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EDITORIAL

Bisphosphonates for osteoarthritis

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Abstract

Synovitis and subchondral bone turnover are associated with pain in osteoarthritis. Bisphosphonates provide tools for investigating these pathogenic mechanisms and also may have therapeutic potential. Translating preclinical findings into new treatments for human osteoarthritis requires a critical appraisal and refinement of animal models, identification of those pathogenic mechanisms that are amenable to intervention, and pharmacological targeting of those mechanisms in the right people at the right time.

Osteoarthritis (OA) is increasingly prevalent as the population ages, and current treatments focus on the relatively short-term relief of symptoms. Clinical trials of disease modification are expensive, requiring prolonged follow-up of large numbers of participants. In the current global financial climate, there is renewed interest in the OA-modifying potential of existing treatments that have been developed for other indications. Bisphosphonates represent one such class of agent, and the paper by Moreau and colleagues [1] in a recent issue of *Arthritis Research & Therapy* provided useful insights into the potential of this class for OA.

Moreau and colleagues reported reduced pain responses when subcutaneous tiludronate was administered to dogs after surgical induction of OA. Furthermore, tiludronate reduced synovitis (effusion, synovial fluid prostaglandin E_2 concentration, and lining cell score) and increased subchondral bone thickness. By contrast, an earlier clinical trial of risedronate in patients with OA revealed a disappointing lack of symptom relief compared with placebo [2]. However, lack of efficacy may be explained by the limited potency of risedronate or, in this heterogenous disease that varies with time, inadequate targeting to those most likely to benefit. Collectively, these reports raise some important questions about the use of bisphosphonates and general issues for the development of new treatments in OA. How clinically relevant are animal models? Which key pathogenic mechanisms are amenable to intervention? How can treatments be targeted to those mechanisms in the right people at the right time?

Surgical models build on the well-recognized association between OA and preceding internal derangement [3]. Their predictable onset and rapid development by comparison with spontaneous models facilitate the testing of pharmacological interventions. Most researchers use small-rodent models of OA, although it has been argued that these may inadequately represent the pathogenic processes in humans because of differences in aging and joint biomechanics. Moreau and colleagues partially avoided these problems by studying OA in dogs, although this raises its own ethical issues. The authors maximized the scientific outputs from their study by reporting multiple clinical, biochemical, and histological outcomes. They minimized animal numbers by referring to historical controls rather than using sham surgery. This does, however, hinder interpretation of whether anti-inflammatory effects are directed at OA itself or post-surgical inflammation.

Bisphosphonates could act through several mechanisms. Abnormal bone turnover in OA leads to a zone of osteoporosis beneath the thickened subchondral plate, altered flexibility, and increased microfracture [4]. Osteoclasts mediate the extension of channels from marrow spaces into the non-calcified articular cartilage. The resulting loss of osteochondral integrity exposes subchondral nerves to proinflammatory and algesic factors from the synovial fluid and permits sensory nerve growth into the non-calcified articular cartilage [5]. Furthermore, osteoclasts may reduce pH at the osteochondral junction, thereby sensitizing and activating sensory nerves through actions on ion channels on their peripheral terminals [6].

The data of Moreau and colleagues are consistent with effects of bisphosphonates on subchondral bone turnover but also suggest possible actions on synovitis. Inflammation is a common feature of OA and is associated both

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with symptoms and with structural progression [7]. Inflammation in OA synovium is characterized by a predominance of macrophages, which can be targeted by bisphosphonates [8]. However, anti-inflammatory cyclo-oxygenase inhibitors and glucocorticosteroids have only short-term effects on pain in humans. This may be because the catabolic effects of these inhibitors and glucocorticosteroids offset potential long-term clinical benefit, and the possibility that bisphosphonates may protect joint structure while inhibiting inflammation deserves further study.

The quest for structural disease modification in OA has focused largely on joint space narrowing, indicative of cartilage loss and meniscal extrusion, and osteophytosis. However, each of these defines structures that may not be direct sources of pain. The data of Moreau and colleagues support the findings of other groups indicating that structural treatments, despite having little effect on chondropathy or osteophytosis, could reduce pain [9]. Magnetic resonance imaging features more closely associated with pain in OA include synovitis and bone marrow lesions.

Bone marrow lesions identify regions of increased subchondral bone turnover and therefore may provide a biomarker that can predict response to bisphosphonates. Laslett and colleagues [10] recently reported a placebo-controlled trial of the potent parenteral bisphosphonate, zoledronic acid, and showed improved pain in people with OA and bone marrow lesions. It remains to be determined, however, whether bisphosphonates act exclusively through subchondral bone turnover or whether they may also be effective if targeted to people during OA-associated synovitis.

Animal models reflect the understanding of the pathogenesis of OA at the time they were developed. Investigating subchondral bone changes and synovitis requires a critical use and refinement of these models. A better understanding of how they reflect the clinical spectrum of OA will facilitate the translation of novel treatments to clinical practice. The bisphosphonate story continues to evolve and there remains optimism that it may lead to targeted treatments with greater effectiveness in the near future.

Abbreviation

OA, osteoarthritis.

Competing interests

The authors declare that they have no competing interests.

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