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PRACTITIONERS SECTION

PAMIDRONATE – A PROMISING NEW CANDIDATE FOR THE MANAGEMENT OF SPONDYLOARTHROPATHY

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ABSTRACT

Bisphosphonate group of agents are known for their anti-bone resorptive properties. However, recently their anti-inflammatory and anti-arthritis properties have come to light. Clinical trials of their use in spondyloarthropathy are showing promising results, especially in patients with shorter disease duration. The adverse event profile is mainly limited to postinfusion arthralgia, myalgia and fever. The concept of pamidronate in spondyloarthropathy management should be evaluated further in light of these clinical studies and could have a major impact on our resource-restricted setting.

KEY WORDS: Pamidronate, Bisphosphonates, Ankylosing spondylitis, spondyloarthropathy

Ankylosing spondylitis (AS) is a frequently occurring chronic disease. For the past several decades, NSAIDs and physiotherapy have been the mainstay of therapy. Most NSAIDs, including the COX-2 inhibitors, are of symptomatic benefit with no disease modifying properties. Sulfasalazine has been evaluated in several trials; however, the results are not consistent. Biological agents have been a major breakthrough in the management of the disease. However, in a country like India these agents will be of limited use in view of the high costs. Hence, the concept of bisphosphonte therapy in AS is worth pursuing in view of its promising reports in western countries.

HISTORY OF BISPHOSPHONATES

Bisphosphonates are pyrophosphate analogues and have been known to the chemists since the 19th century; the first synthesis dating back to 1865.^[1] They were used in industry, mainly as corrosion inhibitors. They were known to inhibit calcium carbonate precipitation and this property led to their use in scaling.^[2] This unique property was later studied both *in vitro* and *in vivo*. These studies revealed their effect on mineralization and bone resorption.^[3,4] They were also found to inhibit ectopic calcification *in vivo* and this led to the hypothesis that local pyrophosphatases

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CHEMICAL STRUCTURE

Bisphosphonates are compounds characterized by two C–P bonds. The P–C–P group is resistant to enzymatic hydrolysis and hence they are not metabolized in the body and excreted unaltered. The P–C–P structure allows a great number of possible variations, mostly by changing the two lateral chains on the carbon. Small changes in the structure of the bisphosphonates can lead to extensive alterations in their physicochemical, biological, therapeutic and toxicological characteristics.

ANTI-ARTHRITIC AND ANTI-INFLAMMATORY EFFECTS

Bisphosphonates have been evaluated in various animal models of arthritis: rat adjuvantinduced polyarthritis, murine-antigen-induced arthritis and a murine model of chronic inflammation; the delayed type hypersensitivity granuloma reaction. They were found to inhibit the chronic inflammatory response associated with delayed type hypersensitivity and erosive arthritis in these animal models.[6-9] Recent work into their mechanism of action has shown that they specifically inhibit the enzyme farnesyl diphosphate synthetase in the mevalonate pathway.^[10] This leads to impaired prenylation of a number of proteins that are involved in inflammatory cascade like the Ras superfamily.[11] Effect has also been noted on cells of the monocyte/macrophage lineage with inhibition of growth, migration, differentiation and viability.^[12,13] Exposure of the cultured macrophages to Pamidronate has been shown to suppress the generation of pro inflammatory cytokines including TNF- α .^[14] This is a dosedependent phenomenon occurring at a concentraion of 10⁻⁵ M. Although these levels are unlikely to be attained by IV Pamidronate in blood, the levels of Pamidronate in the vicinity of resorbing bone are much higher; up to 10⁻³.^[15] Alendronate has been shown to impair the antigen presenting function of the peripheral blood monocytes.^[16] Pamidronate has also been shown to retard structural damage in a TNF- α transgenic mouse model.^[17]

The anti-resorptive properties can also be explained on the basis of the prenylation theory as this affects a number of proteins that ultimately leads to apoptosis of the osteoclasts.^[18]

The evaluation of pamidronate in ankylosing arthritis was prompted by the observation that bisphosphonates reduce chronic inflammation and pathological mineralization in animal models of arthritis.^[19,20]

TRIALS OF PAMIDRONATE IN SPONDYLOARTHROPATHY

In Edmonton, anti-inflammatory properties of pamidronate were evaluated in 16 patients with NSAID refractory active AS.^[21] Sixteen patients with mean disease duration of 12.3 years were randomized to two equal groups. One group received six infusions per month; 30 mg for the first 3 months and 60 mg for the next 3 months while the other group received 60 g per month for 3 months only. An amount of 30-60 mg dose was used in view of the previous

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experience with this dose in Paget's disease and osteoporosis. Clinical outcome measures included the BASDAI for measurement of disease severity, BASFI for measurement of functional impairment, and BASMI for measurement of spinal mobility. Group 1 showed significant improvements in BASDAI and BASMI scores (P<0.03 for both) and in the ESR (P=0.009). Group 2 showed a significant improvement only in the BASMI (P=0.007), with no significant change in BASDAI score or ESR. Five out of the seven patients of group 1 had reductions of the BASDAI score of more than 30% and it persisted for at least 3 months posttreatment. Maximum change in clinical parameters and ESR was observed in the 3-6 month period. Thus, the trial indicated delayed but long lasting and significant effects of pamidronate in NSAID refractory AS.

A second preliminary open study^[22] assessed an intensive regime of Pamidronate (60 mg pamidronate at 1, 2, 14, 28 and 56 days). Nine patients with NSAID refractory peripheral SpA (5-AS, 3-undifferentiated SpA and 1-reactive arthritis) with mean disease duration of 5.5 years were included. Patients were assessed up to 84 days. The study found significant improvement in all clinical and laboratory parameters. The mean BASDAI decreased by 44.2% (P=0.028), mean BASFI by 47% (P=0.015), mean BASGI by 42% (P=0.011), mean ESR by 49.4% and CRP by 66.9%. Additional benefit was also seen in peripheral joints with a decrease in mean tender and swollen joint count by 98.2% (P=0.012) and 93.8% (P=0.017), respectively. Dynamic MR imaging with Gadolinium enhancement was also carried out in these patients at baseline and at posttreatment. Maximal rate and magnitude of the MR signal after Gadolinium enhancement was found to decrease in these patients thus implying the effect on bone marrow edema.

A placebo-controlled trial of pamidronate is not feasible due to the high incidence of posttransfusion (after the first dose) arthralgias and myalgias; thus compromising blinding. An amount of 10 mg dose is the lowest dose of IV pamidronate that has been shown to induce postinfusion arthralgias and myalgias. Hence a randomized, double blind trial^[23] comparing 60 mg vs 10 mg IV pamidronate was conducted. This was also the biggest trial with 84 NSAID refractory AS patients. Seventy-two completed the 6 months therapy. Significant changes in BASFI, BASDAI and BASGI was evident at 6 months (the same were found to be insignificant at 3 months). At 6 months, the mean BASDAI had decreased by 2.22 (34.5%) in the 60 mg group and by 0.93 (15%) in the 10 mg group. Significantly greater reductions in the 60 mg group were also noted for the BASFI (P<0.01), BASGI (P=0.01) and BASMI (P=0.03). Significantly more patients achieved a reduction of >25% in the BASDAI in the 60 mg group vs the 10 mg group (63.4% vs 30.2%; P=0.004).

An open observational study with 12 active AS patients with mean disease duration of 20 years by Haibel et al.^[24] found a significant reduction in the BASDAI (P=0.04), physician and patient global assessment at 3 months. An ASAS 20% response was seen in 2 of 11 patients at the end of 3 months and four of nine patients at the end of 6 months.

Cairns et al.^[25] evaluated the bone markers in patients with AS on Pamidronate. Six infusions per month were given; 30 mg being the starting dose followed by 60 mg. Fifteen patients with mean disease duration of 14.8 years participated in the study. The study revealed a significant fall in degradation products of type-I collagen C-terminal telopeptides (P=0.001), Serum bone GLA protein (P=0.02), bonespecific alkaline phosphatase (P=0.02). Significant improvement was seen in the BASDAI score; but not in BASMI, CRP or ESR.

ADVERSE EVENT PROFILE

Most common adverse event reported after IV pamidronate is flu-like syndrome with fever spike, arthralgias and myalgia. These are largely limited to the first infusion. Another study reported transient arthralgias/myalgias after the first infusion in 68.3% patients.^[23] The adverse events are independent of the dose and are seen irrespective of whether the first dose is 30 or 60 mg.^[26] Prolonged hypocalcaemia is a known but a rare complication of pamidronate infusion.^[27]

CONCLUSIONS

Pamidronate seems to be a potential agent in the management of spondyloarthropathy. This should be viewed in light of the fact that there are very few options in the management of spondyloarthropathies; with TNF- α inhibitors being out of reach of a majority of the population. The disease duration at the start of therapy does seem to affect the outcome of therapy. Postinfusion myalgia, arthralgia, and fever are the commonest adverse effects and are independent of the dose of first infusion. Although disease activity shows an early improvement, a significant improvement in inflammatory markers lags behind the clinical response. Clinical trials with a longer duration should provide significant inputs towards further clinical use of this agent.

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