An open study of pulse pamidronate therapy in severe ankylosing spondylitis, and its effect on biochemical markers of bone turnover.

Andrew P Cairns¹, Stephen A Wright¹, Allister J Taggart¹, Stephen M Coward² and Gary D Wright¹.

¹Department of Rheumatology, Musgrave Park Hospital, Belfast, Northern Ireland, United Kingdom and ²Department of Biochemistry, Musgrave Park Hospital, Belfast, Northern Ireland, United Kingdom.

Corresponding author: Dr Andrew Cairns

Department of Rheumatology

Musgrave Park Hospital

Belfast BT9 7JB

andrewcairns@doctors.org.uk
Sir,

Osteoporosis is a common feature of ankylosing spondylitis (AS), and vertebral fractures are an increasingly recognised complication. Cumulative fracture prevalence rates of between 9.5% and 18% have been reported, with a 6-8 fold relative increased risk of vertebral fracture (1-3). Osteoporosis and new bone formation (syndesmophytosis) suggest that disordered bone turnover plays a role in disease pathogenesis in AS. Bisphosphonates accumulate at sites of increased bone turnover, and inhibit bone resorption by inducing osteoclast apoptosis (4), thereby improving bone density and reducing fracture rates (5). Pulse pamidronate has recently been used with clinical efficacy in the treatment of AS (6,7). Biochemical markers of bone turnover have been used to monitor response to treatment in post-menopausal osteoporosis (8).

The effect of bisphosphonate therapy on biochemical bone turnover markers have not previously been studied in AS. We aimed to study the efficacy of pulse pamidronate therapy in severe AS, and determine its effect on biochemical bone turnover markers.

Patients with severe ankylosing spondylitis were treated with 6 monthly intravenous pulses of pamidronate, receiving 30mg for the 1st infusion and 60mg subsequently. BASDAI and BASMI scores were recorded, and CRP and ESR measured at each visit. Fifteen patients participated (13 male, mean age 44). Mean disease duration was 14.8 years. All patients were receiving NSAIDS. 2 were also receiving sulphasalazine, 1 methotrexate, and 1 azathioprine. No patients were currently receiving an oral bisphosphonate. 4 patients had a history of uveitis, 2 psoriasis, 2 inflammatory bowel disease, and 8 peripheral arthritis.
Fasting blood samples were taken monthly for measurement of biochemical bone turnover markers, according to the manufacturers’ instructions. Degradation products of Type-I collagen C-terminal telopeptides were measured with the serum Crosslaps ELISA assay (Nordic Bioscience Diagnostics A/S, Herlev, Denmark). Serum bone GLA protein was measured using the N-MID Osteocalcin ELISA kit (Nordic Bioscience Diagnostics A/S, Herlev, Denmark). Bone-specific alkaline phosphatase was measured with the Access Ostase assay (Beckman Coulter Inc, Fullerton, California, USA). Non-parametric analyses (Wilcoxon signed-rank tests) on an intention-to-treat basis were used to analyse the data.

Three patients did not complete the study (arthralgia/headache, back pain/nausea, and myalgia respectively). Mean total dose of pamidronate received was 277mg. Initial median serum crosslaps was 1845.0 ng/ml. Mean (SD) population serum crosslaps concentrations are given as 506(255)ng/l for post-menopausal women, 321(155)ng/l for pre-menopausal women and 332(190)ng/l for men. Initial median ostase concentration was 12.4 µg/l. Mean (SD) population ostase concentrations are given as 12.3(4.3)µg/l for men, 8.7(2.9)µg/l for pre-menopausal females, and 13.2(4.7)µg/l for postmenopausal females. Initial median osteocalcin concentration was 19.5 ng/ml. Mean (SD) population osteocalcin concentrations are given as 17.9(6.5)ng/ml for pre-menopausal women, 28.4(9.5)ng/ml for postmenopausal women, and 21.4(9.1)ng/ml for men.

Median serum crosslaps fell from 1845.0 to 556.5 ngl/l (Z=-3.29, p= 0.001) (figure 1). Median serum osteocalcin fell from 19.5 to 16.2 ng/ml (Z=-2.34, p=0.02). Median serum ostase fell from 12.4 to 9.6µg/l (Z=-3.11, p=0.02). Median BASDAI improved from 6.80 to 5.75 (Z=-1.98,
p=0.048), but there was no significant improvement in median BASMI (initial 8.00 v final 7.50, Z=-1.64, p=0.10). There were non-significant trends of reduction in median CRP (initial 36.4 v final 26.6 mg/l, Z=-1.89, p=0.06), and median ESR (initial 38 v final 29 mm/hr, Z=-0.71, p=0.48). There were no significant correlations between clinical measures and bone turnover markers.

In conclusion, pulse pamidronate therapy produced significant reductions in all 3 biochemical bone turnover markers. This was particularly marked for serum crosslaps, the bone resorptive marker, where there was a 69.8% relative reduction. Such marked reduction of the crosslaps concentration suggests that bisphosphonates have a role in the management of the osteoporosis of ankylosing spondylitis. Ultimately studies assessing fracture rates in AS patients on bisphosphonates would be of great interest. One possibility is that by reducing the rate of new bone formation, bisphosphonates may also reduce syndesmophyte formation. However longer term studies controlled studies in patients with early disease are needed to address this issue.

Pulse pamidronate therapy also had a small beneficial effect on disease activity as measured by BASDAI, which has also been demonstrated in a recent randomised controlled study of pamidronate therapy in AS (7). The patients in this study had established, severe disease. All but one would have met recent ASAS criteria for the use of anti-TNF drugs in AS (9). Clinical studies in earlier, less severe disease are required to determine if bisphosphonates may be of benefit to these patients.
References


Figure 1. Median serum crosslaps values

p=0.001