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Infliximab and the bone in Crohn's disease

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SIRS, In parallel to their use for Crohn's disease (CD), anti-tumour necrosis factor (TNF) therapies have become a powerful approach for the treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylarthropathy (SpA) and data are becoming available concerning the effects of anti-TNF on bone remodelling. Our paper clearly indicates that infliximab treatment is associated with an improvement of bone formation as measured by three different markers of bone formation in CD[1]. Similar results were obtained by Ryan *et al*[2]. We agree with Kunisaki *et al.* that the effect on bone formation might be critical and possibly predominant in CD. Indeed, TNF is a cytokine known to inhibit bone formation and the use of anti-TNF therapy might be associated with a direct positive effect on bone remodelling in CD. Another possibility suggested by Kunisaki *et al.* is that the intestinal healing would be associated with an improvement in the absorption of calcium and vitamin D which would result in a better mineralization of bone matrix and an improvement of bone quality. While we agree with this possibility, particularly as a rapid mucosal healing has also been described in CD after infliximab, we favour the hypothesis that an improvement of inflammation and the immune reaction in the intestine is associated with a decrease in local and serum mediators that influence bone remodelling, even if there was no significant correlation in our series between evolution of bone markers and systemic inflammatory markers such as C-reactive protein (CRP). Of interest, serum from children with newly diagnosed inflammatory bowel disease (IBD) who had not received corticosteroid for 1 year reduced osteoblast differentiation and nodule formation, underlying the importance of inflammatory mediators on bone formation.[3]

In our study, we also showed a relevant decrease in serum C-telopeptide of type I collagen (CTX), a marker of bone resorption after infliximab treatment. While levels of serum N-telopeptide cross-linked type I collagen (NTX). Another marker of bone resorption, were found to be slightly decreased in the study by Ryan *et al.*[2], changes did not reach statistical significance. Kunisaki *et al.* did not find any change in bone resorption and suggest that the improvement in bone mineral density (BMD) might be mostly explained by the effect on bone formation. Results concerning CTX and NTX have to be analysed with prudence as small populations of patients are used and the variability estimates, for example, for NTX measurement might reach 10%.[4] Moreover, difference might be influenced by the methodology itself. Ideally, standardization of the timing and collection of samples in fasting patients should be performed to avoid variability because of circadian rhythm. This was not possible to achieve for our multicentric population. However, changes in CTX remained statistically significant in accordance with the recent study by Briot *et al*.[6] These authors confirm a major decrease in CTX levels in patients presenting SpA with a trend to an increase in bone formation, suggesting that anti-TNF therapy is associated with bowel and rheumatic inflammatory diseases, with a decrease in bone resorption and an improvement of bone formation. The mechanisms underlying this decrease in bone resorption remain to be clarified. Soluble receptor activator of NF-κB ligand (sRANKL) as well as its decoy receptor osteoprotegerin (OPG) are certainly relevant candidates for such modulation as sRANKL has been identified as a major mediator in bone resorption associated with chronic inflammation.' Furthermore, we recently showed an increased production of sRANKL and OPG by inflamed mucosa in *CD*.[8] However, in a subgroup of our CD patients treated with infliximab (n = 30). we were unable to find a significant difference in sRANKL and OPG serum levels before and after treatment (2.9 ± 2.38 pg/mL and 2.87 ± 2.43 pg/mL for sRANKL. before and after treatment, respectively; paired t-test: P - 0.93· 1012.8 ± 456.7 pg/mL and 974.9 ± 492.6 pg/mL for OPG. before and after treatment, respectively; paired t-test: P = 0.51). In our hands, an uncoupling effect on bone metabolism was observed in six of 71 patients, it seems therefore that individual response might occur and further studies will be required in large population to determine the relationship between the type of response (i.e. bone formation and/or bone resorption) and CD. Finally, the mechanisms of bone metabolism improvement after infliximab in CD may be complex and possibly heterogeneous among patients, involving both changes in bone formation and resorption through a better control of local inflammation, intestinal mucosal healing and direct inhibition of TNF.

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