Biologicals and bone loss

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Abstract: Inflammatory joint diseases are associated with extra-articular side effects including bone involvement. There is an increased risk of osteoporotic fractures. The pathogenesises of local and generalized bone loss share a common pathway. Early and active rheumatoid arthritis is associated with longitudinal observed bone loss and fracture rate is of vertebral and nonvertebral fractures is doubled compared with matched healthy controls. Lowering disease activity with TNF inhibitors or is associated with stabilisation of bone mineral density by counteracting elevated bone resorption.

Keywords: bone mineral density, rheumatoid arthritis, ankylosing spondylitis biologicals, osteoporosis, fracture risk

Inflammatory joint diseases such as rheumatoid arthritis (RA), as well as other rheumatic conditions such as ankylosing spondylitis, systemic lupus erythematosus or gout, comprise a heterogeneous group of joint disorders that are all associated with extra-articular side effects, including bone involvement. Disease activity, immobility and treatment with glucocorticoids are the main factors that increase the risk of osteoporotic fractures, on top of the background fracture risk based on, amongst others, advanced age, low body mass index, positive family history of osteoporosis and female gender [Cortet et al. 1997, 2000]. Remarkably, it has been found that the pathogenesis of both local and generalized bone loss share a common pathway: the discovery that osteoclasts, stimulated by the receptor activator of nuclear factor kappa B ligand (RANKL) pathway, play a central role in all of these processes [Boyle et al. 2003; Walsh and Gravallese, 2010]. Clinically, the local bone loss leads to periarticular bone loss and bone erosions, the generalized bone loss may lead to an elevated fracture risk.

Generalized bone loss in RA has been documented in cross-sectional studies: a twofold increase in osteoporosis, defined as a T -score < -2.5 and Z -score < -1 was found in 394 postmenopausal, female RA patients and 192 male RA patients [Haugeberg et al. 2000a, 2000b]. Before the introduction of biologicals, high bone loss was also observed in a longitudinal study in early RA: -2.4% at the spine and -4.3% at the

trochanter [Gough et al. 1994]. In a subgroup analysis, bone loss in both the spine and the hips was much larger in those patients with high C-reactive protein (CRP) levels (>20 mg/dl) than in those patients with low CRP levels (<20 mg/dl), e.g. in the spine: -2.1% versus 0.2% , respectively. The same was found in the lumbar spine for patients with low functional capacity (Health Assessment Questionnaire [HAQ] score >1) compared with patients with a better HAQ score (<1): -1.9% versus -0.2% , respectively. Although these data clearly show that active RA has a negative effect on bone mineral density (BMD), the clinically most relevant question is whether active RA is also associated with an elevated fracture rate. Roughly, a doubled fracture rate was documented for both vertebral and nonvertebral fractures [Østravik et al. 2004]. In this cross-sectional study it was shown that the vertebral fracture rate in RA was higher than in healthy controls, matched for age, gender and social background. In a study comparing RA patients with healthy controls, a doubled risk for nonvertebral fractures was observed, with the exception of wrist fractures [van Staa et al. 2006]. Thus, active RA is characterized by local bone loss (erosions), but also by generalized bone loss and, subsequently, fractures.

Against this background, it is relevant that we investigated whether treatment with the tumour necrosis factor (TNF) inhibitor infliximab prevents loss of BMD at the spine and at the hips in patients with RA [Vis et al. 2006]. A total of 102

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patients with active RA, who were treated with infliximab for 1 year, were included in an open cohort study. The BMD of the spine and hip was arrested during treatment with infliximab, whereas BMD of the hand decreased significantly by 0.8% ($p < 0.001$). The BMD of the hip in patients with a European League Against Rheumatism (EULAR) good response showed a favourable change compared with patients with moderate or nonresponse. These results proofed that the usually occurring generalized bone loss in patients with RA can be arrested by the use of aggressive antirheumatic drugs, such as anti-TNF therapy.

Next to BMD changes upon anti-TNF, we investigated the changes in bone markers, to elucidate the underlying mechanism of the favourable effect of anti-TNF [Vis *et al.* 2006]. Bone formation was measured by osteocalcin (OC) and bone resorption was determined by β -isomerized carboxy terminal telopeptide of type 1 collagen (β -CTX); osteoclast regulating proteins including the soluble receptor activator of NF κ B (s-RANKL) and osteoprotegerin (OPG) were determined in serum using an enzyme-linked immunosorbent assay (ELISA) from Immunodiagnostik. Serum β -CTX and RANKL were both significantly decreased compared with baseline at all time points. The decrease in β -CTX was associated with the decrease in DAS-28 and CRP during the 0 to 14 weeks interval. No changes were observed in serum OC and OPG. These data on BMD emphasizes that the arrested bone loss at the spine and hips to a large extent can be described to a decrease in disease activity.

Recently, we also showed that during 'long-term treatment' with infliximab (mean 3.3 years) the changes in BMD were still favourable: +2.55% at the spine and -0.12% at the hip [Eekman *et al.* 2011].

These data were later confirmed in a study with 1-year adalimumab treatment, in which bone loss at the spine and hips was arrested [Wijbrandts *et al.* 2009]. In this study, a subanalysis was performed in which a remarkable phenomena was found: BMD was stable in the nonprednisone users, but a statistically significant increase was found in the prednisone users. The authors suggested that this can be explained by lowering

disease activity with the use of prednisone; however, another explanation could be regression to the mean.

Thus, lowering of the disease activity in RA with the TNF blockers infliximab and adalimumab is associated with stabilizing BMD, and not with the usually observed high bone loss (and fracture risk) in active RA. Mechanistically, the use of a TNF blocking agent counteracts the elevated bone resorption, modulated by elevated RANKL levels, and depressed bone formation, induced by high Dkkp-levels and inhibition of the Wnt signalling pathway [Schett *et al.* 2008].

In addition, the bone sparing effects also seemed to be observed in a 6-month observation study with rituximab in RA patients. Serum β CTX decreased by 37%, whereas serum P1CP increased by 13%. Also in this study, the change in β CTX correlated with changes in disease activity ($r = 0.57$, $p = 0.014$) [Wheater *et al.* 2011].

The same bone sparing effects can be observed in other inflammatory diseases. In an 2-year observational study in patients with ankylosing spondylitis a favourable effect on BMD was found in the large group of responders, on the other hand, bone loss in the small group of nonresponders continued: -1.2% versus -4.1% in the hip, respectively [Maillefert *et al.* 2001].

In a recently published study, ankylosing spondylitis patients were divided into four groups, according to their medications used in the follow-up period: conventional treatment, bisphosphonates, anti-TNF agents or a combination of bisphosphonates and anti-TNF agents. BMD increased more in patients taking bisphosphonates and anti-TNF agents and was associated with a reduction in inflammation [Kang *et al.* 2011].

In summary, RA is characterized by local bone loss (erosions) and by generalized bone loss: both can be counteracted with aggressive treatment with biological therapies. This phenomena has been particularly documented for infliximab, adalimumab and rituximab.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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