Changes of Clinical Response and Bone Biochemical Markers in Patients with Ankylosing Spondylitis Taking Etanercept

JIN-HYUN WOO, HYUN-JOO LEE, IL-HOON SUNG, and TAE-HWAN KIM

ABSTRACT. ***Objective.*** Tumor necrosis factor-α has a prominent role in the inflammatory process and bone resorption in patients with ankylosing spondylitis (AS). We evaluated the markers of clinical efficacy and bone biochemical changes in Korean patients with AS treated with etanercept therapy.

Methods. Serum samples from 26 patients receiving etanercept for refractory AS were obtained at baseline and 12 weeks after treatment. Clinical measures and serum levels of transforming growth factor-ß (TGF-ß), matrix metalloproteinase-3 (MMP-3), macrophage-colony stimulating factor (M-CSF), bone-specific alkaline phosphatase (BALP), osteocalcin, C-telopeptide (CTX), receptor activator of nuclear factor-κB ligand (RANKL), and osteoprotegerin (OPG) were measured at each timepoint.

Results. Significant improvement of the Bath AS Disease Activity Index (BASDAI) and Functional Index (BASFI) was achieved after 12 weeks ($p < 0.001$). ASsessments in Ankylosing Spondylitis Working Group (ASAS) 20 criteria were achieved by 22 patients (84.6%) after 12 weeks' treatment. ASAS 50 and 70 were achieved by 10 (38.5%) and 7 patients (26.9%). Serum levels of BALP and osteocalcin were significantly increased after 12 weeks of treatment ($p < 0.05$). Serum levels of CTX were not changed after treatment. Serum levels of TGF-ß, MMP-3, and M-CSF were significantly decreased after 12 weeks of treatment ($p < 0.05$). Serum levels of OPG and RANKL were not changed. Change of MMP-3 had a high correlation coefficient with changes of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) upon etanercept treatment (CRP, $r = 0.446$, $p = 0.022$; ESR, $r = 0.449$, $p = 0.021$).

Conclusion. In patients with AS, etanercept therapy may be effective for reducing disease activity and improving bone biochemical markers. MMP-3 may be a useful biomarker for monitoring etanercept therapy. (First Release June 15 2007; J Rheumatol 2007;34:1753–9)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS BONE BIOCHEMICAL MARKER ETANERCEPT

Ankylosing spondylitis (AS) is characterized by acute and chronic inflammation in the sacroiliac joint and insertion of tendons or ligaments. AS is frequently associated with spondylitis, peripheral arthritis, and anterior uveitis. AS raises the paradox of a disease characterized by new bone formation at sites of chronic inflammation and bone resorption associated with inflammation[1]. It has been established that bone loss occurs in the early phase of the disease, and many patients with AS have osteoporosis and nontraumatic fractures in spite of their young age. Bone resorption may be correlated with bone biochemical markers and biological measures such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)[2].

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Tumor necrosis factor-α (TNF-α) is a key proinflammatory cytokine in the pathogenesis of AS. Increased expression of TNF-α has been reported in the serum, synovium, and sacroiliac joint in patients with AS[3,4]. Also, axial ankylosis and enthesopathies develop in transgenic mice with increased expression of TNF-α[5]. TNF-α and interleukin 1 (IL-1) act synergistically to release matrix metalloproteinases (MMP) that promote extracellular matrix degradation and remodeling. In a recent report, high levels of MMP-3 and macrophage-colony stimulating factor (M-CSF) expression by microarray analysis were shown in patients with AS. Levels of MMP-3 and M-CSF correlated with clinical measures[6,7].

TNF-α influences bone resorption and osteoclast activity and may be a powerful inhibitor of bone formation[8]. In a model of transgenic mice expressing the soluble TNF receptor, neutralizing TNF-α protects mice from bone loss caused by an estrogen deficiency[9]. Also, TNF-α has a critical role in orthopedic implant osteolysis[10]. TNF-α stimulates osteoblastic cells to express receptor activator of nuclear factor-κB ligand (RANKL) and M-CSF, which in turn promote a macrophage-to-osteoclast transition[11].

Current therapeutic options in the treatment of AS include nonsteroidal antiinflammatory drugs (NSAID) to relieve pain,

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while disease modifying antirheumatic drugs (DMARD), such as sulfasalazine, may benefit peripheral arthritis but do not improve axial involvement[12]. Etanercept is a fully human recombinant TNF receptor p75 and the crystallizable fragment component of immunoglobulin G1, which specifically binds to and neutralizes TNF[13]. Blockage of the proinflammatory effect of TNF may reduce clinical signs and symptoms of AS, improve quality of life[14,15], and decrease spinal inflammation as detected with magnetic resonance imaging (MRI) significantly[16].

Noninvasive assessment of bone turnover has improved in the past few years with the identification of markers of bone resorption and formation. Bone-specific alkaline phosphates (BALP) and osteocalcin are sensitive and specific markers of bone formation[17]. C-telopeptide (CTX) is a bone resorption marker. Bone formation and resorption are normally tightly coupled. RANKL is a potent stimulator of bone resorption through its binding of the receptor activator of nuclear factor-κB in the cell membrane. In contrast, osteoprotegerin (OPG) is a soluble decoy receptor for RANKL that interferes with the RANKL/RANK binding. RANKL and OPG have central roles in the regulation of bone remodeling and loss. RANKL expression was dramatically upregulated in the synovial lining, while OPG immunostaining was restricted to the endothelium in a psoriatic arthritis specimen[18]. Because TNF stimulates osteoblastic cells to express RANKL and M-CSF, etanercept therapy may be effective in improving bone loss. Meanwhile, TGF-ß may play a role in the new bone formation characteristic of AS[4].

Our aim was to evaluate changes of inflammatory and bone biochemical markers in patients with AS treated with etanercept. However, there are no reports of RANKL/OPG and other bone biochemical markers following etanercept treatment in AS. We also studied the relationship between the clinical measures and biochemical markers upon etanercept treatment.

MATERIALS AND METHODS

Patients. Twenty-six patients diagnosed with AS according to the modified New York criteria[19] had active disease that was refractory to NSAID treatment. Patients were excluded from the study if they had previously received TNF inhibitors, including etanercept. Patients were excluded if they had taken estrogen, vitamin D, or calcium supplement. Patients were allowed to have received methotrexate or NSAID only at stable dosages during the study. They received etanercept at a dosage of 25 mg twice weekly by subcutaneous administration during the 12-week study. Our study was approved by the local ethics committees, and patients gave written informed consent before participation.

Clinical outcomes and laboratory methods. Blood samples were obtained at baseline and after 12 weeks of etanercept treatment. CRP, ESR, osteocalcin [intra- and interassay coefficients of variance (CV): < 7%, respectively, normal value range 14–42 ng/ml], CTX (intra- and interassay CV: 3.4%, respectively, normal value range 0.1–0.9 ng/ml), and BALP (intra- and interassay CV: 3.9% and 7.6%, respectively, normal value range 15.0–41.3 U/l) were measured at baseline and after 12 weeks. Serum osteocalcin and CTX were tested using an electrochemiluminescence assay (E170, Roche, Switzerland). A serum BALP assay was performed using an enzyme immunoassay (EIA) method (Metra bap EIA kit, Quidel Corp., Santa Clara, CA, USA). Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[20], Bath AS Functional Index (BASFI)[21], and Bath AS Metrology Index (BASMI)[22] were measured at the same time. Response to etanercept treatment was defined using ASsessments in Ankylosing Spondylitis (ASAS) Working Group 20[23], 50, and 70[24] criteria after 12 weeks' treatment.

Measurement of serum TGF-ß, MMP-3, M-CSF, RANKL, and OPG. Serum samples were obtained at baseline and after 12 weeks of etanercept treatment. Serum samples of healthy individuals (n = 10) were obtained to serve as controls. Serum was stored immediately at –70°C or lower until analysis. Time between taking of blood and further processing was 4 to 52 weeks. Serum levels of TGF-ß, MMP-3, M-CSF, RANKL, and OPG were measured by a commercially available enzyme linked immunosorbent assay (ELISA) kit (TGF-ß, MMP-3, and M-CSF, R&D Systems, Minneapolis, MN, USA; RANKL, Biomedica, Wien, Austria; OPG, RayBio, Norcross, GA, USA). There were intra- and interassay CV for each assay (TGF-ß, 3.2% and 6.4%, respectively; MMP-3, 3.1% and 7.9%; M-CSF, 4.1% and 3.1%; RANKL, 7.9% and 6%; OPG, 5.2% and < 12%). All assays were performed in duplicate.

Statistical analysis. Differences in biomarker values between baseline and after treatment were analyzed using a paired t-test. Nonparametric data were analyzed using the Wilcoxon signed-rank test. Correlation coefficients were calculated with Spearman's rho coefficient (SPSS for Windows v. 13.0; SPSS Inc., Chicago, IL, USA). Differences were considered significant when p values were less than 0.05.

RESULTS

Characteristics of the patients. The study group comprised 25 men and 1 woman, with a mean ± standard deviation (SD) age of 34.5 ± 7.5 years. Among the 26 patients, 11 had axial involvement only, and 15 had axial and peripheral involvement. Twelve had histories of uveitis or iritis. The baseline modified Stoke AS Spinal Score (mSASSS)[25] was 20.1 ± 21.8 (mean ± SD). Demographic characteristics are summarized in Table 1.

Clinical response following etanercept therapy. Both the clinical and laboratory measures of disease activity improved after 12 weeks of etanercept treatment. Significant improvement of BASDAI (6.8 ± 1.3 vs 3.2 ± 2.4; $p < 0.001$) and BASFI (8.5 ± 2.7 vs 3.9 ± 3.0; $p < 0.001$) were achieved after 12 weeks. There was no significant improvement in measures of BASMI. ASAS 20 was achieved by 22 patients (84.6%) after 12 weeks' treatment. ASAS 50 and 70 were achieved by 10 patients (38.5%) and 7 patients (26.9%). CRP and ESR were significantly decreased after 12 weeks' treatment (CRP 4.7 ± 3.9 mg/dl vs 0.4 ± 0.9 mg/dl, $p < 0.001$; ESR 56.1 ± 36.3

Table 1. Baseline demographic characteristics (n = 26).

Characteristics	Value
Age, yrs	34.5 ± 7.5 (21–50)
Female: male	1:25
Disease duration, mo	56.7 ± 55.4 (12–156)
Peripheral arthritis, n (%)	15 (57.7)
HLA B27, n (%)	25 (96.2)
Serum CRP, mg/dl	4.7 ± 3.9
ESR, mm/h	56.1 ± 36.3
mSASSS	20.1 ± 21.8 (2–72)

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score.

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mm/h vs 9.2 ± 11.3 mm/h, p < 0.001, respectively; Table 2). No significant differences were observed between patients having only axial disease or axial and peripheral disease.

Bone biochemical markers following etanercept therapy. Serum levels of BALP and osteocalcin were significantly increased after 12 weeks of treatment (BALP 23.2 ± 8.1 U/l vs 29.0 ± 9.5 U/l, p < 0.001; osteocalcin 16.8 ± 5.3 ng/ml vs 22.1 ± 8.5 ng/ml, p = 0.003). Serum levels of CTX were not changed after treatment. Serum levels of TGF-ß, MMP-3, and M-CSF were significantly decreased after 12 weeks of treatment (TGF-ß control 15,392 ± 2945 pg/ml, AS 17,429 ± 5233 pg/ml vs 15,074 ± 3969 pg/ml, p = 0.004; MMP-3 control 24.1 ± 7.0 ng/ml, AS 70.0 ± 51.5 ng/ml vs 40.6 ± 36.2 ng/ml, p = 0.002; M-CSF control 662.5 ± 179.8 pg/ml, AS 487.0 ± 312.2 pg/ml vs 356.8 ± 224.0 pg/ml, p = 0.035; Figure 1). There were no statistically significant differences between the baseline and 12-week values of RANKL and OPG (Table 2).

Correlation between biomarkers and clinical and laboratory measures. There was a good correlation between MMP-3 and acute phase reactants such as ESR and CRP. MMP-3 was correlated with ESR and CRP at baseline, but the correlation coefficient did not reach statistical significance after treatment (at baseline CRP Spearman's r = 0.464, p = 0.017; ESR Spearman's r = 0.541, p = 0.004; after treatment CRP Spearman's r = 0.149, p = 0.466; ESR Spearman's r = 0.375, p = 0.059; Figure 2). There were significant correlations between changes of MMP-3 and changes of CRP and ESR upon etanercept treatment (CRP Spearman's r = 0.446, p = 0.022; ESR Spearman's r = 0.449, p = 0.021). Also, there was a correlation between changes of osteocalcin and changes of ESR upon etanercept treatment (Spearman's r = 0.398, p = 0.044). There was no correlation between changes of other biomarkers and changes of clinical measures upon etanercept treatment (Table 3).

DISCUSSION

AS is a chronic inflammatory disease and patients with AS have progressive inflammation of axial and peripheral joint and functional impairment. In addition, chronic bone loss and new bone formation at other sites are distinctive features in AS. Lange, *et al* showed decreased bone density even at the initial stage of AS that continued into the advanced stage[26]. Until recently, the options available for the treatment of AS were limited to the use of NSAID, some DMARD, physical therapy, and patient education, but these treatments were often ineffective and have not been shown to slow the progression of the disease. Recently, the advent of a TNF antagonist represented a breakthrough in the treatment of AS[27]. Treatment with TNF antagonist was associated not only with improvement of clinical measures but also with a significant reduction of active inflammatory changes of the spine as detected with MRI[16]. In AS, the local inflammation is followed by ligament ossification involving potentially proinflammatory cytokines such as TNF and IL-1 and growth factors such as TGF-ß and insulin-like growth factors. Because bone loss is evident adjacent to areas of enthesis inflammation[28], TNF antagonist may influence bone loss in AS.

Our data showed that in patients with AS disease activity was significantly decreased and bone biochemical markers were significantly improved after 12 weeks of etanercept treatment. Etanercept treatment resulted in a significant

Table 2. Effect of 12 weeks of etanercept treatment on clinical and biochemical measures.

Measure	Baseline	12 Weeks	p
Clinical measures			
BASDAI	6.8 ± 1.3	3.2 ± 2.4	< 0.001
BASFI	8.5 ± 2.7	3.9 ± 3.0	< 0.001
BASMI	5.1 ± 1.4	4.5 ± 2.2	0.1
Acute phase reactant			
CRP, mg/dl	4.7 ± 3.9	0.4 ± 0.9	< 0.001
ESR, mm/h	56.1 ± 36.3	9.2 ± 11.3	< 0.001
Bone biochemical markers			
BALP, U/l	23.2 ± 8.1	29.0 ± 9.5	< 0.001
Osteocalcin, ng/ml	16.8 ± 5.3	22.1 ± 8.5	0.003
CTX, ng/ml	0.23 ± 0.15	0.23 ± 0.12	0.90
RANKL, pg/ml	6.26 ± 7.48	7.73 ± 18.2	0.61
OPG, pg/ml	541.2 ± 95.5	553.3 ± 79.1	0.61
Other inflammatory markers			
M-CSF, pg/ml	487.0 ± 312.2	356.8 ± 224.0	0.035
MMP-3, ng/ml	70.0 ± 51.5	40.6 ± 36.2	0.002
TGF-ß, pg/ml	17429 ± 5233	15074 ± 3969	0.004

Mean ± SD. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath AS Functional Index; BASMI, Bath AS Metrology Index; CRP: C-reactive protein; ESR, erythrocyte sedimentation rate; BALP, bone specific alkaline phosphates; CTX, C-telopeptide; OPG, osteoprotegerin; M-CSF, macrophage-colony stimulating factor; MMP, matrix metalloproteinase; TGF, transforming growth factor.

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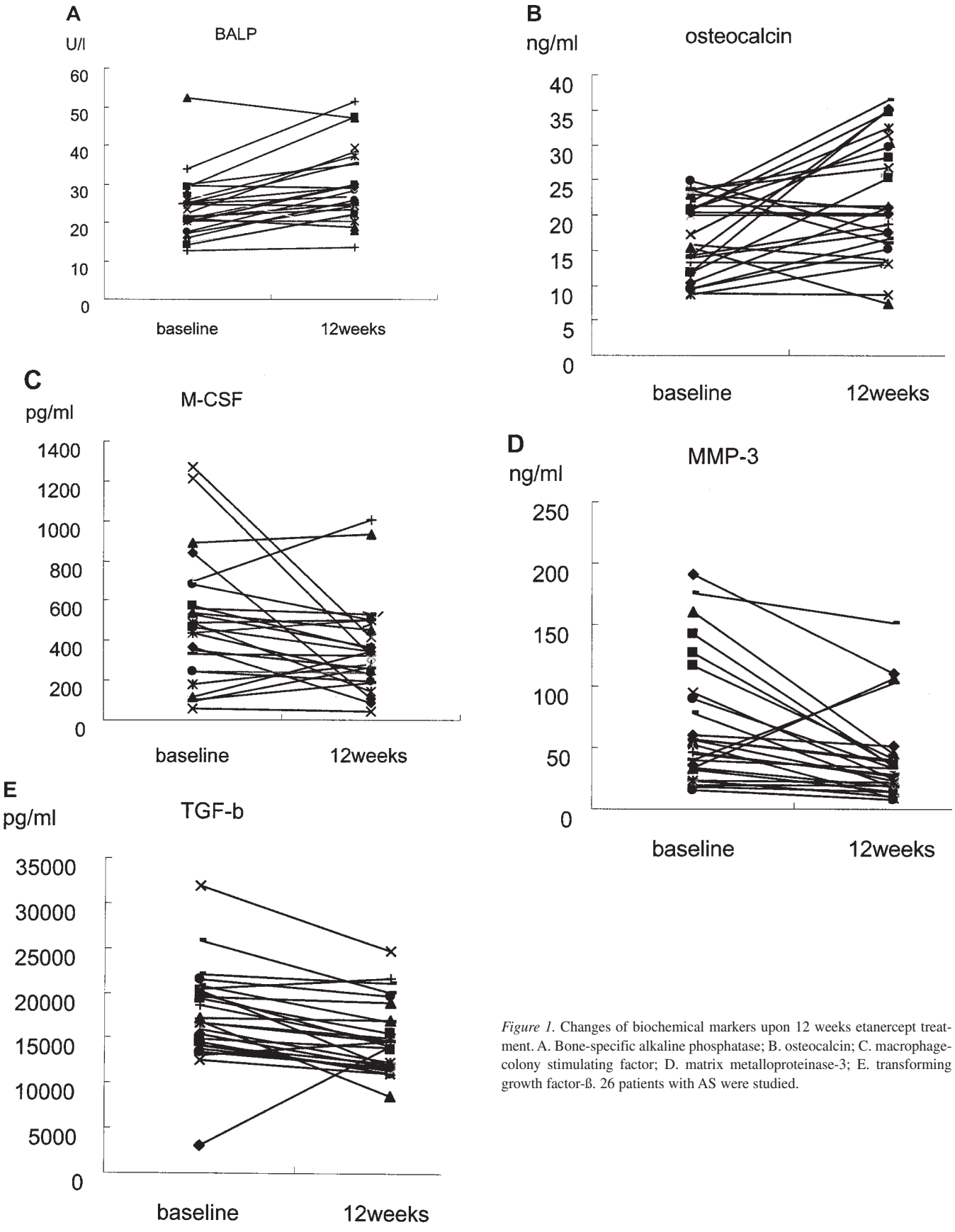

Figure 1. Changes of biochemical markers upon 12 weeks etanercept treatment. A. Bone-specific alkaline phosphatase; B. osteocalcin; C. macrophage-colony stimulating factor; D. matrix metalloproteinase-3; E. transforming growth factor-ß. 26 patients with AS were studied.

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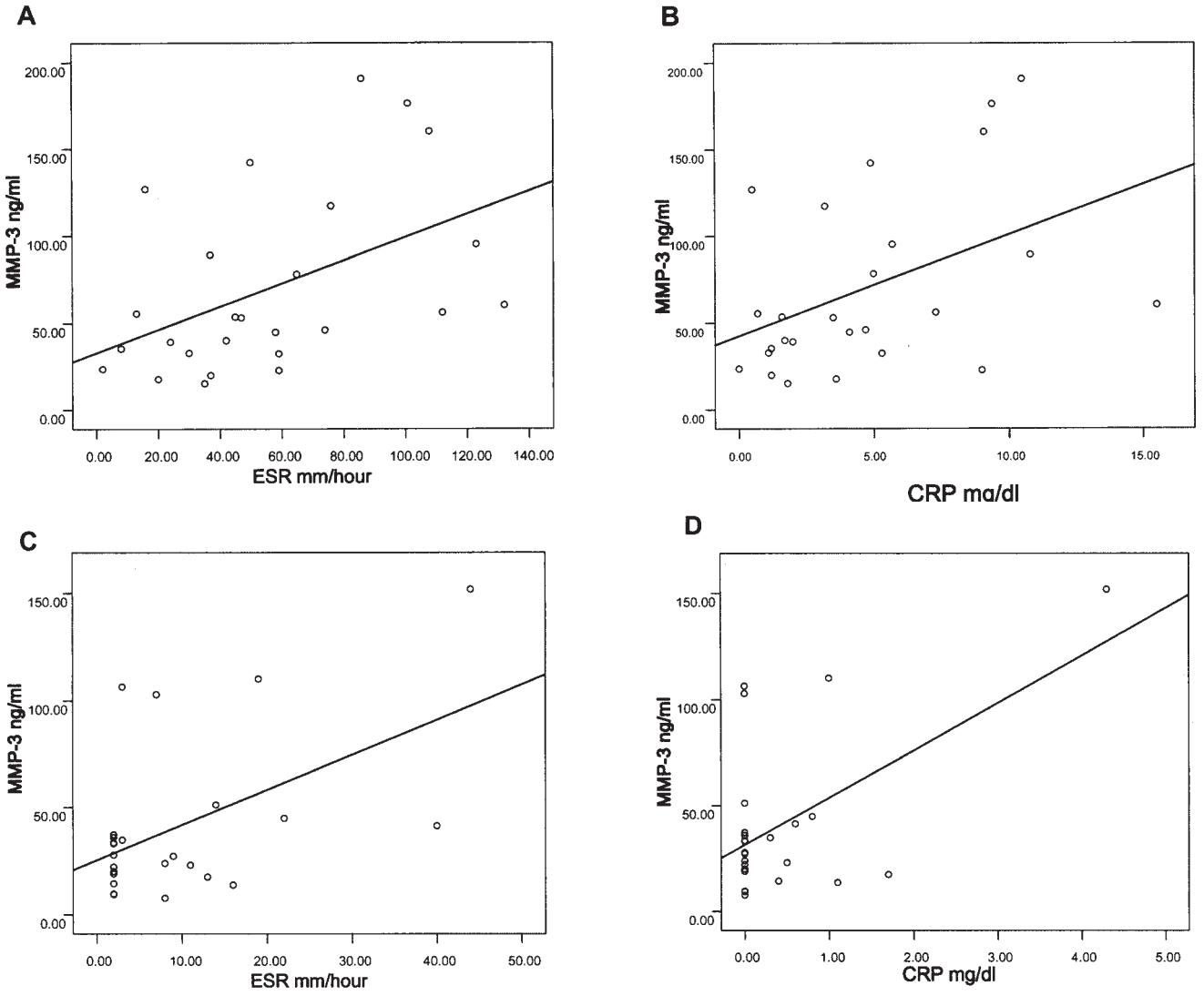

Figure 2. Correlation of serum matrix metalloproteinase-3 levels with A and C, erythrocyte sedimentation rate (ESR), or with B and D, C-reactive protein (CRP) in the 26 patients with AS. A and B: at baseline. C and D: after 12 weeks etanercept treatment.

improvement of bone formation markers such as BALP and osteocalcin. In contrast, serum levels of CTX were not changed after treatment. Osteocalcin, a noncollagenous matrix protein in bone, is produced exclusively by osteoblasts. It is a marker of bone formation that correlates with histomorphometric bone measurements. Speden and colleagues showed that women with AS had reduced bone mineral density (BMD) and significantly lower bone formation markers (BALP and osteocalcin) than non-affected controls[29]. In a study of patients with spondyloarthropathy, it was shown that treatment with infliximab resulted in a significant decrease of bone resorption marker and slight increase of bone formation marker[30]. But our study showed that bone formation markers in patients with AS significantly increased after etanercept treatment, while bone resorption markers were not changed. Although etanercept and infliximab seemed to be similarly effective in the treatment of AS, a differential effect of the 2 drugs on T cell function might be an explanation for this difference[31,32]. But in most conditions bone resorption and formation are tightly coupled, and osteocalcin and BALP levels reflect bone turnover. These results showed that etanercept had a favorable effect on bone metabolism in AS. The increase in markers of bone formation might reflect the inhibition of suppressed bone formation in active AS.

In a previous study, serum OPG levels were significantly lower in patients with AS than in controls, and in contrast to controls, were not positively correlated with age[33]. In addition, serum RANKL levels and the RANKL/OPG ratio were upregulated in patients with AS and had a relationship with BMD and radiological changes[34]. Expression of RANKL was

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Table 3. Correlation coefficients between changes of biomarkers and changes of clinical measures upon 12 weeks of etanercept treatment.

	ESR	CRP	BASDAI	BASFI
TGF-ß	0.257	0.162	0.026	0.115
M-CSF	0.320	0.319	0.142	0.239
MMP-3	0.449*	0.446*	0.022	0.116
BALP	0.236	0.319	0.043	0.133
Osteocalcin	0.398*	0.376	0.099	0.228

* $p < 0.05$. For abbreviations, see Table 2.

upregulated by inflammatory mediators such as TNF, IL-1, IL-6, IL-17, and prostaglandins. The frequency of osteoclast precursors declined substantially in patients with psoriatic arthritis following treatment with anti-TNF agent[18]. In patients with rheumatoid arthritis, serum RANKL levels and the RANKL:OPG ratio were reduced after infliximab treatment[35]. But in our study, serum levels of RANKL and OPG were not influenced by etanercept therapy. Also, the RANKL:OPG ratio was not influenced by etanercept therapy (data not shown). Although TNF has a pivotal role in RANKL activation, osteoclastogenesis was also influenced by other osteoclastogenic cytokines, including IL-1, IL-6, IL-11, IL-13, IL-17, and parathyroid hormone-related peptide (PTHrP)[36].

We showed that serum levels of TGF-ß, MMP-3, and M-CSF were significantly decreased after 12 weeks of treatment. TNF-α stimulates secretion of MMP. In the MMP family, MMP-3 hydrolyzes a number of extracellular matrix components and also activates several pro-MMP, such as pro-MMP-1 and pro-MMP-9[37]. The serum levels of MMP-3 correlate with disease activity in AS[6]. In our study, changes of MMP-3 were correlated with changes of ESR and CRP upon etanercept treatment. MMP-3 may be a useful biomarker in monitoring for etanercept therapy. In other studies, bone resorption markers were correlated with inflammatory markers in psoriatic arthritis[38], but our study showed a lack of correlation between inflammation and bone turnover markers.

Several limitations of our study must be recognized. The sample size of 26 was relatively small, and a larger sample size should be considered in future studies. We did not show the change of BMD after etanercept treatment. We analyzed data at baseline and after 12 weeks of etanercept treatment, so we performed this study for a relatively short duration and did not show the longterm effects of etanercept treatment on bone loss in AS. Moreover, a recent study showed that 2-year etanercept therapy did not inhibit radiographic progression in AS, whereas clinical findings were sustained[39]. Further study is needed to assess the longterm effects of etanercept for bone metabolism and direct changes of BMD. Also, the relationship of inflammation and bone metabolism upon longterm etanercept therapy will be examined in future studies.

Etanercept therapy for patients with AS may be effective for improving bone biochemical markers and reducing disease activity. MMP-3 may be not only a good predictor of disease activity but also a useful biomarker in monitoring for etanercept therapy.

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