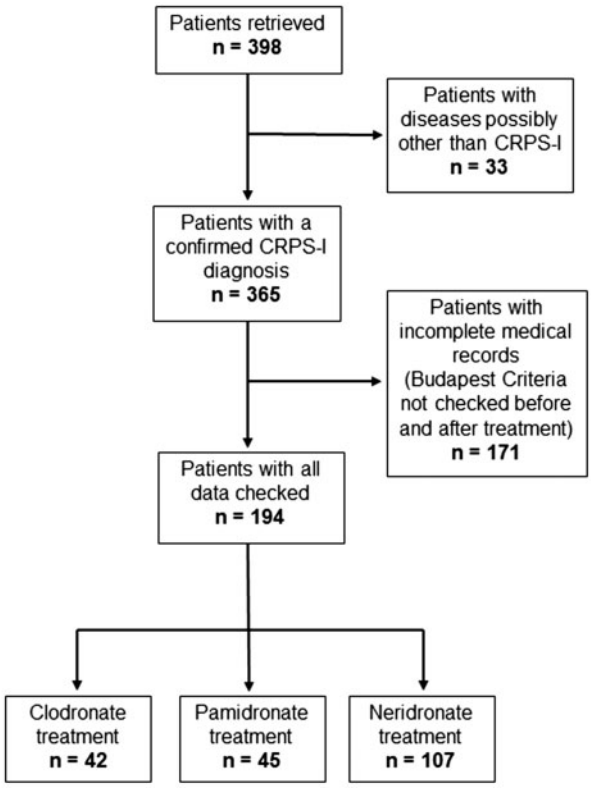

Figure 1 Flowchart illustrating the disposition of patients.

and after treatment; 2) no treatments for CRPS-I, other than anti-inflammatory, or analgesic drugs were administered; 3) other clinical variables included in the data extraction form were available (i.e., precipitating event, pain duration, subtype of disease). The final sample included only patients in whom at the first observation the IASP criteria for research purpose were fulfilled (four symptoms and two or more signs), as confirmed by data reported in clinical records. No patients involved in previous RCT studies were included in this sample.

Treatments

All patients were treated with an i.v. infusion of a bisphosphonate. From January 2009 to April 2010, patients followed a clodronate infusion course according to an already published schedule (300 mg every day for 10 consecutive days) [7]. In an attempt to shorten the therapeutic course, from May 2010 to August 2011, patients were treated with pamidronate 60 mg infusions given four times every third day, in agreement with some open studies [12,13], and an RCT [8], all showing good results in the treatment of CRPS-I. From September 2011 to December 2013, patients were treated with neridronate 100 mg every third day for four occasions [10]. After the bisphosphonate infusions, all patients underwent physiotherapeutic treatment to improve the functional restoration of the affected limb. Before the treatment, an extensive laboratory assessment was performed in all patients to exclude diseases or other conditions that would otherwise account for the degree of pain and clinical signs. Women of childbearing potential were asked to have a negative pregnancy test before the treatment. Informed consent to be treated with bisphosphonate infusions was obtained from each patient.

Data Collection

Demographic data were collected for every patient, together with some disease-related variables such as disease duration, localization of the CRPS-I, potential precipitating events, and previous occurrence of CRPS-I.

At the day of the first infusion and at the following clinical evaluation, scheduled 40 days after the last infusion (day 36–54), all symptoms and signs included in the Budapest 2007 criteria were checked. Allodynia was defined as pain evoked by a light stroking with a small brush and hyperalgesia as pain evoked by a pinprick at the affected site but not at the unaffected site. Clinical subtype, i.e., a "warm" or "cold" phase of the disease, was defined at baseline by assessing the difference in temperature between the involved limb and the contralateral one.

Outcome Assessment

At the following clinical evaluation, patients were asked to report the overall efficacy of the treatment in descriptive terms by a four-point verbal score for pain relief (efficacy verbal score [EVS]), already employed in a previous study [7], scored as 0 = no improvement/worsening; 1 = slight/minor improvement of pain; 2 = significant improvement of pain; 3 = excellent improvement/no pain. When evaluated at the last visit, a patient was defined as a "responder" if all the following criteria were simultaneously met: 1) CRPS-I could no longer be diagnosed accordingly with the Budapest 2007 criteria for clinical purpose (three symptoms and two signs); 2) the EVS was rated ≥ 2; and 3) the patient had stopped taking analgesics or other drugs for controlling pain.

Statistical Analysis

Baseline variables were tested for normality of the distribution with Shapiro-Wilks test. Data are reported as means ± standard deviation (SD) in the case of a normal distribution or medians and interquartile range (IQR) in the case of a non-normal distribution. Comparisons were performed by Student's t-test for unpaired data for variables normally distributed, and Mann-Whitney tests were performed when non-normally distributed variables were analyzed. The Fisher's exact test was applied to analyze categorical variables with the Bonferroni correction when more than two variables were analyzed.

To investigate the effect of each assessed variable on the therapeutic effectiveness of bisphosphonates treatment, a logistic regression analysis was performed. All the variables that were statistically significant in univariate analysis ($P < 0.05$) by comparing responder with nonresponder patients, together with other variables not showing a significant difference but deemed of clinical relevance as possible determinants of therapeutic response (age, gender, site of disease), were entered in the model. To explore the effectiveness of the three therapeutic schedules employed, in a further logistic regression model, the different treatments were entered together with all the variables included in the first model using as reference the treatment with the lowest percentage of patients who were responsive, that is, clodronate.

All the statistical tests were two-sided at the 5% level and performed using SPSS software (v. 17.0, SPSS, Inc., Chicago, IL, USA).

Results

The flow chart illustrating the disposition of patients is depicted in Figure 1, and the baseline values of demographic and clinical variables of 194 patients representing the study sample are displayed in Table 1. The mean age at CRPS-I diagnosis was 57.1 ± 12.9 years, with a greater number of females (122, 62.9%) and a mean age at diagnosis that did not differ between males and females ($P = 0.28$). The disease duration showed a median value of four months (IQR= 2–6). Lower extremity (foot) was more often affected than upper limb (hand), with 119 patients showing a foot disease

Table 1 Demographic and baseline clinical findings in patients with CRPS-I treated with bisphosphonates

Parameter	Patients (N = 194)
Baseline characteristics	
Age, y, mean ± SD	57.1 ± 12.9
Sex, male/female, N (%)	72 (37.1)/122 (62. 9)
Disease duration, mo, median, IQR	4 (2–6)
Previous CRPS-I, N (%)	13 (6.7)
Disease subtype, warm/cold/NA, N (%)	142 (73.2)/31 (16.0)/ 21 (10.8)
Localization, N (%)	
Upper limb	75 (38.7)
Lower limb	119 (61.3)
Predisposing event, N (%)	
Fracture	83 (42.8)
Trauma	43 (22.1)
Surgery	28 (14.4)
Others	11 (5.7)
Unknown	29 (14.9)

CRPS-I = complex regional pain syndrome type I; IQR = interquartile range; NA = not applicable (swinging form or not reported).

(61.3%) and 75 patients showing a hand disease (38.7%). Thirteen patients (6.7%) reported a previous diagnosis of CRPS-I that more often had involved another site (10 cases).

The most common precipitating event was a fracture, reported by 83 patients (42.8%), followed by a trauma without fracture (contusion/sprain), which was identified as the triggering event by 43 patients (22.1%). Twenty-eight patients (14.4%) developed the disease following surgery. For 11 patients (5.7%), the medical record reported several events possibly recognized as a predisposing event (myocardial infarction, hemiparesis, herpes zoster, electrocution, etc.). Finally, in 29 cases (14.9%), no precipitating event was identified. In 142 patients (73.2%), CRPS-I was assessed by a physician as "warm," whereas in 31 cases (16.0%) the disease was described as "cold." In 21 patients (10.8%), this classification was not applicable because of a swing between a warm to cold type, and this feature was not reported in the medical records. No difference was found between the two disease subtypes (age, gender, predisposing event), but the disease duration was longer in the cold subtype (median = 5, interquartile range [IQR] = 4–8; vs median = 3, IQR = 2–5; $P = 0.001$).

The total sample was treated with one of three different bisphosphonate regimens: clodronate in 42 patients (21.6%), pamidronate in 45 patients (23.2%), and neridronate in 107 patients (55.2%). Overall, 139 patients (71.6%) were considered "responders," while 55 patients (28.4%) were defined as "nonresponders." The percentage of responders was, respectively, 64% (27 patients) for clodronate, 71% (32 patients) for pamidronate, and 75% (80 patients) for neridronate (Figure 2). The comparison among the three different treatments (Chi-squared test, adjusting the P values with Bonferroni's correction) did not show significant differences in responsiveness among the three treatment regimens ($P = 0.27$).

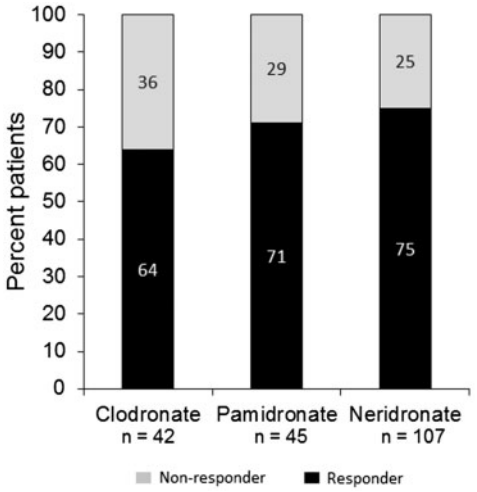

Figure 2 Responder rates of CRPS-I patients treated with different bisphosphonate schedules. No significant difference was found among the treatments.

The comparisons of clinical variables between responder and nonresponder patients are given in Table 2. No difference was found in age at diagnosis, gender, or disease localization. Instead, responder patients showed a disease duration significantly shorter in comparison with nonresponders (median = 3 months, IQR = 2–5; vs median = 5 months, IQR = 3–8; $P = 0.0001$). In the responder group, a warm disease subtype was more frequent (79.8%) relative to nonresponders (56.4%, $P = 0.0001$); conversely, a cold disease was more frequently observed in nonresponder patients (32.7%) than in responder patients (9.3%, $P < 0.05$). By considering the predisposing event, the greatest percentage of responders was found in patients who developed a CRPS-I following a fracture (69 out of 83, 83.1%). This result was significantly greater in comparison with the responder percentage observed in patients in whom the disease was triggered by all other predisposing events ($P = 0.005$) and with the responder percentages observed in CRPS-I following a trauma without fracture ($P = 0.01$) or following surgery ($P = 0.008$).

In Table 3, results from the logistic analyses are reported; in these models, the outcome variable was the therapeutic responsiveness (responder vs nonresponder). The disease duration, a warm disease subtype, and fracture as a predisposing event were

Table 2 Comparisons of demographic and clinical variables between 194 patients with CRPS-I responding/not responding to bisphosphonate treatment

	Responders (N = 139)	Nonresponders (N = 55)	Responder, %
Characteristics			
Age, y, mean ± SD	57.3 ± 12.3	56.5 ± 14.3	
Sex, male/female, N	50/89	22/33	
Disease duration, mo, median (IQR)	3 (2–5)	5 (3–8)*	
Disease localization, lower limb/upper limb, N	83/56	36/19	
Subtype, warm/cold/NA, N	111/13/15	31/18/6*	
Predisposing event, N			
Fracture	69	14	83.1†
Trauma	27	16	62.8‡
Surgery	16	12	57.1§
Others	7	4	63.6
Unknown	20	9	69.0

*$P = 0.0001$ vs responders.
†$P = 0.005$ for fracture vs all other predisposing events.
‡$P = 0.01$ for fracture vs trauma.
§$P = 0.008$ for fracture vs surgery.
CRPS-I = complex regional pain syndrome type I; IQR = interquartile range; NA = not applicable (swinging form and not reported).

significant predictors of responsiveness to bisphosphonate treatment, while age, sex, and disease localization did not influence the outcome. When the different drugs were examined together with the variables included in the first analysis (Model 2), no significant odds ratio for responsiveness was found for a specific treatment. Consistent with the results of the previous model, the variables predictive of a positive outcome were the same, with little difference in the estimated odds.

No patients complained of serious drug-related adverse events (osteonecrosis of the jaw or atypical fractures). Six patients treated with clodronate showed only a moderate hypocalcemia (serum calcium lower than 8.8 mg/dl) without clinical symptoms and not requiring treatment. As expected, the most common side effect in patients treated with an aminobisphosphonate (pamidronate and neridronate) was an acute phase reaction (polyarthralgia and/or fever). This adverse event was reported in 16 patients treated with pamidronate (35.5%) and in 32 patients treated with neridronate (29.9%). These symptoms disappeared in two days after the first infusion, but in 11 patients required acetaminophen treatment 1g t.i.d. for one day. One patient treated with neridronate developed an acute anterior uveitis after the fourth infusion that required topical treatment with steroid and atropine; remission was complete without sequelae.

Discussion

The results of this study suggest that patients affected by CRPS-I with an early disease, a warm disease subtype, and fracture as a predisposing event could be more responsive to intravenous bisphosphonate treatment, regardless of the age, gender, and site of disease.

With the exclusion of the localization of disease (a more frequent lower limb involvement), the sample investigated in this study showed an age distribution, a male-to-female ratio, and types and prevalence of precipitating events similar to those reported in the largest-to-date epidemiological study carried out in the Netherlands [14], suggesting that our sample is quite similar to that observed in a population-based study. The short disease duration (median = 4 months, IQR = 2–6 months) is probably explained by the operating conditions of our department, located in the same hospital in which many orthopedic departments manage patients referred for trauma or fracture and where elective hand and foot surgery is performed daily.

Although the methodological approach in recruiting and evaluating the final sample led to the exclusion of a large number of cases, this strategy was chosen in the attempt to ensure the highest level of diagnostic specificity of the included patients, that is, 0.79 [11], and the highest level of sensitivity on residual signs and symptoms when patients were evaluated at the end of the study with the aim to identify those with a true disease remission (0.99) [11]. In this regard, we used a four-point verbal score for pain relief that, although being a less sensitive tool than absolute pain values assessed by a numerical rating scale, is more focused on pain changes before and after the treatment.

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