Bisphosphonates – Targeting bone in the treatment of spondyloarthritis

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ABSTRACT

The increased prevalence of osteoporosis and recognition of the importance of subchondral bone marrow inflammation in ankylosing spondylitis, together with in vitro *and animal model data indicating that bisphosphonates may possess anti-inflammatory properties, constitute a theoretical rationale for their evaluation in this disease. Open evaluation of intravenous pamidronate in some but not all studies has demonstrated efficacy whilst controlled evaluation of a monthly regime has shown that therapy is efficacious in about 60% of patients, although effects are delayed, treatment being necessary for at least 6 months.*

Recent development of new therapeutic modalities and diagnostic imaging techniques may change the current treatment paradigms for SpA.

Bone - A therapeutic target in spondyloarthritis

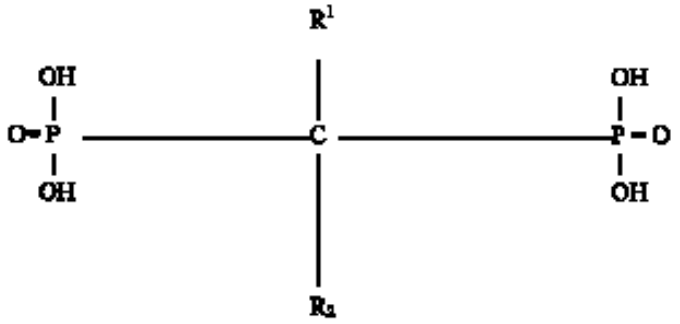
Over the past decade, ongoing refinements in magnetic resonance imaging (MRI) together with reappraisal of the histopathology of early disease have highlighted the significance of inflammation within subchondral bone marrow as an integral component of the primary lesion both in the sacroiliac joint as well as in the enthesis (1-3). Schichikawa *et al*. (4) examined open biopsies from sacroiliac joints of patients with disease of less than two years duration and remarked on the presence of subchondral bone marrow inflammation in all patients, particularly in the iliac portion of the joint. In a more recent analysis, Francois *et al*. (5) confirmed the presence of subchondral bone marrow inflammation as a characteristic feature of sacroiliiitis and noted that enthesitis was unimpressive. Lalou *et al*. (6) compared biopsy material from cruciate ligament entheses in the knee and vastus lateralis femoral entheses in patients with SpA, RA and controls. Bone marrow inflammation and infiltration with CD8+ T-cells was confined to biopsies from patients with SpA.

The extent of change observed on MRI of the sacroiliac joints is commensurate with histopathological grading on biopsies taken at the time of imaging (7). There has also been recognition that active disease is associated with increased bone turnover and excess bone resorption leading to the premature onset of osteoporosis despite the concomitant development of ankylosis (8). Excess bone turnover and penetration of subchondral bone with invasion of cartilage by granulation tissue has also been recognized in the sacroiliac joint of B27 transgenic rats (9).

Bisphosphonates - Potential anti-inflammatory agents

Bisphosphonates are synthetic analogues of pyrophosphate and have found widespread use in disorders of bone metabolism. Their potential value as anti-inflammatory agents was first recognized several decades ago when they were shown to be of benefit in limited numbers of patients with RA (10).

Several observations *in vitro* have suggested that they could exert beneficial anti-inflammatory properties. These include inhibition of antigen presentation by monocytes associated with impairment of IL-1β generation as well as inhibition of macrophage growth, migration, differentiation, and viability (11-13). Their effects on cytokine generation are complex and dependent on the molecular class of bisphosphonate examined, the concentration employed, the cell type examined, evaluation of cultured cells versus whole blood assays, and single versus chronic dosing. Those bisphosphonates containing nitrogen in the R2 side chain (Fig. 1), the so-called aminobisphosphonates



	R^1	R^2
Etidronate	OH	CH_3
Clodronate	Cl	Cl
Pamidronate	OH	$CH_2CH_2NH_2$
Alendronate	OH	$CH_2CH_2CH_2NH_2$
Ibandronate	OH	$CH_2CH_2N(CH_3)$(Pentyl)
Risedronate	OH	CH_2-3-pyridine
Zoledronate	OH	CH_2(1H-imidazole-1-yl)

Fig. 1. The molecular structure of aminobisphosphonates, which contain a nitrogen in the R2 side chain.

such as ibandronate and pamidronate, have been shown to sensitize cells to the generation of pro-inflammatory cytokines in whole blood assays cultured with lipopolysaccharide (14). On the other hand, exposure of cultured macrophage cell lines to pamidronate suppresses generation of pro-inflammatory cytokines (15). This suppression appears to be a dose-dependent phenomenon (observed at concentrations > 10^{-5}M) and unlikely to be evident with serum levels achieved by conventional dosing *in vivo* [peak level attained following a single intravenous infusion of 60 mg pamidronate equals 10^{-5} M (16)]. However, it has been estimated that drug levels in the vicinity of resorbing bone may be as high as 10^{-3}M (17).

Recent work has shown that the aminobisphosphonates specifically inhibit the enzyme farnesyl diphosphate synthase in the mevalonate pathway resulting in decreased generation of prenyl groups which are necessary for the lipid modification of small GTP-binding proteins e.g. Ras, Rac, Rho (18, 19). This is relevant to the mechanism by which inflammation is mediated since the action of many pro-inflammatory cytokines occurs through the Ras superfamily of small monomeric GTPases that transduce a wide array of signals from cytokine cell surface receptors to the nucleus (20). It is of further interest that statins have been shown to possess anti-inflammatory properties since these agents also inhibit an enzyme in the mevalonate pathway (21).

Bisphosphonates, particularly aminobisphosphonates, appear to be particularly efficacious in adjuvant and antigen-induced arthritis but have been less effective in collagen-induced arthritis (22-24). One study has shown that pamidronate retards structural damage in a TNFα transgenic mouse model (25).

Intravenous (iv) administration of aminobisphosphonates in patients induces clinical and immunological effects not observed with oral dosing. A transient acute phase reaction consisting of arthralgias, myalgias, and fever accompanied by short-lived lymphopenia (7-10 days), elevated C-reactive protein, and interleukin 6 levels, has been recognized for several years (26). Lymphopenia recurs with subsequent infusions but is usually less dramatic (unpublished observations). Some have suggested that lymphopenia is a reflection of upregulation of adhesion molecules and redistribution of lymphocytes to certain vascular beds, eg. small intestine (27). However, we have been unable to verify these observations (unpublished). One report describes the use of high dose alendronate, 40mg a day for 90 days, in patients with RA which was followed by amelioration of disease, suppression of pro-inflammatory cytokines and reduced acute phase reactants (28). Another report describes decreased spontaneous IL1β after 1 year in peripheral blood monocytes of RA patients receiving 60mg pamidronate iv every 3 months (29).

In concluding, there is accumulating evidence that bisphosphonates possess anti-inflammatory properties, particularly at the high concentrations found in the vicinity of resorbing bone, which provides a theoretical rationale for their evaluation as anti-inflammatory agents in AS.

Bisphosphonate therapy in spondyloarthritis – Why pamidronate?

Pamidronate is the most potent bisphosphonate available as an intravenous preparation and its tolerability and adverse event profile has been particularly well studied in the long-term management of Paget's disease. It has also been given long-term to breast carcinoma patients with bone metastases at a dose of 90 mg intravenously every three to four weeks for up to two years (30).

The anti-inflammatory properties of bisphosphonates demonstrable *in vitro* are clearly dose dependant. This raises the question as to whether the concentrations required to modify immune cell function *in vitro* can be achieved *in vivo*. In contrast to the orally administered bisphosphonates currently used in clinical practice, the intravenous administration of pamidronate temporarily exposes circulating immune cells and peripheral tissues to relatively high concentrations (10^{-5} M), followed by selective localization to sites of active bone turnover. One study has shown that iv pamidronate induces prompt resolution of bone marrow edema syndrome as documented on MRI (31).

Open studies evaluating pamidronate in NSAID-refractory AS

In Edmonton, two regimes of iv pamidronate in patients with NSAID refrac-

tory AS were evaluated. In the first study, 16 patients with mean disease duration of 12.3 years were examined: one group of 8 patients received six monthly infusions, 30 mg for the first three months and 60 mg for the next 3 months, whilst a second group of 8 patients received 60 mg monthly for three months (32). The 30-60 mg dosage range was chosen as this falls within the range used in the management of Paget's disease and osteoporosis. Adverse events were therefore predictable. Significant improvement was noted in indices of disease activity (BASDAI) (33), metrology (BASMI) (34), and ESR, primarily in those patients who received six rather than three monthly infusions. A 38% reduction in the mean BASDAI score was noted by 6 months. Treatment was well tolerated with only one withdrawal due to adverse events over the six-month period. Five out of 7 patients who completed 6 months of therapy had reductions in BASDAI score of greater than 30% that persisted for at least three months post treatment. This outcome compared favorably with a previous study of AS patients receiving three weeks of an intensive inpatient physiotherapy program where a reduction of 16.4% in the BASDAI score was noted (33). However, 40% of patients reported post infusion arthralgias after the first intravenous infusion, precluding further study using a double-blinded placebo controlled design. The largest changes in clinical parameters and ESR were observed between the 3- and 6-month assessment time points, indicating that further evaluation of monthly pamidronate should incorporate at least a six month observation period.

In a second open analysis, dynamic MR imaging with gadolinium augmentation was used that allows quantification of the severity of inflammation as accumulation of gadolinium depends on blood flow and vascular permeability (35). In addition, a more intensive regime of iv pamidronate administration was examined in view of the observation that pamidronate induces lymphopenia lasting 1-2 weeks that could be associated with immunomodulatory consequences (26). Nine patients with short disease duration (mean of 5.5 years) were studied, of whom 5 had ankylosing spondylitis, 3 had undifferentiated spondyloarthropathy and 1 had reactive arthritis. Sixty milligrams of pamidronate was given intravenously on days 1, 2,14, 28 and 56. All had persistently active peripheral synovitis despite therapy with NSAID. Treatment was well tolerated with all patients completing the study. The mean BASDAI decreased by 44.2%, the Bath AS functional index (BASFI) (36) by 47.3%, the mean swollen joint count by 93.8% and the CRP by 66.9%. Maximal rate and magnitude of enhanced MR signal after gadolinium augmentation decreased after pamidronate therapy, especially in the bone marrow. Clinical benefit was often delayed until patients had received at least four infusions. The more impressive effects of treatment on bone marrow compared to synovial inflammation could reflect both localization of drug to sites of active bone turnover with resultant higher concentrations as well as the short half-life of drug in the peripheral blood (1 hour).

In Berlin, 12 patients (11 male, 1 female), all HLA-B27 positive, mean age 45 (range 25 - 68), mean disease duration 20 years (range 2 - 41) with active ankylosing spondylitis (mean BASDAI 5.5, range 3.8 - 8.1) were treated with pamidronate 60 mg intravenously at day 1, 2, 14, 28 and 56 while they were hospitalized for 14 days. The dose and scheme of administration was chosen based on previous experience (see above). Clinical outcome assessments included BASDAI, function (BASFI), BASMI, patient and physician global assessments (VAS), quality of life (SF-12) and CRP. A BASDAI improvement of 30% after 3 months was taken as the primary outcome parameter. Reduction in NSAID dose was allowed. Most patients (n = 11) received all 5 infusions. Three patients dropped out because of inefficacy. In contrast to the previous report from Edmonton evaluating this regime (35), a BASDAI 30% improvement was noted in only 2/11 patients after 3 months. According to the recently proposed ASAS response criteria, improvement was observed in 2/11 patients after 3 months. There was no significant change at any time in BASFI, BASMI, pain, SF-12 mental score, NSAID usage and CRP. No notable differences were found in the characteristics of patients who improved compared to the remaining patients. Even in those who improved no significant change in CRP-levels were seen. Side effects in 6/12 patients were transient arthralgias and myalgias one day after the first infusion. Two patients had a relapse of anterior uveitis, and one patient had a tympanic inflammation during the infusion period. Taken together, in the Berlin study, there were positive effects in single patients but no dramatic mean changes in the whole group. However, the mean disease duration in this cohort was 20 years which contrasts with the Edmonton cohort (mean disease duration of 5.5 years), which also included patients with uSpA, and there are few reports of any therapeutic being dramatically effective in such long standing disease.

A preliminary report from Cordoba describes 8 AS patients with mean disease duration of 14 years that were given 60 mg pamidronate monthly for 6 months (37). A significant reduction in mean BASDAI (50%) was reported but not the BASFI or acute phase reactants. However, the mean baseline BASFI in these patients was only 3.7 indicating a relatively low degree of functional impairment to begin with.

A further preliminary report from Montreal describes an open trial of 14 AS patients, mean disease duration of 13.2 years, who were given 60mg pamidronate monthly for 6 months (38). Two patients withdrew after 3 months for musculoskeletal side effects, one patient received 60 mg pamidronate every 2 weeks for 3 months only, and 2 patients did not attend for 6 month follow up, one for development of vertebral fracture and one was lost to follow up. Intention to treat analysis revealed no significant differences in clinical or laboratory outcomes although 5 of 9 patients who completed the 6-month course had an ASAS 20 response.

In summary, the limited open analyses have not provided consistent data but suggest that efficacy is delayed and that

a 6-month trial is necessary to adequately assess the effects of pamidronate.

Controlled evaluation of pamidronate in NSAID-refractory AS

The observation that the most impressive changes in clinical parameters in the first open study from Edmonton were observed between the three and six month assessment time points and the high incidence of post infusion arthralgias and myalgias on first exposure to pamidronate led to the design of a double-blinded dose response comparison of 60 mg versus 10 mg given iv monthly for six months. The 10 mg dose is the lowest dose of iv pamidronate shown to induce post infusion arthralgia and myalgia (26).

Eighty-four patients with NSAID refractory AS from university and community based practice, were randomized to treatment and 72 completed six months of therapy (39). Treatment was well tolerated despite the high incidence of post-infusion reactions following the first exposure to pamidronate. Only one patient withdrew from the 60 mg group because of adverse events. Significant efficacy was not observed at 3 months but significant reductions in disease activity (BASDAI), and improvement in function (BASFI), patient global (BASGI) (40) and metrology (BASMI), was evident by six months. Sixty-three percent of patients had at least a 25% reduction in the BASDAI. A recent preliminary report indicates that the minimally clinically detectable change in the BASDAI is 23% (41), suggesting that the majority of patients who received 60 mg of pamidronate experienced clinically meaningful improvement. This compared with only 30.2% of patients who received the 10 mg dose. Post hoc analysis employing the ASAS working group response criteria (42) indicated that 60.2% of patients were considered responders in the 60mg group versus 28.2% who received 10 mg. In fact, the 25% reduction in BASDAI response criterion captured virtually all responders defined by the ASAS working group criteria (unpublished data). 39% of patients experienced a ≥ 50% reduction in the BASDAI although further analysis did not reveal any predictive demographic or clinical variables.

There were no significant differences between the 60 mg and 10 mg groups with respect to changes in acute phase reactants. Several factors could account for this: (i) The mean levels for ESR and CRP were only modestly elevated at baseline, especially in the 60 mg group; (ii) Dosing may have been inadequate; (iii) In view of the short serum half-life of pamidronate of only one hour, this agent is likely to exert anti-inflammatory effects primarily at sites of active bone turnover in subchondral bone where it is concentrated rather than on the adjacent synovitis, consistent with the lack of significant effect on peripheral joint pain. It is also recognized that there is a poor correlation between clinical measures of disease activity and levels of acute phase reactants.

Conclusions

Intravenous pamidronate therapy may constitute a new therapeutic advance in the management of NSAID refractory AS. Several questions need to be addressed.

Since response to treatment is delayed, requiring a six-month trial of therapy, additional studies should clarify potential demographic and clinical variables predictive of response. In this regard, bone edema observed on MRI might be an appropriate starting point. Additional studies should examine different dosing schedules, particularly in the context of ensuing response duration, and the effects of oral administration with considerably more potent bisphosphonates e.g risedronate, recognizing that anti-resorptive potency may not reflect anti-inflammatory activity. With the availability of validated measures for assessing structural damage in AS based on plain radiographic analysis e.g. the BASRI (43), it is increasingly essential to incorporate long-term studies of at least one year duration. However, limited sensitivity to change over time using these instruments is still a significant impediment to the practical evaluation of structural damage. By analogy with RA and with the sensitivity afforded by MRI, future therapeutic studies should target patients early in the disease course and aim for clinical and radiological remission. Finally, it is now perhaps appropriate to consider potential combination strategies with other therapeutics shown to be beneficial in spondyloarthritis such as salazopyrin and anti-TNF directed therapies. In particular, although anti-TNF directed therapies appear to be highly effective in ankylosing spondylitis, they require repeated administration, long term side effects remain to be determined, and costs are formidable. Future therapeutic studies are, therefore, likely to examine concomitant use of less costly therapies that might serve to minimize the frequency of administration of the more costly therapies.

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