
Infliximab in spondylarthropathy- Influence on bone density

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Clin Exp Rheumatol 2002; 20 (Suppl. 28): S185-S186.

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Key words: Anti-TNF, osteoporosis, bone mineral density, spondylarthropathy.

ABSTRACT

Osteoporosis is frequently associated with Ankylosing Spondylitis (AS). Bone mineral density (BMD) decreased predominantly in patients with active disease. Moreover, conventional therapy, i.e. NSAID seems to have no influence in the bone loss. It has been suggested that local or systemic inflammatory cytokine release might be implicated in bone loss. Monoclonal antibody to TNF α in patients with AS demonstrated significant clinical response with significant reduction in the acute-phase reactants ESR and CRP.

We evaluated the changes in bone mineral density (BMD) in patients with Spondylarthropathy (SpA) treated with infliximab (a human/mouse neutralizing chimeric monoclonal antibody). We included 29 patients. In 6 months, there was a statistically significant increase in BMD both at the spine and total hip. There was an increase in osteocalcin between baseline and week 6. These data suggest a benefit of anti-TNF α therapy on BMD in patients with SpA, may be through an uncoupling effect on bone cells.

It has been recognized for a long time that osteoporosis is frequently associated with Ankylosing Spondylitis (AS). Two longitudinal studies in early AS have shown that spine and hip bone mineral density (BMD) decreased predominantly in patients with active disease (1,2). Moreover, conventional therapy, i.e. NSAID seems to have no influence in the bone loss (1).

The etiology of SpA-associated osteoporosis remains controversial. Among possible mechanisms, inflammatory mediators released during the course of AS, and decreased mobility of patients, might play a role in the occurrence of osteoporosis, by directly affecting bone remodeling.

It has been suggested that local or systemic inflammatory cytokine release might be implicated in bone loss. This bone loss could be related to an in-

crease in bone resorption, and correlations have been established between some biochemical markers of bone resorption on one hand, and erythrocyte sedimentation rate (ESR), and serum C-reactive protein (CRP) level on the other (1, 3). Among factors which can influence bone resorption and osteoclast activity, TNF play a prominent role. This cytokine has been shown to mediate the increase of bone resorption both in systemic osteoporosis related to estrogen deficiency (4), and in periarticular or periprosthetic bone erosions. In a model of transgenic mice expressing soluble TNF receptor to neutralise TNF, animals were protected from estrogen deficiency-related bone loss (5). TNF is also a powerful inhibitor of bone formation (6). TNF appears to have osteoclastogenic properties which are mediated to have osteoclastogenic properties.

However, data on bone formation in AS are controversial, with some studies but not others, showing a decrease in bone formation (7, 8). A negative relationship between serum osteocalcin and serum inflammatory parameters has been observed (9). In ovariectomized rats and mice, it has been shown that the administration of TNF binding proteins stimulated bone formation (10). The mechanism of anti TNF induced bone formation could be either increased osteoblast activity, recruitment of osteoblasts or activation of resting lining cells. However bisphosphonates, which are potent anti-osteoclastic drugs, and able to increase BMD, have no effect on the urinary excretion of free D-Pyr. Whether peptide-bound cross-links markers may have different behaviour during anti-TNF therapy needs further studies. On the other hand, anti-TNF might have indirect effects on bone through the cytokine cascade. Some inflammatory cytokines, including TNF, stimulate the production of osteoprotegerin, a potent inhibitor of osteoclast activity, by human bone marrow stromal cells (11).

Infliximab is a human/mouse neutralising chimeric monoclonal antibody of IgG1K isotype with specificity and high affinity for TNF. It has been successfully used in the treatment of rheumatoid arthritis, Crohn's disease, and spondyloarthropathy (SpA) (12, 13). Monoclonal antibody to TNF in patients with SA demonstrated significant clinical response with significant reduction in the acute-phase reactants ESR and CRP.

We evaluated the changes in bone mineral density (BMD) in patients with Spondylarthropathy (SpA) treated with infliximab (14).

We included 29 patients (6 women; 23 men) aged 22-68 years, having persistently active SpA despite high dose of non-steroid anti inflammatory drug and/or treatment with methotrexate or sulfasalazine. Median duration of disease was 13 years (range: 3-30). Twenty-five patients were treated with 5 mg/kg and 4 with 3 mg/kg of infliximab at week 0, 2, 6 and then received either no infusion (n = 3), or additional infusion of infliximab every other month (n = 6), or in case of relapse only. Lumbar and femoral BMD was measured by dual energy X-ray absorptiometry at baseline and 6 months later. Serum osteocalcin (marker of bone formation) and urinary deoxypyridinoline (marker of bone resorption) were measured in a sub group at all visits.

In 6 months, there was a statistically significant increase in BMD both at the spine and total hip and trochanter. There was an increase in osteocalcin between baseline and week 6. No change in marker of bone resorption was observed at the same time point. There was no

change in biochemical markers between baseline and final visits. These data suggest a benefit of anti-TNF therapy on BMD in patients with SpA, may be through an uncoupling effect on bone cells.

Finally, TNF has been shown to increase bone resorption and decrease bone formation (4, 6). Particularly, an increased mobility of patients might have been an additional cause for increased bone density. Immobility is a well-known risk factor for bone loss but some authors found low bone density in patients with regular exercise therapy, or did not find any relationship between bone loss and baseline functional index or spine mobility (2). However, due to confounding factors, the evaluation of the relationship between the level of physical activity and BMD remains difficult in SpA.

Thus, the positive effects of inhibition of TNF on bone resorption might be annulated by down-regulation of osteoprotegerin. Additional results are needed to assess the bone cell effect of anti-TNF therapy.

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