Editorial

Bisphosphonates in Complex Regional Pain syndrome type I: how do they work?

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ABSTRACT

Complex Regional Pain syndrome type I (CRPS-I) is a disease characterised by extreme pain for which no gold-standard treatment exists to date. In recent years a possible role for bisphosphonates in the treatment of CRPS-I has been proposed. These drugs were first used for their effect in decreasing pain in bone diseases in which bisphosphonates act through their antiosteoclastic properties (metastatic disease, Paget disease, myeloma). In CRPS-I, enhanced osteoclastic activity has never clearly been demonstrated and the benefit shown is possibly exerted by different mechanisms of action. In this paper we review other conjectural mechanisms involved in reducing pain intensity and improving clinical signs and functional status in these patients. The results of most studies on this topic show that bisphosphonates may be effective in the early phases of the disease, when scintigraphic bone scan more frequently shows a local radiotracer accumulation that possibly means a high local concentration of the drug. These features probably represent the required conditions by which bisphosphonates might modulate various inflammatory mediators that are upregulated in CRPS-I. Patients in whom a scintiscan is often negative (long-standing disease or a primarily cold disease) could be less responsive to this treatment. With these limitations, bisphosphonates appear to present a therapeutic strategy that has been proven to reliably offer benefits in patients with CRPS-I.

Complex Regional Pain syndrome type I (CRPS-I) is a severely disabling pain syndrome for which no definite treatment algorithm has been yet established. To date, five randomised controlled trials (1-5) and a number of open studies have provided evidence of efficacy associated with bisphosphonates (BPs) in decreasing pain and swelling as well as improving functional status in patients CRPS-I.

Due to the local radiological osteoporosis observed in some patients, BPs and other bone targeting drugs (*e.g.* calcitonin) have been used in the treatment of CRPS-I patients. However, it remains questionable that inhibitors of osteoclast-mediated bone resorption are used to treat a disease in which an enhanced osteoclastic activity has never been clearly demonstrated, particularly in the early phases of the disease when BPs seem to be associated with the most clinically relevant benefits. In fact, neither studies on markers of osteoclastic activity (3, 6), nor the few available histopathological investigations on bone (7, 8) have demonstrated an enhanced osteoclastic activity that has erroneously been inferred by radiological and bone scan features of this disease. Most dynamic scintigraphic studies that used Technetium-labelled BP as radiotracer, showed a prolonged and greater uptake in the later stages of the assessment that could not be justified solely by increased blood flow and/or increased microvascular permeability which was responsible for radiotracer uptake in the early phases of the scintigraphic assessment (such as uptake that first normalised over time) (9, 10). Since increased bone turnover in affected bones has never been reported in the early stages of the disease, it is more likely that this avid and peculiar BP uptake relies on a number of available binding sites related to an uncovered trabecular bone surface due to the lining cells disappearance (8) and passive chemoadsorption to hydroxyapatite (HAP) crystals. The lining cells death has been described together with a reduced number of osteoclasts and osteoblasts, and osteocyte degeneration (7,

8). The radiotracer distribution is likely similar to an *in vivo* accumulation of the drug at the disease site. This large drug concentration achieved probably accounts for mechanisms of action that are not usually active when these molecules are employed to treat osteoporosis and other bone diseases in which an increased bone turnover is truly present.

A few weeks after the onset of CRPS-I, features of bone marrow vascular disorder such as adipocytes necrosis and plasma exudation with venous dilatation and thickening of the arteriolar walls are observed (8). A peculiar characteristic shared by other vascular bone diseases such as bone marrow oedema syndromes (*e.g.* transient osteoporosis of the hip) and early stages of avascular necrosis is a mineralisation disturbance and an elevated osteoid volume (11). This finding might be the basis for the impressive loss of bone density assessed with different techniques (12-14) a few weeks after disease onset that cannot be justified by an osteoclast-mediated process, but more likely by a HAP chemical dissolution related to a tissue hypoxia, an increased anaerobic glycolysis, and lastly, by a low local pH overcoming the local buffering capacity as demonstrated by an increased local lactic acid concentration (15).

In a pioneering phase of BP research, one of the earliest effects proposed for the action of BPs in the preservation of bone integrity is their ability to prevent HAP crystal dissolution in an acid milieu when adequate drug concentrations are reached (16), so possibly maintaining a structural integrity of bone architecture in CRPS-I patients. Nevertheless, the assumption that the therapeutic effects of BPs might only be due to a structural preservation of bone seems to be too simplistic and other mechanisms of action are likely involved in counteracting pain and the signs of neurogenic inflammation in these patients. For example, it has long been known that BPs decrease lactic acid production from various cell types (17) and, as reported above, CRPS-I patients show a local acidosis, probably as a result of hypoxia following microvascular disturbances (15); this tissue acidosis is a well-known cause of pain in ischaemic tissues (18). By reducing local acidosis, BPs can lower the neuropeptide release from primary afferents that not only innervate surface tissues, but also the bone (19), where they express acid sensing receptors (TRPV1 and ASICs) (20), thus are equipped to respond to an acid stimulus. In an animal model investigating hyperalgesia induced by bone inoculation of breast cancer cells, BP administration (zoledronate) reduced pain possibly through a decreased mRNA expression of acid sensing receptors (TRPV1 and ASICs) in the dorsal root ganglia (21). Finally, due to the high local concentration of BPs, it cannot be excluded that the same mechanism might also work in other leukocyte populations that accumulate at the site of disease as demonstrated by radiolabelled autologous leukocyte scans (22).

Among the cells that may represent a possible target for BPs, monocytes and macrophages are specifically inhibited in their proliferation (23), activation (24) and viability (23, 25) and this effect seems to be specific for bone marrow resident mononuclear phagocytes (26). Recently, elevated blood levels of some proinflammatory subgroups of the monocyte/macrophagic lineage have been reported in patients with CRPS-I (27). Although the cross-sectional design of this study does not allow clarification of the role of these cells (elevated levels before disease onset implies a predisposing role, whereas elevated levels after disease onset implies a maintenance role), it is conceivable that monocytes/macrophages play a role in sustaining neurogenic inflammation in acute CRPS-I. Macrophages together with neutrophils, mast cells and other tissue resident cells are activated by nerve, bone and superficial tissue injury (28), resulting in the release of inflammatory cytokines which are found to be significantly increased in CRPS-I patients in local blister fluid, circulating plasma, and cerebrospinal fluid (29-31). Many studies have shown that BPs decrease the production of tumor necrosis factor-α and other proinflammatory mediators both in vitro and in patients suffering from other inflammatory diseases (32, 33).

Another possible target of BPs might be the increase of local nerve growth factor (NGF). In injured tissues, activated macrophages express high levels of NGF that support a direct effect on nociceptive stimulus by activation of primary afferent neurons that express NGF receptors (34). This drives a release facilitation of substance P (SP) and calcitonin gene-related peptide (CGRP) (35). In an animal model of CRPS induced by a distal tibial fracture, anti-NGF antibodies reduced neuropeptide levels and nociceptive sensitisation, as well as inhibited distal femur bone loss (36). Increased local levels of NGF may further promote a vicious cycle by inducing the diffentiation and activation of monocytes and macrophages (37). Moreover, NGF increases TRPV1 expression in the sensory neurons (38) and, both directly and through SP, induces keratinocyte proliferation and activation (39), such as a cellular line probably involved in maintaining inflammation, nociceptive sensitisation and microvascular disturbances in CRPS-I (40). Keratinocytes, in turn, are able to express NGF (41), cytokines (42) and perhaps endothelin-1 (43), so maintaining inflammation, nociceptors sensitisation and microvascular disturbances. In an *in vitro* study on normal human keratinocytes, BPs inhibited cell growth in a dose-dependent manner (44) and this mechanism may contribute to decreased cutaneous inflammatory signaling in CRPS-I patients, thereby reducing extravasation and limb oedema and increasing local cytokine production.

A further possible mechanism of action by which some BPs may reduce pain in CRPS-I relies on their ability to inhibit farnesyl pyrophosphate synthase and then interfere with the post-translational modification of small GTPases such as *ras*, *rab*, *rho* and *rac* (45). These molecules are involved in the regulation and activity of membrane receptors coupled to intracellular G-proteins that represent one of the major classes of membrane signaling proteins (46). These receptors have been found to upregulate nociceptive signalling in peripheral sensory neurons where they are widely expressed (47).

The marked affinity of BPs for calcium ions may induce a local decrease of calcium when the drug reaches a local elevated concentration through a physicochemical effect (chelation) and formation of complexes or aggregates (48). It has been shown that BPs inhibit *in vitro* calcium-induced contraction of smooth muscle, possibly by inhibition of intracellular calcium mobilisation and a reduced influx of extracellular calcium (49). By considering that some calcium blockers (*e.g.* nifedipine and tadalafil) seem to induce a clinically relevant reduction in pain in CRPS-I patients (50, 51), a possible mechanism of action of BPs might be a reduction in cytosolic calcium concentration so acting in a similar manner to calcium channel blockers (52).

Finally, experimental studies suggest that BPs are able to prevent osteoblast and osteocyte apoptosis regardless of the proapoptotic stimulus used (53), counteracting one of the more frequent features reported in bone histopathological investigations in the early stages of the disease (7, 8).

As reported above, there are a number of possible mechanisms of action through which BPs can work in CRPS-I. We do not believe that BPs represent a panacea for all patients. Many of these hypothetical mechanisms are driven by local accumulation of BPs, so a negative bone scan in the delayed phase would exclude paediatric cases and patients suffering from a long standing disease or a primarily "cold" disease in whom bone scan is often negative. When BPs are the therapeutic drug of choice, they should be used taking into account some peculiar features that differentiate each molecule belonging to this family in terms of bioequivalent doses. In a recently published study (1), the choice to use neridronate was based on its binding affinity for HAP crystals that *in vitro* and *in vivo* is similar to alendronate and greater than pamidronate (54). Moreover, neridronate is available in 100 mg ampoules, so a high IV dose is feasible. The chosen regimen has been discussed in the paper (1).

In conclusion, what do the clinical effects of BPs tell us about CRPS-I ? We are in agreement with other researchers (55, 56) that deep-tissue involvement may be a key to trigger or maintain the disease even if such involvement is overlooked due to difficulties in undertaking pathophysiological investigations. There is accumulating evidence about the central role of bone in CRPS-I that can be gathered from investigations on different aspects of the disease. Besides the findings considered above, it should be kept in mind that bone marrow and mineralised bone receive a great number of peptidergic sensory fibers that can be involved in the retrodromic release of CGRP and SP (19) and one of the more resembling animal model of the disease is induced by a bone fracture in which SP signaling contributes to the vascular and nociceptive abnormalities (57). Epidemiological studies report that osteoporosis is a disease significantly associated with a greater incidence of CRPS-I and among the general population, postmenopausal women in whom fragility fracture are frequent represents the subgroup which shows the highest CRPS-I incidence (58). In addition, other bone diseases with a high propensity to fracture, for example osteogenesis imperfecta, are possibly complicated by CRPS-I (59). Finally, bone injuries (*e.g.* fracture, surgical intervention and sprain) are the most common predisposing events that trigger CRPS-I (56).

References

1. VARENNA M, ADAMI S, ROSSINI M *et al.*: Treatment of complex regional pain syndrome with neridronate: a randomized, double-blind, placebo-controlled study. *Rheumatology* (Oxford) 2013; 52: 534-42.
2. ADAMI S, FOSSALUZZA V, GATTI D, FRACASSI E, BRAGA V: Bisphosphonate therapy of reflex sympathetic dystrophy syndrome. *Ann Rheum Dis* 1997; 56: 201-4.
3. VARENNA M, ZUCCHI F, GHIRINGHELLI D *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.
4. ROBINSON JN, SANDOM J, CHAPMAN PT: Efficacy of pamidronate in complex regional pain syndrome type I. *Pain Med* 2004; 5: 276-80.
5. MANICOURT DH, BRASSEUR JP, BOUTSEN Y, DEPRESEUX G, DEVOGELAER JP: Role of alendronate in therapy for posttraumatic complex regional pain syndrome type I of the lower extremity. *Arthritis Rheum* 2004; 50: 3690-7.
6. RENIER JC, BASLE M, ARLET J *et al.*: L'os et le métabolisme phosphocalcique dans l'algodystrophie. *Rev Rhum Mal Osteoartic* 1983; 50: 23-31.
7. 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.
8. ARLET J, FICAT CCJ: Vascular explorations and pathology of reflex sympathetic dystrophy. *Baillere's Clin Orthop* 1996; 2: 273-90.
9. LEE GW, WEEKS PM: The role of bone scintigraphy in diagnosing Reflex Sympathetic Dystrophy. *J Hand Surg* 1995; 20A: 458-63.
10. LEITHA T, KORPAN M, STAUDENHERZ A, WUNDERBALDINGER P, FIALKA V: Five phase bone scintigraphy supports the pathophysiological concept of a subclinical inflammatory process in reflex sympathetic dystrophy. *Q J Nucl Med* 1996; 40: 188-93.
11. HOFMANN S, FIALKA V, KRAMER J *et al.*: Bone marrow oedema syndrome of the hip and its relationship to avascular necrosis and reflex sympathetic dystrophy. *Baillere's Clin Orthop* 1996; 2: 291-313.
12. CHAPURLAT RD, DUBOEUF FP, LIENS D, MEUNIER PJ: Dual energy X-ray absorptiometry in patients with lower limb reflex sympathetic dystrophy syndrome. *J Rheumatol* 1996; 9: 1557-9.
13. ARRIAGADA M, ARINOVICHE R: X-ray bone densitometry in the diagnosis and follow-up of reflex sympathetic dystrophy syndrome. *J Rheumatol* 1994; 21: 498-500.
14. BICKERSTAFF DR, CHARLESWORTH D, KANIS JA: Changes in cortical and trabecular bone in algodystrophy. *Br J Rheumatol* 1993; 32: 46-51.
15. BIRKLEIN F, WEBER M, NEUNDÖRFER B: Increased skin lactate in complex regional pain syndrome: evidence for tissue hypoxia? *Neurology* 2000; 55: 1213-5.
16. EVANS JR, ROBERTSON WG, MORGAN DB, FLEISCH H: Effect of pyrophosphate and diphosphonates on the dissolution of hydroxyapatites using a flow system. *Calcif Tissue Int* 1980; 31: 153-9.
17. FAST DK, FELIX R, DOWSE C, NEUMAN WF, FLEISCH H: The effects of diphosphonates on the growth and glycolysis of connective-tissue cells in culture. *Biochem J* 1978; 172: 97-107.
18. MACMAHON SB, JONES NJ: Plasticity of pain signaling: role of neurotrophic factors exemplified by acid-induced pain. *J Neurobiol* 2004; 61: 72-87.
19. MACH DB, ROGERS SD, SABINO MC *et al.*: Origins of skeletal pain: sensory and sympathetic innervation of the mouse femur. *Neuroscience* 2002; 113: 155-66.
20. WALDMANN R, CHAMPIGNY G, LINGUEGLIA E, DE WEILLE JR, HEURTEAUX C, LAZDUNSKI M: H(+)-gated cation channels. *Ann NY Acad Sci* 1999; 868: 67-76.
21. NAGAE M, HIRAGA T, YONEDA T: Acidic microenvironment created by osteoclasts causes bone pain associated with tumor colonization. *J Bone Miner Metab* 2007; 25: 99-104.
22. TAN EC, OYEN WJ, GORIS RJ: Leukocytes in complex regional pain syndrome type I. *Inflammation* 2005; 29: 182-6.
23. CECCHINI MG, FELIX R, FLEISCH H, COOPER

PH: Effect of bisphosphonates on proliferation and viability of mouse bone marrow-derived macrophages. *J Bone Miner Res* 1987; 2: 135-42.
24. STEVENSON PH, STEVENSON JR: Cytotoxic and migration inhibitory effects of bisphosphonates on macrophages. *Calcif Tissue Int* 1986; 38: 227-33.
25. ROGERS MJ, CHILTON KM, COXON FP *et al*.: Bisphosphonates induce apoptosis in mouse macrophage-like cells *in vitro* by a nitric oxide-independent mechanism. *J Bone Miner Res* 1996; 11: 1482-91.
26. CECCHINI MG, FLEISCH H: Bisphosphonates in vitro specifically inhibit, among the hematopoietic series, the development of the mouse mononuclear phagocyte lineage. *J Bone Miner Res* 1990; 5: 1019-27.
27. RITZ BW, ALEXANDER JM, NOGUSA S *et al*.: Elevated blood levels of inflammatory monocytes ($CD14^+CD16^+$) in patients with complex regional pain syndrome. *Clin Exp Immunol* 2011; 164: 108-17.
28. MARCHAND F, PERRETTI M, MCMAHON SB: Role of the immune system in chronic pain. *Nat Rev Neurosci* 2005; 7: 521-32.
29. ALEXANDER GM, VAN RIJN MA, VAN HILTEN JJ, PERREAULT MJ, SCHWARTZMAN RJ: Changes in cerebrospinal fluid levels of pro-inflammatory cytokines in CRPS. *Pain* 2005; 116: 213-9.
30. MAIHÖFNER C, HANDWERKER HO, NEUNDÖRFER B, BIRKLEIN F: Mechanical hyperalgesia in complex regional pain syndrome: a role for TNF-alpha? *Neurology* 2005; 65: 311-3.
31. UÇEYLER N, EBERLE T, ROLKE R, BIRKLEIN F, SOMMER C: Differential expression patterns of cytokines in complex regional pain syndrome. *Pain* 2007; 132: 195-205.
32. SANSONI P, PASSERI G, FAGNONI F *et al*.: Inhibition of antigen-presenting cell function by alendronate *in vitro*. *J Bone Miner Res* 1995; 10: 1719-25.
33. MAKSYMOWYCH WP: Bisphosphonates. Anti-inflammatory properties. *Curr Med Chem Anti Inflamm Anti Allergy Agents* 2002; 1: 15-28.
34. BENNETT DL, KOLTZENBURG M, PRIESTLEY JV, SHELTON DL, MCMAHON SB: Endogenous nerve growth factor regulates the sensitivity of nociceptors in the adult rat. *Eur J Neurosci* 1998; 10: 1282-91.
35. DONNERER J, SCHULIGOI R, STEIN C: Increased content and transport of substance P and calcitonin gene-related peptide in sensory nerves innervating inflamed tissue: evidence for a regulatory function of nerve growth factor *in vivo*. *Neuroscience* 1992; 49: 693-8.
36. SABSOVICH I, WEI T, GUO TZ *et al*.: Effect of anti-NGF antibodies in a rat tibia fracture model of complex regional pain syndrome type. *Pain* 2008; 138: 47-60.
37. EHRHARD PB, GANTER U, STALDER A, BAUER J, OTTEN U: Expression of functional trk protooncogene in human monocytes. *Proc Natl Acad Sci USA* 1993; 90: 5423-7.
38. JI RR, SAMAD TA, JIN SX, SCHMOLL R, WOOLF CJ: p38 MAPK activation by NGF in primary sensory neurons after inflammation increases TRPV1 levels and maintains heat hyperalgesia. *Neuron* 2002; 36: 57-68.
39. LI WW, GUO TZ, LI XQ, KINGERY WS, CLARK JD: Fracture induces keratinocyte activation, proliferation, and expression of pro-nociceptive inflammatory mediators. *Pain* 2000; 151: 843-52.
40. MARINUS J, MOSELEY GL, BIRKLEIN F *et al*.: Clinical features and pathophysiology of complex regional pain syndrome. *Lancet Neurol* 2011; 10: 637-48.
41. BURBACH GJ, KIM KH, ZIVONY AS *et al*.: The neurosensory tachykinins substance P and neurokinin A directly induce keratinocyte nerve growth factor. *J Invest Dermatol* 2001; 117: 1075-82.
42. MCKENZIE RC, SAUDER DN: The role of keratinocyte cytokines in inflammation and immunity. *J Invest Dermatol* 1990; 95: 105S-7S.
43. BIRKLEIN F, SCHMELZ M: Neuropeptides, neurogenic inflammation and complex regional pain syndrome (CRPS). *Neurosci Lett* 2008; 437: 199-202.
44. RESZKA AA, HALASY-NAGY J, RODAN GA: Nitrogen-bisphosphonates block retinoblastoma phosphorylation and cell growth by inhibiting the cholesterol biosynthetic pathway in a keratinocyte model for esophageal irritation. *Mol Pharmacol* 2001; 59: 193-202.
45. LUCKMAN SP, HUGHES DE, COXON FP, GRAHAM R, RUSSELL G, ROGERS MJ: Nitrogen-containing bisphosphonates inhibit the mevalonate pathway and prevent post-translational prenylation of GTP-binding proteins, including Ras. *J Bone Miner Res* 1998; 13: 581-9.
46. HOLLMANN MW, STRUMPER D, HERROEDER S, DURIEUX ME: Receptors, G proteins, and their interactions. Anesthesiology 2005; 103: 1066-78.
47. MALIN SA, MOLLIVER DC: Gi- and Gq-coupled ADP (P2Y) receptors act in opposition to modulate nociceptive signaling and inflammatory pain behavior. *Mol Pain* 2010; 6: 21.
48. FLEISCH H: Bisphosphonates: mechanisms of action. *Endocr Rev* 1998; 19: 80-100.
49. PASPALIARIS V, LEAVER DD: Clodronate inhibits contraction and prevents the action of L-type calcium channel antagonists in vascular smooth muscle. *J Bone Miner Res* 1991; 6: 835-41.
50. MUIZELAAR JP, KLEYER M, HERTOGS IA, DELANGE DC: Complex regional pain syndrome (reflex sympathetic dystrophy and causalgia): management with the calcium channel blocker nifedipine and/or the alpha-sympathetic blocker phenoxybenzamine in 59 patients. *Clin Neurol Neurosurg* 1997; 99: 26-30.
51. GROENEWEG G, HUYGEN FJ, NIEHOF SP *et al*.: Effect of tadalafil on blood flow, pain, and function in chronic cold complex regional pain syndrome: a randomized controlled trial. *BMC Musculoskelet Disord* 2008; 9: 143.
52. ROSSIER JR, COX JA, NIESOR EJ, BENTZEN CL: A new class of calcium entry blockers defined by 1,3-diphosphonates. Interactions of SR-7037 (belfosdil) with receptors for calcium channel ligands. *J Biol Chem* 1989; 26: 16598-607.
53. PLOTKIN LI, WEINSTEIN RS, PARFITT AM, ROBERSON PK, MANOLAGAS SC, BELLIDO T: Prevention of osteocyte and osteoblast apoptosis by bisphosphonates and calcitonin. *J Clin Invest* 1999; 104: 1363-74.
54. NEVES M, GANO L, PEREIRA N *et al*.: Synthesis, characterization and biodistribution of bisphosphonates Sm-153 complexes: correlation with molecular modeling interaction studies. *Nucl Med Biol* 2002; 29: 329-38
55. WASNER G: Vasomotor disturbances in complex regional pain syndrome. A review. *Pain Med* 2010; 11: 1267-73.
56. CODERRE TJ, BENNETT GJ: A hypothesis for the cause of complex regional pain syndrome-type I (reflex sympathetic dystrophy): pain due to deep-tissue microvascular pathology. *Pain Med* 2010; 11: 1224-38.
57. GUO TZ, OFFLEY SC, BOYD EA, JACOBS CR, KINGERY WS: Substance P signaling contributes to the vascular and nociceptive abnormalities observed in a tibial fracture rat model of complex regional pain syndrome type I. *Pain* 2004; 108: 95-107.
58. DE MOS M, DE BRUIJN AGJ, HUYGEN FJPM, DIELEMAN JP, STRICKER BH, STURKENBOOM MC: The incidence of complex regional pain syndrome: A population-based study. *Pain* 2007; 129: 12-20.
59. MCKIERNAN FE: Musculoskeletal manifestations of mild osteogenesis imperfecta in the adult. *Osteoporos Int* 2005; 16: 1698-702.