Editorial

Bone and Matrix Remodeling Markers: A New Tool for Assessment of Treatment Efficacy in Ankylosing Spondylitis?

Bone mass involvement is now a well recognized feature associated with ankylosing spondylitis (AS)[1]. Bone loss is due to an imbalance between bone formation and bone resorption in close relationship to inflammation and production of cytokines, activating osteoclast activity through the RANK-RANK ligand pathway, also leading to increased matrix turnover. This dimension of the disease may be estimated using serum biologic markers of bone and matrix turnover, which may serve as surrogate disease activity markers.

Anti-tumor necrosis factor (TNF) agents for the treatment of AS have demonstrated clear effectiveness regarding clinical symptoms and variables of inflammation, as well as abnormalities on magnetic resonance imaging or bone mineral density (BMD) assessment. Nevertheless, the management of these biological agents in this disease lacks simple and reliable biologic markers for assessment of disease and evaluation of prognosis, i.e., not only in support of the therapeutic decision but also the unbiased evaluation of the therapeutic benefit.

In this issue of *The Journal*, Woo, *et al*[2] evaluated serum samples of 26 patients with AS before and after 12 weeks of treatment with etanercept. Bone remodeling factors as well as growth factors were measured. As expected, most patients exhibited clinical improvement. Bone formation markers (bone alkaline phosphatase, osteocalcin) were significantly increased, whereas C-telopeptide of type-I collagen (CTX) levels (reflecting bone resorption) remained unchanged under treatment. Serum levels of osteoprotegerin (OPG) and RANK ligand did not change, but serum levels of transforming growth factor-ß (TGF-ß), macrophage colony-stimulating factor (M-CSF), and matrix metalloproteinase-3 (MMP-3) were significantly decreased after 12 weeks of treatment. Interestingly, change of MMP-3 showed the best correlation with changes in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in the course of anti-TNF treatment.

These results raise the question of the use of biochemical bone and matrix remodeling markers as a tool to assess treatment efficacy, or disease activity in general. There is no recommended biologic marker for disease activity assessment in AS to date[3]. Activity is mainly evaluated using the Bath AS Disease Activity Index (BASDAI), which is subjective and patient-sided. Consequently, the therapeutic response is assessed by a reduction in the BASDAI score, or the ASsessments in Ankylosing Spondylitis Working Group (ASAS) response criteria[4], including global evaluation by the patient, pain, function, and clinical inflammation (the last 2 items on the BASDAI).

ESR and CRP are often not performed in AS patients, and therefore not taken into account in the ASAS core set[3]. It would be worthwhile to evaluate in such an AS population (i.e., having active symptoms with normal ESR or CRP, which is not unusual) the baseline results and changes in bone and matrix remodeling markers under treatment, to look for their superiority.

A majority of the studies about bone in AS revealed increased resorption markers that correlate with inflammation[2] and a reduction during TNF blockade[5], and some demonstrated low OPG[6] or elevated soluble RANK ligand levels[7]. The results of Woo, *et al* are not in agreement with these previous studies: there were no changes in CTX levels, or in OPG or RANK ligand after 12-week treatment with etanercept, whereas this was observed in RA under infliximab treatment[8]. The absence of a control group represents a weakness of their study, but nevertheless, the discordance with previous studies shows that the results may not be extrapolated to every AS group. So CTX and RANKL/OPG may not represent the ideal candidate for assessing therapeutic response in AS.

MMP-3 changes correlated with ESR/CRP changes under etanercept therapy in the patients of Woo, et al. MMP-3 secretion is stimulated by TNF-α, and serum levels of

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MMP-3 may represent a proxy for TNF biological activity. Previous studies found a correlation between this biologic marker and AS activity[9,10]; and there was a reduction in MMP-3 after treatment with infliximab[9] and etanercept[11]. This may represent a new tool that is easier to use and more sensitive to change in the short-term than BMD or radiographic assessment. Moreover, Maksymowych, *et al*[12] recently showed that MMP-3 levels were correlated with a 2-year radiographic progression in Modified Stoke AS Spine Score. Nevertheless, in the study of Woo, *et al*, change in MMP-3 during anti-TNF therapy did not correlate with change in BASDAI.

Anabolic markers potentially involved in bone and matrix remodeling may also be of interest. M-CSF was found to be decreased by Woo, *et al* after 12 weeks of etanercept. M-CSF was shown to be stimulated by the activity of TNF on osteoblastic cells, but changes were not correlated with changes in BASDAI, ESR, or CRP. Yang, *et al*[9] found no change in serum M-CSF values after infliximab therapy. Woo, *et al* found decreased TGF-ß levels after etanercept, but variations were not correlated with changes in ESR, CRP, or BASDAI. In our experience, serum TGF-ß levels in AS were not different from controls and did not correlate with clinical activity (BASDAI) or measures of inflammation (CRP, ESR) in patients with AS[13].

Other potential bone-related candidates may appear, based on pathophysiological knowledge and preliminary data. Interleukin 17 (IL-17) is a proinflammatory cytokine with involvement in bone remodeling. We found[14] that IL-17 levels in the serum of patients with AS were elevated compared to controls and correlated with tartrate resistant acid phosphatase (a marker of bone resorption), but not with BASDAI or laboratory measures of inflammation.

Bone morphogenetic protein-7 (BMP-7) acts as a bone anabolic agent, also involved in ossification of inflammatory enthesitis, and may upregulate IL-17 mRNA[15]. Elevated serum levels of BMP-7 were found in patients with AS, but these did not correlate with BASDAI or inflammation[14].

Potential cartilage biomarkers (turnover, biosynthesis, collagen cleavage) were assessed by Kim, *et al*[16] in 23 AS patients receiving infliximab. Baseline levels were elevated versus controls, and only the ratio of biosynthesis marker to collagen cleavage marker correlated with CRP, and may therefore serve as a disease activity tool in AS. No changes were found after infliximab therapy, but in responders, the correlation between this ratio and CRP could be found.

All these candidate biomarkers would have to demonstrate that they bring more information to an individual patient than do ESR, CRP, and BASDAI. The future may lie in a combination of several different markers, but this approach would need to be evaluated.

Obviously, we are still on a quest for an operational biological marker of disease activity in AS, and work is progressing. Anti-TNF therapy, as a model of rapid efficacy, may offer an opportunity to test relevant candidates.

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