THERAPY

Bisphosphonates for early complex regional pain syndrome

Geoffrey Littlejohn

Neridronate, an aminobisphosphonate, has shown promise in reducing the often extreme and intransigent pain of complex regional pain syndrome. Welcomed clinically, what can this finding tell us about the enigmatic mechanisms of bisphosphonates and of complex regional pain syndrome alike?

Littlejohn, G. *Nat. Rev. Rheumatol.* **9**, 199–200 (2013); published online 29 January 2013; doi:10.1038/nrrheum.2013.6

In terms of quality of life, complex regional pain syndrome (CRPS) is a high-impact disorder, owing mainly to the effect of extreme levels of pain. Mechanisms that cause CRPS remain unclear and, as a consequence, predictable and effective treatment is often suboptimal.[1] Findings of a placebo-controlled trial reported by *Varenna et al.*,[2] that the aminobisphosphonate neridronate shows significant benefits in patients with CRPS, are therefore important to clinicians dealing with this disorder.

CRPS has been known by many different names, and diagnostic criteria have evolved over time. As no gold-standard diagnostic test exists, CRPS is evaluated on the phenotypic clinical presentation (Figure 1). Combinations of symptoms and signs representing changes in sensory, vasomotor, sudomotor and/or oedema, and motor and/or trophic domains are assessed and scored in order to facilitate diagnosis.[3] Pain is the dominant feature; when CRPS is precipitated by a physically traumatic event the pain is disproportionate to the expected outcome of that trauma. Alternative causes of the particular clinical presentation are always to be considered. Prognoses with current treatments are better in early stages of CRPS, dominated by vasomotor and oedema changes, compared with later stages, in which trophic changes and persisting pain can occur. The management of any patient with CRPS at any time is, however, problematic.

The mechanisms of CRPS are indeed complex. After a decade or so of progress in understanding, the autonomic nervous system is no longer thought to be the key driver of CRPS.[1] By contrast, major changes occur within the pain-related nervous system, ranging from the brain to the area of clinical involvement.[4] Changes of cortical organization occur in a predictable fashion in the somato-sensory, motor and related brain regions of the involved limb, and contribute to ongoing symptoms.[5] Central sensitization in the spinal cord alters sensory input from not only nociceptive A-δ and C fibres, but also from the A-β mechano-receptor fibres. Increased activity in any of these systems (usually in all of them at once) associates with the clinical signs allodynia—induction of pain by innocuous stimuli—and hyperalgesia, in which painful stimuli trigger an exaggerated pain response. Activation of the C-fibre system also results in release of potent neuropeptides at the site of the CRPS. These neuropeptides, which include substance P and calcitonin gene-related peptide, among others, act locally to cause vasodilatation and plasma extravasation,[6] termed neurogenic inflammation. Neuropeptides are also involved in local activation of mast cells, with subsequent release of pro-nociceptive substances, such as β-nerve growth factor (β-NGF). Besides neuromediators, increased levels of inflammatory cytokines are also present in early CRPS.[4,7]

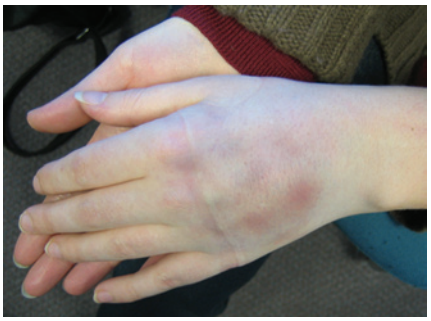

Figure 1 | Clinical signs of CRPS. The photo shows CRPS of the left hand and wrist in a young woman, several weeks after she sustained minor trauma to the region. Characteristically, regionalized abnormal swelling, discolouration and coolness are accompanied by extreme sensitivity to light touch. Abbreviation: CRPS, complex regional pain syndrome.

Thus, key mechanisms contributing to CRPS comprise regionalized feedback loops involving neurogenic inflammation, central sensitization and cortical reorganization, each contributing in different ways and at different time periods to the clinical presentation of the syndrome. Unsurprisingly, many different management strategies, with varying benefit, have been used to treat CRPS.[1]

Aminobisphosphonates are effective in decreasing bone pain in metastatic disease, Paget disease, myeloma and regional osteoporosis.[7,8] They are also known to be beneficial in some patients with CRPS, based on anecdotal observations and small studies,[7,9,10] but evidence supporting their benefit in CRPS has not previously been of high quality. The investigation by Varenna *et al.*[2] is the best study conducted to date, with 82 patients fulfilling current diagnostic criteria for CRPS evaluated for clinically meaningful outcomes and followed over a 1-year time period.[2] All patients had pain rated at >50 on a 100 mm visual analogue scale (VAS). Previous or concomitant therapy use is not discussed in the report.

Nitrogen-containing bisphosphonates have high affinity for the surface of bone and are taken up by osteoclasts during osteolysis. As well as neridronate, used in the current trial,[2] these potent agents

include disodium pamidronate, alendronic acid, ibandronate sodium, risedronate sodium and zoledronic acid.[7] These compounds decrease osteoclast function and hence modulate bone resorption; the process occurs through a number of mechanisms, particularly inhibition of the enzyme farnesyl diphosphate synthase.[7] In CRPS, aminobisphosphonates seem to be most effective in high doses and in the current trial,[2] 100 mg doses of neridronate were given intravenously four times over 10 days, estimated to be equivalent to pamidronate at 90 mg given four times over 4–10 days.

A ≥50% reduction of the pain VAS score was seen in 73% of patients in the neridronate group versus 32% in the placebo group, at 40 days (a 40.7% treatment difference; 95% CI 20.8–60.5%, $P = 0.0003$).[2] Reduction in pain was associated with decreased allodynia, hyperalgesia and oedema, and improvements in quality of life indices correlated with these pain-related clinical outcomes. Subsequent treatment of patients from the placebo group after the 40-day mark with the active medication produced similar outcomes to those in the patients initially treated with neridronate, such that in the total group, no patient had clinical features of CRPS at 1 year. The study entry criteria note that all these patients initially had CRPS for less than 4 months and all showed abnormal changes on bone scintigraphy scans; these features identify a sub-group of patients with CRPS who are likely to have active bone-related pain mechanisms.[2]

Given these promising results, are there any downsides to using bisphosphonates as early as practical in CRPS? Almost a third of patients treated with neridronate developed polyarthralgia and a fifth developed fever at the time of infusion, with much lower frequencies in the placebo group.[2] These findings are to be expected with high-dose parenteral bisphosphonate therapy and require co-administration of paracetamol during the course of the infusions. Routine assessments to check for renal impairment or low levels of vitamin D or calcium prior to infusion will minimize other adverse effects of bisphosphonates, such as hypocalcaemia. The risk of osteonecrosis of the jaw has not been evaluated in this setting.

How bisphosphonates influence the mechanisms that drive CRPS is unknown. Substantial changes in bone physiology in CRPS are reflected in various imaging abnormalities early in the clinical course. These features include signs of bone marrow oedema on MRI scans, osteopenia and/or osteoporosis on plain radiographs and change in blood flow on technetium perfusion bone scans. These changes probably relate to the effects on bone of the various inflammatory mediators that are upregulated in CRPS. Bisphosphonates might modulate these effects, particularly the release of protons from activated osteoclasts, thus reducing the acidic sensitization of bone nociceptors.[7] Perhaps in patients with bisphosphonate-responsive CRPS, these peripheral bone-related mechanisms provide key counteracting input to the amplified nociceptive feedback loops described above, and the abnormal pain response seen in CRPS is subsequently downregulated. Notably, bisphosphonates also have effects on cells other than osteoclasts, such as macrophages and microglia, including those that produce the pro-nociceptive β-NGF. This microglia-mediated mechanism may account for the potent antinociceptive effects of bisphosphonates seen in various animal models of non-bone pain, emphasizing the additional central actions of bisphosphonates on pain.[7]

The effects of bisphosphonates in CRPS raise new questions about the mechanisms of CRPS and about the pleiotropic qualities of bisphosphonates. In adults, early use of high-dose nitrogen-based bisphosphonates now rates high on the evidence-based list of appropriate treatments for this enigmatic condition.

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Competing interests
The author declares no competing interests.

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CRYSTAL ARTHRITIS

Is HLAB genotyping the future of gout pharmacogenomics?

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Pharmacogenomic advances have increased understanding of allopurinol-associated severe cutaneous adverse reactions (SCARs), demonstrating that *HLAB*5801* is a strong risk factor for their development. In some populations, all patients with allopurinol-induced SCARs carry this allele. New treatment recommendations outline how this discovery should influence gout therapy, particularly the use of allopurinol.

Singh, J. A. *Nat. Rev. Rheumatol.* **9**, 200–202 (2013); published online 12 February 2013; doi:10.1038/nrrheum.2013.20

Allopurinol is the most commonly used medication for the treatment of hyperuricaemia in patients with gout. Allopurinol hypersensitivity syndrome (AHS) is a rare but important complication of allopurinol therapy, given that the associated mortality