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REVIEW

Treatment of complex regional pain syndrome type I with bisphosphonates

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ABSTRACT

Complex regional pain syndrome type I (CRPS-I) is a common and disabling disorder affecting a peripheral limb, usually developing after a trauma to an extremity. CRPS-I is characterised by presence of spontaneous pain, allodynia and hyperalgesia, disproportionate to the inciting event and by a variety of autonomic disturbances and trophic abnormalities. The pathophysiology of CRPS-I has not been fully understood. Experimental models have suggested that an initial triggering event may produce the release of proinflammatory neuropeptides and cytokines, generating a sort of neurogenic inflammation. Thereafter, increased microvascular permeability and intramedullary pressure, reduced oxygen extraction and cellular hypoxia maintain and make the disease worse, producing metabolic tissue acidosis. In this context, it is probable that, far from being a key player, the sympathetic nervous system contributes interacting with these mechanisms and producing vasomotor disturbances. Bisphosphonates (BPs) are potent inhibitors of osteoclastic activity widely used for the management of osteoporosis and other metabolic bone diseases. Their primary pharmacological action is the reduction of bone turnover. An enhanced osteoclastic activity has never been clearly demonstrated in CRPS-I. Therefore, it is likely that the positive effects of BPs in this condition are not related to their antiresorptive properties, but to a more complex interaction between these pharmacological agents and the pathophysiological mechanisms underlying CRPS-I. Results of several clinical trials have suggested the potential beneficial effects of BPs in CRPS-I. In five randomised controlled trials, oral and intravenous alendronate and intravenous clodronate, pamidronate and neridronate demonstrated to be effective in reducing pain and improving physical function in patients presenting with CRPS-I, with a good profile of safety and tolerability. Although these trials have a number of limitations, including the small samples enrolled, there is sufficient evidence to support the use of BPs as agents of choice in the management of CRPS-I.

Key messages

- Most of medications proposed for the management of complex regional pain syndrome type I (CRPS-I) demonstrated poor or partial efficacy.
- Results of randomised controlled trials have suggested potential beneficial effects of bisphosphonates (BPs) in CRPS-I.
- There is sufficient evidence to support the use of BPs as preferred agents in the management of CRPS-I in clinical practice.

INTRODUCTION

Complex regional pain syndrome type I (CRPS-I), also named as Reflex Sympathetic Dystrophy, is a common and disabling disorder affecting a peripheral limb. CRPS-I usually develops after a noxious event, such as a trauma or surgery to an extremity, without any nerve injury/damage. CRPS-I is classically distinguished from CRPS-II that occurs after injury/damage to a peripheral nerve.[1–7]

At present, several pharmacological treatments (eg, analgesics, anaesthetics, anticonvulsants, antidepressants, oral muscle relaxants, corticosteroids, calcitonin, bisphosphonates and calcium channel blockers) have been proposed to reduce pain and pain sensitisation, and to improve functional status in patients presenting with CRPS-I. While most of these medications demonstrated poor or partial efficacy on the short term, bisphosphonates (BPs) showed better long-term beneficial effects on pain reduction and functional recovery.

This narrative review summarises recent insights about the treatment of CRPS-I with BPs from the last Osteo-Rheumatology Meeting, which took place in Genoa (Italy) on October 2014. The main objectives of this overview are to summarise briefly current knowledge about the pathophysiology of CRPS-I, to highlight the potential mechanisms of action of BPs in CRPS-I and finally, to summarise main results of randomised-controlled trials (RCTs) undertaken to evaluate the efficacy of BPs in CRPS-I.

CRPS-I: CLINICAL PRESENTATION AND DIAGNOSIS

Several different diagnostic criteria have been proposed, and recently updated 'Budapest Criteria' have been widely accepted, to diagnose CRPS-I.[4–6] The diagnosis is made using clinical criteria and is based on the sole clinical history and examination. The symptoms are preceded by a trauma or injury to an extremity. CRPS-I is characterised by the presence of spontaneous or stimulus-induced pain, disproportionate to the inciting event, allodynia and hyperalgesia. These symptoms are associated to a wide variety of autonomic and motor disturbances, or trophic abnormalities, including oedema, changes in skin blood flow or abnormal sudomotor activity in the region of pain. Although any limb may be affected, upper limb is involved more frequently than lower limb.[1–3 7]

There are no specific laboratory or radiological diagnostic procedures for CRPS-I, but a variety of tests may be useful to exclude other clinical conditions.[2] Since a localised reduced bone density of the affected limb is a frequent finding in advanced stages of the disease, standard X-rays assessment may be used to look for osteopenia. X-rays are not a sensitive test, and typical signs of subchondral atrophy are visible only when the bone has lost about the 30% of its mineral content.[3 7 8] Three-phase bone scintigraphy has been considered an objective diagnostic technique, although not specific enough for the diagnostic purpose. Indeed, it may be useful to reinforce the diagnosis, and to identify patients that will benefit from BP treatment.[2 8] Typically, a pattern of increased uptake, in all three phases, is found during the first 6 months of the disease in the joints of the affected limb. This pattern is particularly evident during the delayed phase. Finally, MRI may demonstrate bone marrow oedema of the affected limb, and may be helpful for excluding other diagnoses.[2 3 8]

Nevertheless, none of the aforementioned techniques is currently considered required for the diagnosis of CRPS-I.

CRPS-I: PATHOPHYSIOLOGY

The pathophysiology of CRPS-I has not been fully understood.[1–3] Although several noxious events may produce the disease, in some cases it is not possible to identify the precipitating cause. Trauma is the most frequent precipitating factor of CRPS-I, with fractures accounting for up to 50% of the cases. Other causes include immobilisation, stroke, heart attack and iatrogenic injury (eg, carpal tunnel decompression).[1–3]

During the 20th century, the deregulation of the sympathetic nervous system was regarded as the leading mechanism producing the clinical picture of CRPS-I.[1–3] In the past decade, several lines of evidence suggested that the sympathetic dysfunction could be a contributing factor in the pathogenesis of CRPS-I, but that it is not the main aetiological player in the chain of events producing the disease.

Several animal models have suggested that the release of proinflammatory neuropeptides (calcitonin gene-related peptide and substance P) and cytokines (tumour-necrosis factor α, interleukin-1 and interleukin-6) is the initial event generating and maintaining the early phase of CRPS-I, by producing a sort of neurogenic inflammation.[9 10] These cytokines and neuropeptides are also responsible for the clinical presentation of the disease characterised by pain, allodynia, hyperalgesia and oedema.

In the early phase, a central role is probably played by the nerve growth factor (NGF) released by macrophages and mastcells.[11] The NGF determines the liberation of two neuropeptides, substance P and calcitonin gene-related peptide, which produces vasodilation, increased microvascular permeability, protein extravasation and oedema.[2 11–14] Also tumour necrosis factor α, interleukin-1 and interleukin-6 are involved in this phase, sustaining neuroinflammation.[2 15] The resulting impaired microcirculation probably maintains and worsens the disease, generating the final picture of CRPS-I, characterised by metabolic tissue acidosis.[16–20] This second phase is distinguished by increased microvascular permeability and intramedullary pressure, reduced oxygen extraction and cellular hypoxia that involve several tissues, including muscle and bone.[16–20] Finally, the generation of free radicals and the reduction of pH further support the persistence of pain and the release of neuropeptides.

In this framework, the sympathetic nervous system probably contributes by interacting with the above-described mechanisms, producing vasomotor disturbances. In the early phase of CRPS-I, the vasodilation is probably also related to a decreased basal sympathetic function and, therefore, vasoconstrictor activity (as demonstrated by the impairment of vasoconstrictor reflexes).[2] During the late 'cold' phase, the vasoconstriction should be intended as a consequence of dysregulated sympathetic function and adrenergic supersensitivity.[2]

One of the peculiar finding of CRPS-I is the osteopenia in the subchondral and subcortical areas of the affected limb. The pathogenesis of the massive bone loss observed just a few weeks after the onset of the disease is still unclear. Studies investigating markers of osteoclastic activity, and the few histopathological investigations performed in patients presenting with CRPS-I excluded the role of an increased bone resorption mediated by enhanced osteoclastic activity, particularly in the early phase of the disease.[16 21–24] It is more likely that the osteopenia is the consequence of chemical dissolution of hydroxyapatite crystals produced by tissue hypoxia, increased anaerobic glycolysis, and low local pH.[16 18 24]

BISPHOSPHONATES: OVERVIEW

Bisphosphonates are potent inhibitors of bone resorption widely used in the management of osteoporosis and other metabolic bone diseases, such as Paget's disease

and cancer-related bone pain.[25–27] The primary pharmacological action of BPs is the reduction of bone resorption by inhibition of osteoclastic activity.[25 26] Owing to the coupling of bone resorption and formation, BP treatment also reduces osteoblasts activity and bone formation. This occurs at a slower rate, with the new steady state of lower bone turnover reached after 3–6 months from the start of treatment.[25 26]

Bisphosphonates are taken up by the skeleton, primarily at active remodelling sites, and bind strongly to bone mineral.[25 26] At the tissue level, BPs are liberated from the bone in the acidic environment of the resorption lacunae, during the resorption phase and are taken up by osteoclasts, probably by fluid-phase endocytosis. They inhibit osteoclasts activity by different intracellular actions.[25 26] BPs without a nitrogen atom in their molecule (eg, clodronate) incorporate into ATP and generate metabolites such as AppCp-type nucleotides which induce osteoclast apoptosis. Nitrogen-containing BPs (eg, alendronate, neridronate, pamidronate) induce changes in the cytoskeleton, leading to inactivation and potentially apoptosis of osteoclast. This action is mainly the result of the inhibition of farnesyl pyrophosphate synthase, an enzyme of the mevalonate biosynthetic pathway.

In early trials of BPs in CRPS-I, the investigation of these compounds or other bone targeting agents (eg, calcitonin) was mainly justified by the local radiological osteoporosis observed in some patients presenting with this complex disease.[16 24] However, the mechanism trough which BPs are effective in CRPS-I has not been completely understood, and it is unlikely that it is just related to an inhibition of osteoclast-mediated bone resorption, since, as previously described, an enhanced osteoclast activity has never been demonstrated in CRPS-I. In a recent Editorial published by Varenna *et al*[16], it has been proposed that mechanisms other than their antiresorptive activity are involved in the beneficial effects of BPs in CRPS-I.

Typically, three-phase bone scintigraphy using technetium-labelled bisphosphonate in patients presenting with CRPS-I demonstrates a pattern of increased uptake in all three phases.[16 28 29] Increased blood flow and microvascular permeability are surely responsible for the radiotracer uptake in the early phase. On the other hand, the sole blood flow and permeability cannot explain the prolonged and greater uptake in the joints of the affected extremity during the delayed phase.[16] Since increased bone resorption cannot be an explanation for this avid uptake, it has been proposed that this peculiar and relevant concentration of BPs in the affected limb may be the consequence of a huge number of biding sites available due to the disappearance of lining cells from the trabecular surface.[16 22 30] Therefore, BPs could bind to the bone tissue via passive chemoadsorption to hydroxyapatite crystals on an uncovered trabecular bone surface. This is supported by observations of reduced number of lining cells, osteoblasts and osteoclasts and osteocytes degeneration in the affected joints of the patients.[22 30] Once a high concentration of BPs is reached at the tissue level, it is likely that these compounds counteract the pathophysiological events involved in CRPS-I trough different mechanisms, including the prevention of hydroxyapatite crystals dissolution, the reduction of lactic acid production by different cell types, the inhibition of macrophages and monocytes proliferation, activation and viability (that sustain neuroinflammation), the reduction of NGF and other cytokines production and finally, the prevention of osteoblasts and osteoclasts apoptosis.[16 24]

In conclusion, the potential beneficial effects of BPs in CRPS-I are not related to their traditional antiresorptive activity, but to a more complex interaction between these pharmacological agents and the pathophysiological events generating and maintaining CRPS-I.

BISPHOSPHONATES IN CRPS-I: RANDOMISED CLINICAL TRIALS

A number of well-designed, randomised, placebo-controlled trials (RCTs) investigating the beneficial effects of BPs in CRPS-I have been published in the past 30 years, with the first RCT published in 1997 by Adami *et al*.[31]

To date, five RCTs of alendronate (two trials), pamidronate (one trial), clodronate (one trial) and neridronate (one trial) have been published.[21 31–34] Table 1 depicts the general characteristics of these RCTs. The methodological quality of these five RCTs has been evaluated using the Jadad score (table 1).[35 36] The Jadad scale for RCTs is a simple, short, reliable and valid 3-item scale developed to assess the quality of clinical reports in pain relief. The Jadad scale evaluates three main elements (items): randomisation procedure, blinding allocation and dropout (the fate of all patients should be known). Methodology is usually considered high when the score is 3 and more; while a score of less than 3 comprises an increased risk for bias. As depicted in table 1, all five RCTs presented a score ≥3, with only two of them presenting a score=3.

Adami *et al*[31] randomised 20 patients presenting with CRPS-I to receive intravenous alendronate 7.5 mg or placebo for three consecutive days. Patients were assessed (visual analogue scale, VAS) at baseline and weekly, and after 14 days all participants (alendronate and placebo) had a second treatment course with alendronate, independently of the results of the blind treatment. Alendronate-treated patients demonstrated a significant reduction of pain, tenderness and swelling and a significant improvement of motion compared to placebo-treated participants during the first 2 weeks. The participants who received placebo did not demonstrate significant improvements of the symptoms, which started to ameliorate after alendronate treatment. At the end of the 4 weeks, spontaneous pain and tenderness were more suppressed in the participants who received two treatment courses of alendronate (respectively, 62%

Table 1 Randomised controlled trials investigating the effects of bisphosphonates in complex regional pain syndrome type I: characteristics of the trials

References	Jadad Score	Treatment		Number of patients (F)	Age (years) Mean (SD) or Range	Diagnostic criteria	Disease duration (weeks or months) Mean (SD)	Follow-up (days) Double-blind (Open-label)	Additional treatment
		Active	Control						
Adami S *et al*[31]	3	Alendronate 7.5 mg intravenous for 3 days	Placebo intravenous for 3 days	20 (12)	39–80	Kozin	ALD: 16 (17) weeks PLB: 19 (19) weeks	14 (+14)	Physical therapy
Varenna M *et al*[21]	5	Clodronate 300 mg intravenous for 10 days	Placebo intravenous for 10 days	32 (19)	56 (9)	Kozin	4.0 (2.3) months	40 (+140)	None
Robinson JN *et al*[32]	3	Pamidronate 60 mg intravenous single time	Placebo intravenous single time	27 (9)	30–60	IASP	21.6 (NR) months	90	Paracetamol, codeine, dextropropoxyphene
Manicourt DH *et al*[33]	5	Alendronate 40 mg oral for 56 days	Placebo oral for 56 days	39 (21)	45 (12)	IASP Budapest	ALD: 7 (2) months PLB: 8 (3) months	84 (+84)	Physical therapy
Varenna M *et al*[34]	5	Neridronate 100 mg intravenous four times	Placebo intravenous four times	82 (53)	NRD: 58 (13) PLB: 57 (10)	Budapest	NRD: 4.7 (4.1) weeks PLB: 5.0 (4.6) weeks	40 (+50)	NSAIDs, paracetamol

ALD, alendronate; CRPS, complex regional pain syndrome; Double-blind, during the double-blind phase of the study; F, female; iv, intravenous; IASP, International Association for the Study of Pain; NR, not reported; NRD, neridronate; Open-label, during the open-label phase of the study; NSAIDs, non-steroidal anti-inflammatory drugs; PLB, placebo.

and 53%) compared to those who received placebo and alendronate (respectively, 48% and 46%).

Varenna *et al*[21] tested the efficacy of intravenous clodronate in a RCT of 32 patients presenting with CRPS-I. Participants were randomised to receive intravenous clodronate 300 mg or placebo daily for 10 consecutive days. They were assessed at baseline and 40 days after the end of treatment. Thereafter, in an open extension, patients who received placebo were treated with clodronate (same dosing regimen). After 40 days, clodronate-treated patients demonstrated a significant improvement of pain (assessed by VAS) and clinical status (assessed by clinical global assessment) compared to baseline and to the placebo group. At the end of the double-blind phase, 11 out of 15 clodronate-treated patients reported a significant improvement of pain (assessed with an efficacy verbal score), while only four patients in the placebo group (17 participants) reported a slight improvement of pain. Assuming that the pain improvement in the two groups was similar (ie,not the case), the estimated number needed to treat (NNT) with clodronate to achieve a significant pain reduction was 2.0.

When the clodronate infusions were administered to the placebo-treated patients (open-extension phase), significant clinical improvements were observed with a trend similar to the double-blind phase. Pooling the results of all patients, the mean percent decrease of VAS at day 40 was about 63%. Interestingly, the patients demonstrated a continuous clinical improvement up to 180 days.

Intravenous pamidronate 60 mg as a single infusion was tested against intravenous placebo in a 3-month RCT of 27 patients.[32] After 3 months, the overall improvement of pain score and patient's global assessment of disease severity score was greater in the treatment group compared to placebo group. Pamidronate-treated patients demonstrated also significant higher scores in physical function compared to controls.

One RCT investigated the potential beneficial effects of an oral nitrogen-containing bisphosphonate in the management of CRPS-I.[33] This is a quite unique study considering the way of administration of the BP and the design. Forty patients were randomly assigned to receive for 8 weeks oral alendronate 40 mg or placebo daily. After the first 8-week treatment course and a 4-week off-treatment period, all participants (alendronate and placebo) who agreed underwent an open-label, 8-week extension of alendronate treatment. Over the times of the follow-up (four, eight and 12 weeks), alendronate therapy demonstrated to produce a significantly greater reduction of pain (VAS score) and oedema of the affected limb, and a significantly greater increase of pressure tolerance and joint mobility scores, compared to placebo. The beneficial effects of alendronate were already significant at week four. During the open-label extension, patients previously treated with placebo, demonstrated, with alendronate, significant improvements in the VAS, pressure tolerance and joint mobility scores, starting on week four (week 16 from trial

baseline) and peaking at week eight. Finally, those patients who received the second course of alendronate showed a new progressive improvement of the symptoms (pain, pressure tolerance and joint mobility), suggesting that the positive effects of the initial 8-week period of treatment did not reach the plateau.

Intravenous neridronate has been tested against placebo in the largest and most informative RCT ever conducted with a BP in CRPS-I.[34] This was a well-designed, multicenter RCT undertaken in 82 participants from six centres. Varenna *et al* randomised participants to receive intravenous neridronate 100 mg or placebo every third day four times starting on day 1 and ending on day 10. Patients were assessed at baseline, at the end of therapy (day 10), and after 20 and 40 days. At the end of the follow-up and after 10 days of wash-out, placebo-treated patients were given neridronate following the same dosing regimen, and were followed for 40 days.

During the first 20 days of follow-up, a reduction of pain score (VAS) was observed in the two groups, with the difference becoming significant in favour of neridronate at day 20. During the following 20 days, no further decrease of pain score was observed in the placebo group, while a continuous and significant decrease was demonstrated in the neridronate group. At the end of the double-blind phase, 73% of the neridronate patients versus 33% of the controls demonstrated a VAS score decrease of 50% or greater, with a significant difference between the two groups of about 40%. The estimated NNT to achieve a pain reduction of at least 50% with neridronate was 2.4. Neridronate produced also significantly greater improvements in physical performances (SF-36), oedema and evoked pain compared to placebo. Finally, with 68 patients taking painkillers at study entry, 100% of patients on neridronate and 45% of those on placebo discontinued these drugs. During the open-label phase participants previously treated with placebo demonstrated significant clinical improvements with neridronate therapy, with a trend similar to that observed during the double-blind phase.

Safety was also assessed in the above-described RCTs. BPs were generally well tolerated, producing only expected and self-limiting specific adverse effects including upper gastrointestinal intolerance associated with oral use of alendronate and symptoms related to an acute phase reaction (diffuse musculoskeletal pain and fever) after exposure to intravenous nitrogen-containing BP (alendronate, pamidronate and neridronate).

Overall these data demonstrated that oral and intravenous alendronate, and intravenous clodronate, pamidronate and neridronate are effective in improving pain, physical function and oedema in patients presenting with CRPS-I. A recent network meta-analysis has further confirmed these results, highlighting that bisphosphonates should be the pharmacological agents of choice in the management of this condition, given also the limited efficacy demonstrated by other medications.[36]

A number of limitations of these RCTs should be highlighted. First, the populations included were heterogeneous and the diagnostic criteria used for the diagnosis of CRPS-I were quite different. Second, the interpretation and comparison of the results between the RCTs was hampered by relevant differences in the tools used to assess efficacy and in results reporting. Finally, in all the RCTs except one,[34] were included patients with long-standing disease. In these studies, the Authors did not assess the potential interaction between diseases duration and clinical efficacy of BPs, and did not evaluate in details whether the efficacy of BPs was affected by the disease duration.[34] This last point is particularly relevant, since, as recently noted, it is likely that BPs are able to exert their beneficial effects in CRPS-I only in the early phase of the disease, when a three-phase bone scintigraphy using technetium-labelled bisphosphonate demonstrates a pattern of increased uptake, indicating local drug accumulation.[24] The efficacy of BPs in patients presenting with a long-standing or 'cold' disease, in whom bone scans are negative, may be less pronounced or even absent.

CONCLUSION

Although very limited data are available, with only five RCTs published to date, BPs showed to be effective in the management of CRPS-I, producing short-term and long-term positive clinical outcomes. Further RCTs are warranted to confirm the results of these trials in larger samples, to define the optimum dose, frequency and duration of therapy in patients refractory to previous treatments, and to test the potential beneficial effects of new dosing regimens and ways of administration (eg, intramuscular clodronate or neridronate).

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