Long-term effectiveness and predictors of bisphosphonate treatment in type I complex regional pain syndrome

G. Adami¹, A. Fassio¹, M. Rossini¹, F. Montanari¹, S. Manfrè², G. Bonasera¹, D. Bertelle¹, C. Benini¹, O. Viapiana¹, V. Braga³, D. Gatti¹

¹Rheumatology Unit, University of Verona; ²Pharmacy Service, University of Verona Hospital Trust; ³ULSS 9, Verona, Italy.

Abstract

Objective

Complex regional pain syndrome (CRPS) is a painful disease that leads to chronic pain and disability. Bisphosphonates are largely used in the real-life for the treatment of CRPS, but data on long-term effectiveness and its predictors are lacking.

Methods

We conducted a longitudinal observational study on patients with type I CRPS treated with IV neridronate (100 mg on 4 occasions). Clinical and demographic characteristics were collected at baseline, after 3 months (M3) and after 12 months (M12). Multivariable logistic regression was employed to determine the factors associated with long-term response to treatment.

Results

103 patients with type I CRPS treated with IV neridronate were included in the study. Mean VAS pain at baseline was 79.1 mm and decreased significantly at M3 (-45.9 mm, 95% CI 40.1 to 51.8) and M12 (-61.6 mm, 95% CI 55.3 to 67.9). Hyperalgesia and allodynia resolved in 84.3% and 88.1% of patients at M12. Loss of motion resolved in 53.5% of patients. The predictors of excellent response were gender (male better), predisposing event to CRPS (no event being better than any predisposing event), site of CRPS (lower limb being better), and early response at M3 on VAS pain (2.5 times the chance of being excellent responder every 10 mm decrease).

Conclusion

In this real-life study neridronate was associated with rapid and progressive improvement of symptoms of CRPS which was maintained up to 3 years of follow-up. The predictors of excellent response were early response, lower limb localisation, absence of predisposing events and male gender.

Key words
Complex regional pain syndrome type I, algodystrophy, neridronate, bisphosphonate
Introduction
Complex regional pain syndrome (CRPS) is severely painful disease of peripheral limbs characterised by focal osteoporosis and painful symptoms (hyperalgiesia, allodynia, oedema, and atrophy) (1). CRPS is generally classified into two types: type I, which typically occurs after a trauma or an injury (fracture more commonly) in the affected limb, and type II (causalgia), which occurs after a peripheral nerve damage (2). Even if some patients might have a spontaneous reduction in pain over the time, CRPS, if not treated, frequently lead to disabling symptoms, such as skin atrophy and muscle contracture (3-5). For this reason, treatment should be started as soon as feasible and should be aimed at both early pain reduction and long-term disability prevention. Bisphosphonates have been largely utilised for the treatment of CRPS. A recent meta-analysis showed that intravenous (IV) bisphosphonates represent the most effective treatments for type I CRPS (6). In addition, IV bisphosphonates are generally safe and well tolerated, apart from the acute phase reaction (APR) that happens in slightly less than one third of patients (7). In contrast, other treatments for CRPS are not as efficacious as bisphosphonates and/or are burdened by severe adverse effects or excessive costs (e.g. ketamine) (8, 9). Neridronate, a nitrogen containing bisphosphonate, is approved for the treatment of CRPS in Italy at the dose of 400 mg IV in 4 days. At the dose of 50 mg/month IM, neridronate has been shown to reduce serum CTX by more than 70% within a short period (10). It has also been shown that 25 mg/month of IM neridronate roughly equals to 70 mg/week of PO alendronate in terms of bone mineral density (BMD) variations over 1 year treatment (10) and that 100 mg of IV neridronate equals to 90 mg of EV pamidronate in terms of potency (11, 12). This indicates that 400 mg IV of neridronate roughly equals to 4,500 mg of PO alendronate and 360 mg of IV pamidronate.

The aim of the present study is to describe the real-life effectiveness of IV neridronate on both pain and long-term disability in patients with type I CRPS. Secondary objective is to determine the factors associated with long-term disability and response to treatment.

Methods
Study population
We conducted a longitudinal, observational study on patients with CRPS type I treated with IV neridronate (100 mg on 4 occasions, 400 mg total dose). We collected demographic and clinical data of patients with type I CRPS from the medical records of our outpatient clinic (Rheumatology Unit of the University of Verona, Italy) between January 2015 and January 2021. The following clinical and demographic parameters were collected: gender, age, weight, height, subtype of CRPS (warm or cold), predisposing event to CRPS, site of CRPS, smoking status, alcohol intake, comorbidities. Patients were assessed, as per clinical practice, at baseline and after 3 (M3) and 12 months (M12) from first infusion. Patients were also contacted via telephone between January 2022 and June 2022 for follow-up visit (last visit). We included consecutive patients with: 1) diagnosis of CRPS type I classified according to Budapest diagnostic clinical criteria (13), 2) treated with IV neridronate 400 mg within 4 months from symptoms onset, 3) patients who agreed to participate to the REUMABANK protocol and who signed informed consent.

For the enrolment in the present study, we also established the following exclusion criteria: patients with moderate or severe chronic kidney disease (CKD) [defined as estimated glomerular filtration rate (eGFR) <45 ml/min as measured by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation], patients receiving renal replacement therapy, kidney transplant receivers, patients with active cancer, patients receiving anti-hormonal treatment for breast or prostate cancer, and patients affected by other conditions known to affect the bone.

Outcomes assessment
Primary outcomes of the study were VAS pain reduction at M3 and M12. Pain was measured using a visual analog score (VAS) in mm (0[anchor]–
Secondary outcomes were: presence or absence of hyperalgesia (tested as pain to light stroking with a small brush scored by the direct comparison with the contralateral unaffected limb); presence or absence of hyperalgesia (stimulus evoked by a pinprick being perceived as more painful or lasting longer than the duration of the stimulus in the affected limb compared with the contralateral limb); oedema severity (local oedema scored as 0 = none, 1 = mild, 2 = moderate, 3 = severe, evaluated at ankle and midfoot level for the foot involvement, wrist, center of hand dorsum and finger for hand involvement scored by the direct comparison with the contralateral unaffected limb); loss of motion severity (0 = none, 1 = mild, 2 = moderate, 3 = severe, evaluated at ankle and finger joints for foot involvement and wrist and finger joints for hand involvement scored by the direct comparison with the contralateral unaffected limb).

Definition of responders and early responders
We determined “responders” and “early responders” to be those who achieved a ≥50% VAS score reduction between (baseline/pretreatment) and M12 (responders) and M3 (early responders). Reduction of VAS pain below this threshold has been suggested as the minimally clinically important difference (MCID) in CRPS type I (14).

Definition of excellent responders
We defined “excellent responders” based on full recovery from loss of motion at M12 AND VAS pain at M12 less than 20 mm (excellent responders were those patients with mild/moderate/severe loss of motion at baseline who had none loss of motion at M12 AND VAS pain less than 20 mm).

Factors associated with excellent response to treatment
We determined the predictors of excellent response of patients with CRPS treated with IV neridronate. We conducted a binary logistic regression to determine the predictors of excellent response. Covariates included in the analysis were early VAS pain absolute reduction (VAS pain reduction from pre-treatment to M3), gender, age, BMI, predisposing event to CRPS (fracture vs. orthopaedic surgery vs. trauma without fracture vs. no event), site of CRPS, and VAS pain at baseline. Our aim was also to investigate the best threshold of VAS pain reduction early during treatment course that predicted excellent response. We then categorised early pain change score as a series of dichotomous variables: <20% reduction versus ≥20 reduction; <30% reduction versus ≥30 reduction; <40% reduction versus ≥40 reduction or <50% reduction versus ≥50; <60% reduction versus ≥60 reduction; <70% reduction versus ≥70 reduction; <80% reduction versus ≥80 reduction. Several logistic models were fit. The aim of these models was to compare models’ characteristics (discrimination and calibration): [model A = 20% threshold]; [model B = 30% threshold]; [model C = 40% threshold]; [model D = 50% threshold]; [model E = 60% threshold]; [model F = 70% threshold]; [model G = 80% threshold]). For discrimination we employed the area under the receiver operating characteristic curve (AUCROC), measured as the c-statistic (15), which is obtained from the multivariable logistic model. C-statistic of 0.5 shows randomly guessing model c-statistic of 1.0 shows perfect discrimination (15). We employed the Akaike Information Criterion (AIC), a goodness of fit test to assess calibration.

Group comparisons were performed with t-student and Mann-Whitney U-tests (for normally and non-normally distributed continuous variables, respectively). Wilcoxon’s Signed Rank test was used to test changes over time in categorical variables. Mixed-effect analysis for multiple comparisons and repeated measure (MMRM) was employed to determine the effect of treatment on VAS pain. Differences were considered significant at p<0.05.

All statistical analyses were performed using SPSS v. 26 (SPSS, Inc., Chicago, IL, USA) and GraphPad Prism 9.3.1 (GraphPad Software, San Diego, CA, USA). The study was conducted according to the protocol REUMABANK approved by the University of Verona local Ethics Committee, in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Results
Study population
103 patients (78 female, 75.7%) were included in the study. Mean age was 55.7±13.1 years, the majority had a fracture as predisposing event to CRPS and more than 70% had CRPS of the lower limb. All patients were followed-up with an in-person visit at M3, 97 (94.2%) at M12 and 78 (75.7%) were contacted at a median follow-up of 3.6 years (IQR 2.5–5.2). The baseline characteristics of the study population are reported in Table I. 86 (83.5%) had
Hyperalgesia at baseline, 61 (59.2%) had allodynia at baseline, 92 (89.3%) presented any grade of oedema (mild/moderate/severe) at baseline and 102 (99.0%) reported any grade of loss of motion (mild/moderate/severe) of the affected limb at baseline.

Treatment response
VAS pain decreased significantly from an average value of 79.1 mm to 33.1 mm at M3 (-45.9 mm, 95% CI 40.1 to 51.8, -58.1% reduction) and to 17.5 mm at M12 (-61.6 mm, 95% CI 55.3 to 67.9, -77.9% reduction); p-values of the MMRM analysis are given in Figure 1. 72 (69.9% of 103) patients were responders (≥50% VAS score reduction) at M3. 83 (89.2% of 93) patients were responders at M12. A total of 72 (73.5% of 98) patients attained VAS pain ≤20 mm at M12. Most of the symptoms improved during the follow-up (Fig. 2). Hyperalgesia and allodynia resolved in 84.3% and 88.1% of patients at M12. Oedema severity improved in almost all patients and resolved in 61.8%. Loss of motion resolved in slightly more than half of patients (53.5%: “excellent” responders). Twenty-eight patients (27.2%) reported an APR within 72h from first neridronate infusion. No unsolicited severe adverse event related to neridronate were reported in the follow-up.

Predictors of excellent response to IV neridronate
VAS pain at M3 and M12 was significantly lower in excellent responders (mean decrease 55.6 mm [95% CI 47.5 to 63.8] and 69.8 mm [95% CI 62.3 to 77.3], respectively) compared non-excellent responders (mean decrease 36.3 mm [95% CI 29.0 to 43.6] and 51.7 mm [95% CI 41.9 to 61.4]) (Fig. 3). Predictors of excellent response are presented in Table II (binary logistic regression analysis). The predictors of excellent response (loss of motion resolved at M12) were: absence of predisposing event to CRPS (no predisposing event being better than any predisposing event), site of CRPS (lower limb being better than upper limb), sex (male being better than female) and greater early VAS pain absolute reduction at M3 (2.5-fold higher chance of being excellent responder every 10 mm decrease at M3).

Discussion
We conducted an observational longitudinal study on patients affected by type I CRPS treated with IV neridronate, an amino bisphosphonate approved for treatment of CRPS in Italy. We found that neridronate was associated with a rapid reduction of pain and symptoms of CRPS. Interestingly, pain significantly improved also between M3 and M12. More importantly, approximately half of the patients attained long-term and persistent recovery from loss of motion of the affected limb (excellent responders). Our short-term results are largely comparable with randomised placebo-controlled trials (RCTs) of neridronate in CRPS (16, 17). In the RCT with IV neridronate (400 mg to-
tal dose) versus placebo published in 2013 (16), VAS pain decreased by 47 mm at 40 days, in our study VAS pain decreased by 46 mm at M3. Similar proportion of patients obtained ≥50% VAS score in the short-term (73.2% in the IV neridronate RCT vs. 69.9% in our real-life study). Again, in the RCT with intramuscular (IM) neridronate (400 mg total dose) (17) short-term results were in line with our findings. Populations’ characteristics of the studies were remarkably similar. The proportion of female patients were similar across the studies. Again, symptoms of the populations were comparable (e.g. allodynia was present in 83% of our patients, 60.9% in the RCT with IV neridronate and 80% in the RCT with IM neridronate), as well as the pain level at baseline (VAS pain around 70 to 75 mm on average). Other amino and non-amino bisphosphonates have been proven efficacious in type I CRPS as confirmed by a recent meta-analysis (6).

Approximately 50% of patients were excellent responders (i.e. full recovery from loss of motion) and the factors associated with response were: the precipitating event (no predisposing event being better than any predisposing event), site of CRPS (lower limb being better than upper limb), sex (male being better than female) and greater VAS pain reduction. Varenna et al. also conducted a short-term (40 days of follow-up) observational study on the effectiveness of various bisphosphonates (18). The authors found that fractures and shorter disease duration were associated with good response to bisphosphonates in terms of pain reduction. However, Varenna and colleagues defined the responsiveness to treatment based on pain level and analgesic use. In contrast, besides the definition used by Varenna and colleagues, we used a more stringent, and arguably more clinically relevant, definition of responders (“excellent response”), which is based on loss of motion, and we studied such long-term response at a median follow-up time of 3.6 years. The IM neridronate RCT extension was published in December 2022. In this study, the patients in the placebo arm were subsequently treated with neridronate IV at the end of the double-blind phase of the study and followed up to month 12. Overall, the authors showed a similar proportion of patients responding to neridronate (both IV and IM treatment) at month 12 compared to our real-life experience (88% vs. 89.2%) (19).

Our findings on long-term disability are biologically and clinically plausible. Fractures, especially involving the upper limb, might lead to loss of motion (20, 21), which, might be only partially related to CRPS. However, we found that early VAS pain reduction was significantly and strongly associated to lower risk of loss of motion at 12 months, implying that pain related to CRPS itself is also a major determinant of disability and patients should be treated early and aggressively with efficacious medications. We also aimed to find the best threshold for early response on pain that could better predict loss of motion in the long-term. Using an iterative process, we found that the best threshold...
of VAS pain reduction at M3, in terms of prediction ability, was 70% (model F), no further improvement was seen with greater VAS pain reduction. In other words, patients with >70% VAS reduction at M3 were more likely to respond also in terms of lower risk of loss of motion at M12.

In two high-quality randomised clinical trials on CRPS-I, the adopted definition of “responder” underpinned a 50% VAS pain reduction (16, 17). This definition was previously formulated based on Global Perceived Effect (GPE) for pain relief (14). We hereby propose a further one, related to functional disability (i.e. excellent response: loss of motion resolved at M12). Ultimately, we set the threshold for the early satisfactory percentage of VAS pain reduction at 70%. Such a result might have immediate clinical fallouts. As an example, as concerns prognosis or for the consideration of a possible re-treatment.

Our study has strengths and limitations. To our knowledge this is the first long-term real-life study on patients with type I CRPS treated with IV bisphosphonates. The most important strength regards the long-term follow-up and quite large sample size. We included patients with type I CPRS (almost all with warm sub-type) treated early after symptoms onset, with characteristics that were fairly comparable with other RTCs. However, although we conducted the study on the most common form of CRPS our results are not generalisable to all patients (e.g. type II CPRS and type I CPRS cold sub-type). Since disease duration has been associated with treatment response to bisphosphonates (18) we cannot speculate on patients with disease duration longer than 4 months.

In conclusion, neridronate treatment was associated with rapid and sustained improvement of symptoms of type I CRPS. Predisposing event, affected site, gender, and early response to treatment were predictors of long-term response to treatment.

Key messages
- In this real-life analysis, neridronate treatment was associated with rapid and progressive improvement of symptoms of CRPS type I.
- Improvement of symptoms was maintained up to 3 years of follow-up.
- The predictors of excellent response were early response, lower limb localisation, absence of predisposing events and male gender.

References