Editorial

Bisphosphonates for Arthritis — A Confusing Rationale

Bisphosphonates are among the most successful group of therapeutics introduced for diseases that afflict humanity. Their ability to regulate bone turnover through suppression of osteoclast activity together with their selective localization in bone has inspired their widespread use in a variety of disorders of bone metabolism, namely, osteoporosis, Paget's disease, and skeletal metastases, as well as less familiar disorders such as fibrous dysplasia, sympathetic dystrophy, and Charcot's arthropathy[1-3]. Disordered bone metabolism, both systemic and local, is clearly a major feature of many rheumatic conditions as exemplified by rheumatoid arthritis (RA), which is associated with both generalized as well as periarticular osteoporosis. In addition, there is now compelling evidence that joint erosion is crucially dependent on osteoclast activity that is in turn regulated by proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin 17 (IL-17) as well as the major activator of osteoclast function, osteoprotegerin ligand[4,5].

It has hardly been a gigantic leap of faith, therefore, to propose that bisphosphonates might be effective, not only for the management of systemic osteoporosis, but also as a useful adjunct in preventing structural damage locally. Indeed, evaluation of these agents in immunological functional assays *in vitro* and in animal models of arthritis reported several decades ago also suggested that these compounds might possess useful antiinflammatory properties[6,7]. Despite this apparently sound rationale, one could reasonably argue, based on studies performed to date, that bisphosphonates have yet to live up to their promise in the treatment of inflammatory and erosive arthritis.

The 2 year randomized trial of etidronate in RA by Valleala and colleagues published in this issue of *The Journal* is in many ways typical of studies to date evaluating bisphosphonates in RA[8]. Forty patients with RA of less than 5 years' disease duration were randomly allocated to either antirheumatic therapy plus intermittent cyclical oral etidronate or antirheumatic therapy alone. There was no matching placebo, and vitamin D status of study patients was not available. Changes to concomitant disease modifying antirheumatic therapy and/or oral steroids were then permitted as considered appropriate by the treating physician, although apart from stipulating numbers of disease modifying antirheumatic drugs (DMARD) used at baseline and end of the study, no information is provided regarding specific DMARD usage during the trial within each treatment group. Etidronate treated patients showed a decline in mean prednisone dose over the duration of the trial, while the control group showed a slight increase. Clearly, this study was not sufficiently powered to detect statistically significant differences. No significant differences in measures of disease activity [Disease Activity Score 28 (DAS), C-reactive protein (CRP), erythrocyte sedimentation rate] or structural damage (erosion score, joint space narrowing score) were evident. A significant decline in some bone markers was evident (serum amino-terminal propeptide of Type I procollagen and serum carboxy terminal telopeptide of Type I collagen), but not in one other marker measured [serum amino-terminal telopeptide of Type I collagen (NTx)]. However, baseline levels of these markers were well within the reference range, and study inclusion criteria required only 4 swollen joints out of 66 and elevated acute phase reactants either at baseline or within the previous 12 months. Mean DAS 28 score at baseline indicated moderately active disease that did not change a great deal over the 2-year course of the study despite *ad libitum* use of DMARD, although notable reductions in CRP were evident. Correlation analysis showed that the best marker for predicting change in radiographic scores was the serum NTx, although none of the markers correlated with variables of disease activity. The authors suggest that the effects of etidronate therapy on serum NTx were minor because this agent is incapable of preventing the collagen breakdown

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associated with inflammatory and erosive joint diseases. They, however, justify the use of etidronate for this particular trial rather than more potent bisphosphonates, such as alendronate or risedronate, on the basis that non-aminobisphosphonates such as clodronate and etidronate appear to be more effective in the collagen induced model of arthritis. In addition, it is stated that previous RA trials with the aminobisphosphate pamidronate had shown that it was unable to prevent focal bone erosions despite a reduction in systemic bone loss.

Aminobisphosphonates such as pamidronate, alendronate, and risedronate are considerably more potent than non-aminobisphosphonates in suppressing bone markers such as NTx and in *in vitro* assays of osteoclastic activity[9,10]. The apparent lack of efficacy of pamidronate in RA seems, therefore, disappointing, and together with the data provided by Valleala and colleagues casts serious doubts on the merits of bisphosphonate therapy as a therapeutic approach for inflammatory and erosive arthritis. However, this nihilistic view is unwarranted. The rationale for the choice of bisphosphonate and the setting(s) for their optimal use warrant further reexamination.

The molecular pharmacology of bisphosphonates has been carefully examined and it is now well established that the non-aminobisphosphonates, such as etidronate and clodronate, exert at least some of their effects following metabolism by macrophage and osteoclast cell lines to non-hydrolyzable methylene-containing analogs of ATP, which are potent inhibitors of numerous ATP-dependent enzymes[11]. Aminobisphosphonates, on the other hand, inhibit one or more enzymes in the mevalonate pathway, leading to decreased generation of 2 isoprenoid lipids, farnesyl diphosphate and its metabolite, geranylgeranyl diphosphate, which are necessary for the lipid modification (prenylation) of GTP-binding proteins[12]. This is necessary for the translocation of such proteins from the cytosol to the membrane fraction where they act as a molecular switch transducing a wide array of extracellular growth and differentiation signals from cell surface receptors to the nucleus.

Early experiments performed *in vitro* compared the effects of clodronate and pamidronate on cultured cells of the monocyte/macrophage lineage. Pamidronate was shown to be more potent than clodronate in suppressing cell proliferation, cell growth, cell migration, costimulatory activity for T cells, and inhibition of lipopolysaccharide (LPS) stimulated secretion of proinflammatory cytokines IL-1ß and TNF-α[7,13-15]. These effects were generally observed at concentrations $> 5 \times 10^{-5}$ M. However, absorption of all bisphosphonates through the gastrointestinal tract is very poor, resulting in very low serum concentrations, casting doubt on the relevance of these observations to administration of drug *in vivo*. On the other hand, these agents do have a strong affinity for hydroxyapatite in bone, where it has been estimated that drug concentrations may approach 10^{-3} M[16]. The presence of bone particles enhances the cytotoxicity of clodronate for macrophages by a factor of roughly 240 by concentrating drug at the bone surface[17]. The presence of subchondral bone marrow inflammation and high rates of bone turnover have now been recognized in both RA and ankylosing spondylitis (AS); it likely facilitates concentration of drug within subchondral bone to levels that could impair macrophage function[18,19].

An alternative experimental approach has been to compare the potency of these compounds when encapsulated in liposomes, which allows increased delivery of drug into cells, particularly endocytic cells such as macrophages. In contrast to the observations with free drug, *in vivo* studies with liposomal formulations showed that clodronate was more toxic than pamidronate for splenic macrophages[20]. Further, additional studies using liposome encapsulated compounds showed that non-aminobisphosphonates inhibited, in a dose-dependent fashion, both proinflammatory cytokine and nitric oxide secretion from LPS activated macrophages, while an aminobisphosphonate, ibandronate, which is about 50 times as potent as pamidronate in assays of osteoclastic bone resorption, enhanced LPS induced secretion of IL-1ß and IL-6, but did not affect TNF-α or nitric oxide secretion[21]. Intravenous administration of aminobisphosphonates to patients for the treatment of Paget's disease is associated with an acute phase response characterized by transient pyrexia, lymphopenia, elevated CRP, and an increase in circulating IL-6 and TNF-α[22]. In contrast, this has not been observed with either etidronate or clodronate. These observations have led some to propose that bisphosphonates can generally be subdivided into proinflammatory aminobisphosphates and antiinflammatory non-aminobisphosphonates[23].

These conclusions are almost certainly an oversimplification. The acute phase response seen *in vivo* is primarily observed following the first intravenous infusion of aminobisphosphonate and is usually not observed following subsequent infusions, even when rechallenged several months later[24]. There is also little data documenting the effects of chronic bisphosphonate administration on immune function *in vivo*. One study examined 32 patients who received 40 mg of alendronate or placebo orally for 90 days[25]. A significant decrease of IL-1ß, IL-6, and TNF-α was observed after 30 days and persisted after 90 days, accompanied by significant reductions in ESR, CRP, and swollen joint count. As for animal models of arthritis, several studies have established the antiinflammatory efficacy of both amino and non-aminobisphosphonates in the treatment of adjuvant arthritis[26-28]. There have been no studies directly comparing amino and non-aminobisphosphonates. With respect to collagen induced arthritis, pamidronate lacked efficacy in one study[29], while clodronate given in doses 5-fold greater than pamidronate modestly decreased clinical and histological signs of

arthritis in another study[30]. In one comparative study, it was shown that alendronate lacked efficacy as compared to clodronate given in substantially higher doses (> 20-fold)[31]. Even then, despite a significant decrease in the incidence and severity of the arthritis, clodronate appeared to be no different from the saline control or aminobisphosphonate treatment groups with respect to the severity of bone destruction within joints. Several reports have examined liposomal clodronate administered systemically and demonstrated amelioration of established adjuvant antigen and collagen induced arthritis[32,33]. There have been no reports evaluating liposomal aminobisphosphonates in these animal models, although intraarticular administration of ibandronate in one study exacerbated antigen induced arthritis[34]. On the other hand, one study showed that pamidronate prevents joint erosions in TNF-α transgenic mice and is synergistic with osteoprotegerin[35]. One may, therefore, reasonably conclude that although there is evidence in support of their efficacy in arthritis, there is little evidence to support selection of a specific bisphosphonate(s) for longterm administration.

What conclusions can be drawn from studies in human arthritis? There have been 6 double-blind, placebo-controlled trials of bisphosphonates in RA — 4 with pamidronate, one with alendronate, and one with clodronate. In the first study with pamidronate, 40 patients were randomized to either 30 mg of pamidronate by monthly intravenous infusion or placebo for 48 weeks[36]. No significant effects on disease activity or radiological progression were evident despite significantly reduced markers of bone resorption, although all patients had already been stabilized on a disease modifying agent, penicillamine, and this was not discontinued prior to study entry. In contrast, a second study examined the effects of a single intravenous infusion of placebo or 20 or 40 mg of pamidronate in 30 patients with active RA[37]. At 21 days after the infusion, there was a significant clinical improvement with both doses of pamidronate and improvement in the ESR and CRP after the 40 mg dose. This same group then examined 105 RA patients randomized to either 300 mg oral pamidronate daily or placebo for 3 years[38]. No significant treatment group difference in disease activity or radiological scores was evident. Interpretation of these data is complicated by the fact that the study was not designed to evaluate antiinflammatory efficacy but rather changes in bone mineral density; disease activity was low at baseline and improved significantly in both treatment groups. Despite this, a change in concomitant DMARD therapy was required significantly more commonly in placebo patients than in those receiving pamidronate. Maccagno, *et al* examined oral pamidronate 1000 mg per day in 27 patients in a one-year placebo-controlled trial[39]. Despite more severe disease at baseline, pamidronate treated patients experienced significant improvement in disease activity and erosion score. A small double-blinded study of 36 patients with RA, randomized to either placebo or 1600 mg of clodronate, demonstrated a significant fall in the CRP by one month and a trend towards improvement in the articular index at 24 weeks in patients who received clodronate[41]. In summary, different patient selection criteria and clinical trial designs, differences in therapeutic regimes, and small patient numbers do not allow any firm conclusions to be drawn, although there appears to be marginal evidence for efficacy when higher doses of pamidronate have been examined.

More intensive therapy with intravenously administered pamidronate has been examined in patients with AS refractory to nonsteroidal antiinflammatory drug therapy. A controlled, dose-response evaluation comparing 60 mg versus 10 mg given monthly for 6 months demonstrated a delayed onset of clinical efficacy that was primarily evident in those patients with axial inflammation[42]. Improvement in acute phase reactants and peripheral joint pain was not evident, although numbers were small. These findings were consistent with a previous open label study using contrast enhanced dynamic magnetic resonance imaging to evaluate inflammation within periarticular bone marrow and synovium[43]. Amelioration of inflammation was more evident within bone marrow than in synovium. This is hardly surprising given that the half-life of bisphosphonate in peripheral blood is only about 1 hour[44]. Administration on a monthly basis is, therefore, highly unlikely to ameliorate synovial inflammation. The more impressive effects observed in AS compared to RA likely reflect the higher cumulative dose of drug administered, together with the preeminence of osteitis versus synovitis in AS.

What can we conclude from the clinical studies performed to date and what does the future hold for the concept of bisphosphonates in arthritis?

1. Serum concentrations achieved with currently available bisphosphonates using doses typical for osteoporosis are unlikely to be associated with any clinically meaningful immune modifying effects. To expect amelioration of synovitis with orally administered drug is, therefore, not realistic.
2. Significant antiinflammatory effects may be observed within bone marrow, since it is likely that selective localization of drug at the sites of high bone turnover typically associated with inflammation will lead to sufficiently high concentrations capable of inducing alterations in macrophage function and/or cytotoxicity. Consequently, inflammatory arthritides where osteitis is a prominent component are more likely to be responsive to bisphosphonate therapy. This may also be worth examining in certain categories of patients with osteoarthritis[44].
3. No conclusions can yet be drawn regarding the potential efficacy of bisphosphonates in ameliorating structural damage in RA. The most potent aminobisphosphonates

currently available that are associated with the most profound reductions in bone markers, such as NTx, have yet to be examined in sufficiently powered controlled trials.

4. There is emerging evidence that bisphosphonates may be chondroprotective. One study has shown that bisphosphonates prevent chondrocyte apoptosis following culture with dexamethasone[45], while alendronate has been shown to inhibit active collagenase-3 (matrix metalloproteinase 13) at concentrations attainable *in vivo*[46]. Clinical studies have demonstrated reduced breakdown of Type II collagen in postmenopausal women treated with either ibandronate or alendronate using a novel assay measuring urinary C-telopeptide of Type II collagen[47,48]. We have demonstrated reductions in surrogate markers of articular cartilage degradation, such as metalloproteinases 1 and 3, in AS patients treated with pamidronate[49].

In the latter context, it should be recognized that bisphosphonates exert distinct effects on different cell types, promoting apoptosis in osteoclasts but preventing apoptosis in chondrocytes and osteoblasts[45]. It may therefore be a mistake to assume that the relative antiresorptive potencies of the different agents necessarily reflect their additional biological properties on other cell types. Finally, it may also be a mistake to assume that the effects observed *in vitro* or with short term administration *in vivo* necessarily predict what might be observed during chronic administration *in vivo*.

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