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## *PERSPECTIVES*

# Anti-TNFα Therapy and Prevention of Bone Loss in Rheumatoid Arthritis

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**Abstract**

Systemic osteoporosis is a well-known complication of rheumatoid arthritis (RA). The bone loss is related to the characteristics of the patient (typically a postmenopausal woman), corticosteroid therapy, and the underlying disease. The increase in bone resorption related to chronic inflammation is increasingly recognized. Anti-TNFα therapy is an effective therapy for RA, and could have a positive effect on bone loss through its potent anti-inflammatory effect. A tight control of inflammation is now the gold standard in RA, and is an effective way to prevent bone loss. *IBMS BoneKEy*. 2011 March;8(3):154-158.


## Introduction

Rheumatoid arthritis (RA) is a systemic, chronic inflammatory disease characterized by distal and symmetrical synovitis, leading to joint destruction. It is the most frequent inflammatory joint disease, affecting 0.5% of the general population, with a female preponderance and an increased prevalence with age. The main extra-articular complications of RA are bone complications including local peri-articular osteopenia (around the inflamed joints) and erosions, and systemic osteoporosis. A number of factors contribute to osteoporosis in RA including age and gender since RA is typically a disease of postmenopausal women, reduced physical activity related to functional impairment and disability, and steroids. All of these factors are strong determinants of the increased risk of fractures, which has been demonstrated consistently in several studies. However, the disease itself is a risk factor for osteoporosis and fractures, independently of steroids, because of inflammation-induced bone loss (1). Prospective studies have shown that optimal control of inflammation is the best strategy to prevent bone complications in RA. Anti-tumor necrosis factor α (TNFα) therapy is now the standard in RA treatment (Table 1). TNFα plays a central role in bone resorption, in both RA and postmenopausal osteoporosis. Thus, anti-TNFα therapy may play a role in the treatment of RA-induced bone loss.

## Inflammation-Related Osteoporosis

Patients with RA are at increased risk of fractures, and fracture risk remains elevated after excluding patients who have taken steroids (2). Several studies suggest that, beside the well-demonstrated deleterious effect of corticosteroids on bone, inflammation itself has a potent role in bone loss. Studies in early RA have shown that vertebral fractures can occur in the first year of the disease, and there is no relationship between cumulative prednisone dose and the presence of vertebral deformities (3-5). Disease activity is consistently associated with low bone mineral density (BMD) (6). Generalized bone loss is observed in early RA, associated with disease activity measured by C-reactive protein (CRP); suppression of disease activity stabilizes this bone loss (7). Moreover, in a 2-year follow-up study, patients whose disease became inactive partially recovered from their initial bone loss (7). A similar relationship between sustained inflammation and BMD loss has been shown in ankylosing spondylitis, a disease in which steroids are not used (1).

Table 1. Available TNFα blockers

- Soluble receptor: etanercept (ENBREL®)
  - Dimeric fusion protein, consisting of the TNFα receptor linked to IgG
- Monoclonal antibodies:
  - Infliximab (REMICADE®)
  - Adalimumab (HUMIRA®)
  - Certolizumab (CIMZIA®)
  - Golimumab (SIMPONI®)

Even in the general population, a small elevation of CRP within the normal range increases non-traumatic fracture risk (8).

The activation of T cells under a Th1 profile results in the stimulation of cells responsible for both cartilage degradation (through metalloproteinase secretion) and calcified cartilage and bone destruction (through the activity of TNF and interleukins (ILs) on bone cells). The main pro-inflammatory cytokines TNFα, IL-1 and IL-6 act on osteoblasts to promote RANKL expression, and osteoclast activity. This effect on osteoclastogenesis is reinforced by the IL-17 pathway (9-11). Moreover, TNFα has down-regulatory effects on osteoblasts (both on differentiation and on mineralization and bone matrix synthesis), and induces apoptosis of osteoblasts. These osteoimmunological results explain the occurrence of osteoporosis and bone destruction during inflammatory processes.

**Bone Effects of Inflammation Control**

Based on the clinical and experimental evidence of the relationship between inflammation and bone loss, one may speculate that any effective anti-inflammatory treatment could have beneficial effects on bone. Actually, this is true, even for low-dose corticosteroids. However, this “low-dose” must be clarified for this purpose. In a prospective, randomized, placebo-controlled study, Laan and colleagues demonstrated that “low-dose” steroids induced spinal bone loss, measured by QCT, over 20 weeks, in 40 patients with RA, but these patients were treated with 10 mg per day for 12 weeks, and the average dose during follow-up was 7.5 mg/d (12). In a study by Gough *et al*. (7) involving 148 patients with early RA, the greatest bone loss was observed in patients receiving 1-5 mg/d, and the loss was greater than in patients receiving more than 5 mg/d, suggesting that at low-dose, steroids are toxic for bone formation, without an effect on inflammation-induced bone loss, the control of which requires higher doses. Thus, interpretation of the clinical studies must take into account the characteristics of patients, and disease activity and inflammation during follow-up. In a study by Van Staa *et al*. demonstrating the increased risk of fracture in RA, the use of disease-modifying anti-rheumatic drugs (DMARDs) in the studied population was low (2). Management of RA has changed over the past several years and the efficacy of treatments has improved dramatically. In a study of 76 RA patients over a decade, Kroot *et al*. (13) did not observe a BMD loss higher than the age-expected effect; 90% of these patients had already been treated with a DMARD during the first year of follow-up, suggesting a strategy based on early control of inflammation.

**BMD Effects of Anti-TNFα**

TNFα promotes bone resorption and is thus a potential target in any condition characterized by increased bone resorption, including postmenopausal bone loss. Estrogen deficiency induces bone loss by enhancing TNFα (14), and transgenic mice

expressing soluble TNFα receptor are protected against ovariectomy-induced bone loss (15). TNFα antibodies prevent bone loss in collagen-induced arthritis, and decrease bone resorption assessed by urinary deoxypyridinoline (D-pyr) (16).

Uncoupling between bone destruction and bone formation is observed in RA, at least in destructive disease. The bone formation markers osteocalcin and pro-collagen serum type I N-terminal propeptide (P1NP) increase 2 and 6 weeks after initiation of the anti-TNFα monoclonal antibody infliximab in RA patients; as expected, serum C-terminal cross-linked telopeptide of type I collagen (CTX-I), and sRANKL as well, are decreased over 1 year of infliximab treatment (17). In a multi-center study of the bone effects of infliximab, Chopin *et al*. showed a decrease in serum C-terminal cross-linked telopeptide of type I collagen (ICTP), later than CTX-I (suggesting different resorption processes), and a favorable change in the ratio between markers of bone formation and bone resorption (18).

Several studies show the beneficial effect of anti-TNFα therapy on BMD; a potential benefit regarding osteoporosis and fracture risk cannot be assessed in the absence of controlled studies. Actually, this is not feasible today as it would be unethical to prevent the use of anti-TNFα therapy in patients with active RA (*i.e.*, at high risk of bone erosions).

Lange *et al*. studied 26 patients (19 women) with persistently active RA (mean disease duration of 9.8 years); after 12 months of infliximab therapy there was a significant increase in BMD at the femoral neck (0.84 ± 0.33 to 0.95 ± 0.15 g/cm²) and at the spine (1.07 ± 0.14 to 1.10 ± 0.23 g/cm²); there was a trend for a correlation between changes in BMD and changes in DAS 28 (a disease activity score) but not with changes in biochemical markers of bone remodeling (19). In another study of 102 patients, 53 years of age on average, 82% female, and with active and severe RA (82% erosive disease) treated with infliximab for 1 year, spine and hip BMD were unchanged (17). Interestingly, half of these patients were receiving steroids. This is similar to the results of a study comparing 10 patients with infliximab and methotrexate to 10 patients receiving placebo and methotrexate; BMD loss was significantly reduced in the infliximab group compared to the placebo group at the femoral neck and total hip, but not at the spine. In this study there was an association between measures of disease process and bone loss (20).

In an historical control study (21), Marotte *et al*. compared bone changes in 90 RA patients treated with infliximab to those in 99 RA patients followed earlier, before the launch of anti-TNFα therapies. In the control group, they measured a 2.5% and 3.9% decrease in femoral neck and lumbar spine BMD, respectively, in contrast to the absence of change in the infliximab-treated group.

An open label, prospective study was conducted in 50 patients receiving the anti-TNFα monoclonal antibody adalimumab and followed for 1 year (22). At baseline both lumbar spine and femoral neck BMD were correlated with disease duration and activity; there was no further bone loss during follow-up. A key result of this study is that in patients who used prednisone during follow-up, there was actually an increase in femoral neck BMD: +2.5% after 1 year in patients using prednisone at a mean dose of 7.4 ± 2.3 mg/day, versus -0.7% in patients without concomitant prednisone. A similar trend was observed at the lumbar spine. This strongly suggests that the better the control of inflammation, the better the bone effect.

Finally, the BeSt study (23) compared prospectively the efficacy of 4 treatment strategies in RA: sequential monotherapy of several DMARDs, step-up combination therapy, initial combination therapy with tapered high-dose prednisone, and initial combination therapy with infliximab. There were no significant BMD changes over 1 year in this study. Of importance is the strategy underlying this study: sequential assessment of patients with therapeutic strategies aiming for a complete control of inflammation.

## Conclusion

Anti-TNF$\alpha$ therapy is the standard in RA treatment. TNF$\alpha$ blockade is not only able to prevent joint destruction, but is also able to prevent bone loss in RA patients. Other possible targets for prevention of inflammation-induced osteoporosis include antigen-presenting cells (rituximab, a monoclonal antibody against CD 20); costimulation between T and B cells (abatacept, a recombinant fusion protein blocking the CD28-CD80/86 pathway); and other cytokines (tocilizumab, a humanized anti-IL-6 receptor monoclonal antibody). Clinical remission is now a realistic target in RA, with the objective of complete absence of synovitis. Complete suppression of inflammation is also the objective for optimal prevention of osteoporosis.

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