Anti-tumor Necrosis Factor Therapy Increased Spine and Femoral Neck Bone Mineral Density of Patients with Active Ankylosing Spondylitis with Low Bone Mineral Density

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ABSTRACT. ***Objective.*** To evaluate the effect of anti-tumor necrosis factor (TNF) therapy on bone mineral density (BMD) in patients with active ankylosing spondylitis (AS) with low BMD.

Methods. Eighty-nine patients with active AS with low BMD were randomly divided into either a study group or a control group. The study group received etanercept (50 mg/week) or adalimumab (40 mg/2 week) subcutaneously for 1 year. BMD of lumbar spine and femoral neck was measured by dual energy X-ray absorptiometry, and bone turnover markers serum C telopeptide of type-I collagen (sCTX) and serum procollagen type-I N propeptide (PINP) were detected by ELISA at baseline and at end of study.

Results. After 1 year, compared with baseline, there was a significant increase in spine and femoral neck BMD by a mean ± SD of 14.9% ± 15.6% ($p < 0.0001$) and 4.7% ± 7.9% ($p < 0.0001$) in the study group. In the control group, there was a significant decrease in spine and femoral neck BMD by a mean ± SD of –8.6% ± 9.7% ($p < 0.0001$) and –9.8% ± 11.5% ($p < 0.0001$). Compared with baseline, sCTX was significantly decreased in the study group (–40% at 1 yr, $p < 0.0001$), but bone-specific alkaline phosphatase and PINP increased (45.6%, $p < 0.0001$ and 30.8%, $p < 0.0001$, respectively).

Conclusion. In patients with active AS with low BMD, the spine and femoral neck BMD increased after anti-TNF therapy for 1 year, and it was accompanied by a significant decrease in bone resorption markers and an increase in bone formation markers. (First Release June 15 2015; J Rheumatol 2015;42:1413–17; doi:10.3899/jrheum.150019)

Key Indexing Terms:
ANTI-TNF THERAPY
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BONE TURNOVER MARKER

Ankylosing spondylitis (AS) is a chronic inflammatory disease that primarily affects the axial skeleton. The disease is characterized by new bone formation that leads to syndesmophytes and ankylosis of the spine and sacroiliac joints. It is associated with systemic osteoporosis[1].

The prevalence of osteoporosis in AS has been reported to range from 18.7% to 62%[2], and the prevalence of axial osteoporosis is increased even in the early and mild forms of AS[3]. Low bone mineral density (BMD) is widespread in patients with AS, with 54% at the lumbar spine and 51% at the femoral neck. Of those patients with AS with low BMD, there are 39% and 38% in the osteopenia range, and 16% and 13% experiencing osteoporosis at the lumbar spine and the femoral neck, respectively[4]. Patients with low BMD have significantly higher modified Stoke Ankylosing Spondylitis Spine Score (mSASSS), Bath Ankylosing Spondylitis Metrology Index, inflammatory markers, and higher disease activity[5,6]. Low BMD in the femoral neck is an independent risk factor of vertebral fractures[7]. Thereby, it is important to treat the low BMD of patients with AS.

In patients receiving anti-tumor necrosis factor (anti-TNF) therapy, in parallel with significant improvement of symptoms and decrease of the inflammation, an increase in the lumbar spine and hip BMD has been reported[8,9,10,11]. However, the consequences of the present studies on this field seem to be conflicting[8] because they enrolled the whole AS group rather than only the patients with active AS with low BMD. Actually, effective treatment for low BMD is urgent for the patients with active AS with low BMD. The aim of our study was to assess the effect of anti-TNF therapy on BMD in such patients.

MATERIALS AND METHODS

Study design. This was a 1-year open-label study on patients with active AS

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with low BMD that was carried out in a single center. The enrolled patients were randomly divided into 2 groups: the study group and the control group. TNF-α blocker [etanercept (ETN) 50 mg/week or adalimumab (ADA) 40 mg/2 week] was provided in the study group for 1 year, and sulfasalazine (SSZ; 1.0 g, twice a day) was offered in the control group for 1 year. The patients in both groups took calcium (1.0 g/day) and Vitamin D (800–1000 IU/day). Within 12 weeks of the study, the patients could take nonsteroidal antiinflammatory drugs (NSAID).

ETN was administered subcutaneously once (50 mg) or twice (25 mg) a week. ADA (40 mg) was administered subcutaneously on alternate weeks. The choice of a TNF-α blocking agent was based on the judgment of the rheumatologist and/or the specific preference of the patients. Reasons for discontinuation of TNF-α blocking therapy included intolerance because of adverse events, inefficacy, or other reasons.

Clinical and laboratory assessments, BMD, and bone turnover markers were assessed at baseline and at the end of the treatment.

Patients. Among the patients who visited the Department of Rheumatology in our university hospital from February 2013 to February 2014, a total of 89 patients with AS according to the modified New York criteria for AS[12] had active disease defined by the Bath AS Disease Activity Index (BASDAI) > 4 (range 0–10)[13], and had low BMD simultaneously. Low BMD was defined as lumbar spine and/or hip BMD Z score < 1 at baseline.

Exclusion criteria were previous or current antiosteoporotic treatments and a history of fractures, because they can greatly influence bone metabolism. Patients who accepted glucocorticoids or any anti-TNF therapy in the last 3 months were also ruled out. Those who had a history of alcohol dependence (daily alcohol more than 50 g), type 2 diabetes, thyroid or parathyroid diseases, or tuberculosis were also excluded. The female patients who were postmenopausal or pregnant were also not enrolled. Written informed consent was obtained from each participant before blood sampling, and the study protocol was approved by the local ethics committee (IRB00001052-14016).

Clinical and laboratory assessments. Demographic data were collected including age, symptom duration, HLA-B27 status, history of extraarticular manifestations, and use of NSAID.

BASDAI, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were used to evaluate disease activity. Functional conditions of the patients were evaluated using the Bath Ankylosing Spondylitis Functional Index (BASFI).

Presence of syndesmophytes was assessed at baseline and at the end of followup by standard radiographs of the cervical and lumbar spines. Radiographs were scored by 2 independent readers according to the mSASSS.

Bone turnover marker measurement. Serum marker of bone resorption [serum C-telopeptides of type-I collagen (sCTX)] and bone formation markers [procollagen type-I N-terminal peptide (PINP) and bone-specific alkaline phosphatase (BALP)] were measured by ELISA. Serum samples were stored within 1 h at –20°C until analysis.

BMD measurement. The BMD of the lumbar spine (L2–L4) and femoral neck were measured at baseline and the end of treatment by dual energy X-ray absorptiometry (DEXA; Medlink). During the study, the BMD of every patient was measured by the same machine. The BMD measurement revealed Z scores, and the mean value of BMD among the patients was compared with that of age-matched healthy persons.

Z scores were used to define low BMD. Many studies used T scores for definition of low BMD, irrespective of the age of participants studied. Because most of our patients (98%) were aged < 50 years, T score was not appropriate for our study. The International Society for Clinical Densitometry recommended BMD Z scores instead of BMD T scores in premenopausal women and men under the age of 50[14].

Statistical analysis. Data were demonstrated as mean ± SD for the continued variables and as numbers (percentage) for the categorical variables. Between-group comparisons were carried out using the Wilcoxon test for continuous variables. Within-group relative changes (%) of the observed indexes from baseline were stated as descriptive statistics, and the comparisons were performed by Student t test or Wilcoxon signed-rank sum test as appropriate. Pearson and Spearman correlation coefficients were used as appropriate to analyze the relation between improvement of BMD and the changes in clinical assessments. A p value < 0.05 was considered statistically significant. SPSS V. 19.0 for Windows (SPSS) was used for statistical analyses.

RESULTS

Among the 89 enrolled patients, 42 who accepted anti-TNF therapy (ETN n = 25, ADA n = 17) were classified into the study group, and the 47 who received SSZ were classified into the control group. There was no difference between the 2 groups in age, sex, smoking, body mass index, BASDAI, BASFI, mSASSS, CRP, ESR, and BMD at baseline (Table 1). However, in the control group, the percentage of current NSAID use was more than that in the study group ($p < 0.0001$).

In the study group, 39 patients remained at study end, and 3 patients dropped out because of side effects of anti-TNF therapy. In contrast, 6 patients in the control group dropped out of the study because of AS progression.

Disease activity, functional conditions, and systemic inflammation. After 1 year of therapy, compared with the baseline, a significant improvement of disease activity assessed by the scores of the BASDAI (–49%, $p < 0.0001$) and functional conditions assessed by BASFI (–47%, $p < 0.0001$) was observed in the study group, and a significant decrease of systemic inflammation assessed by ESR (–55%, $p < 0.0001$) and CRP (–72%, $p < 0.0001$) was observed. However, the improvements in BASDAI, BASFI, ESR, and CRP were not so significant in the control group (Table 2).

BMD of lumbar spine and femoral neck. Compared with the baseline, BMD of lumbar spine and femoral neck were significantly decreased in the control group after 12 months (lumbar –8.6% ± 9.7%, $p < 0.0001$; femoral neck –9.8% ± 11.5%, $p < 0.0001$). Compared with the baseline, BMD of lumbar spine and femoral neck were significantly increased in the study group (lumbar 14.9% ± 15.6%, $p < 0.0001$; femoral neck 4.7% ± 7.9%, $p < 0.0001$; Table 2). Moreover, the improvement of BMD was correlated with the decrease of ESR ($r = –0.373$, $p = 0.006$) and CRP ($r = –0.458$, $p = 0.004$).

Bone turnover marker. Compared with the baseline, sCTX was significantly decreased in the study group (–40% at 1 yr, $p < 0.0001$), and BALP and PINP were increased (+45.6%, $p < 0.0001$; +30.8%, $p < 0.0001$). Compared with the baseline, sCTX, BALP, and PINP were not significantly changed in the control group (Table 2).

mSASSS. Compared with the baseline, there was no significant change of mSASSS after 1 year of anti-TNF therapy (19.8 ± 23.4 vs 18.2 ± 21.0), and mSASSS was not changed in the control group (18.4 ± 21.7 vs 20.2 ± 23.6).

Fracture rates. After 1 year, 2 patients with vertebral fractures were found in the control group by radiographs.

Table 1. Comparison between the study group and the control group at baseline. Values are mean (SD) or % unless otherwise specified.

Characteristics	Study Group, n = 42	Control Group, n = 47	p
Age, yrs	39.6 (7.5)	41.9 (8.7)	0.385
Male	88	85	0.758
Smoking	28	35	0.452
Disease duration, mos	16.4 (4.8)	17.5 (5.9)	0.541
BMI, kg/m^2	22.5 (2.72)	23.3 (3.01)	0.221
Extraarticular manifestations	14	15	0.652
Current use of NSAID	33	59	0.0001
HLA-B27–positive	95	91	0.921
ESR, mm/h	29 (23)	33 (21)	0.318
CRP, mg/l	21.4 (16.64)	25.3 (18.72)	0.478
BASDAI	5.84 (1.80)	5.06 (1.27)	0.397
BASFI	4.87 (1.96)	4.39 (2.14)	0.480
mSASSS	19.8 (23.4)	18.4 (21.7)	0.280
Lumbar spine BMD Z score	–2.05 (1.01)	–1.97 (0.94)	0.119
Femoral neck BMD Z score	–1.98 (0.92)	–2.17 (1.12)	0.194
BALP, U/l, median (IQR)	17.5 (2.8–38.6)	14.8 (3.5–35.1)	0.235
PINP, ug/l, median (IQR)	43.1 (15.1–84.3)	45.9 (16.4–95.6)	0.319
sCTX, pg/ml, median (IQR)	246.0 (33.7–734.5)	223.5 (23.1–687.4)	0.124

BMI: body mass index; NSAID: nonsteroidal antiinflammatory drugs; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; BASDAI: Bath AS Disease Activity Index; BASFI: Bath AS Functional Index; mSASSS: modified Stoke AS Spine Score; BMD: bone mineral density; BALP: bone-specific alkaline phosphatase; IQR: interquartile range; PINP: procollagen type-I N-terminal peptide; sCTX: serum C-telopeptides of type-I collagen; AS: ankylosing spondylitis.

Table 2. Comparison of changes from baseline in 2 groups at 1 year. Values are % unless otherwise specified.

Characteristics	Study Group, n = 39	Control Group, n = 41	p <
Body weight	+3.7	+1.6	0.0001
ESR	–55	–30	0.0001
CRP	–72	–40	0.0001
BASDAI	–49	–26	0.0001
BASFI	–47	–25	0.0001
Lumbar spine BMD Z score	+14.9	–8.6	0.0001
Femoral neck BMD Z score	+ 4.7	–9.8	0.0001
BALP	+45.6	+9.6	0.0001
PINP	+30.8	+5.6	0.0001
sCTX	–40	–3.2	0.0001

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; BASDAI: Bath AS Disease Activity Index; BASFI: Bath AS Functional Index; BMD: bone mineral density; BALP: bone-specific alkaline phosphatase; PINP: procollagen type-I N-terminal peptide; sCTX: serum C-telopeptides of type-I collagen; AS: ankylosing spondylitis.

Vertebral fractures were absent in the study group, although the difference was not statistically significant.

Body weight. Compared with the baseline, body weight in the study group increased by 3.7%, while in the control group, it increased by 1.6% at the end of the study.

DISCUSSION

In our study, to assess the effect of anti-TNF therapy on the BMD of patients with AS, measurements of both BMD and the bone turnover markers were performed. To our knowledge, this was the first time that patients with AS and low BMD were the subjects in a study of anti-TNF therapy and BMD. Z scores instead of T scores were also used to evaluate BMD, because Z scores were more appropriate for the patients with AS in our study. Our study found that anti-TNF therapy increased the BMD of the spine and femoral neck in patients with active AS with low BMD. This effect was also supported by a decrease in the marker of bone resorption and an increase of bone formation markers.

In our study, in the anti-TNF therapy group, BASDAI was significantly decreased and BASFI was significantly improved compared with the control group, suggesting that the increase of BMD in patients with AS who took anti-TNF therapy may result from the control of inflammation and the increasing level activity secondary to improved health status.

TNF-α can promote the differentiation and activation of osteoclasts that lead to the bone resorption. On the other hand, it can inhibit differentiation and maturation of osteoblasts and promote their apoptosis, thereby decreasing bone formation[15]. Because of the increased bone resorption and decreased bone formation, BMD declines. It is hoped that anti-TNF therapy has the ability to prevent or even reverse the loss of BMD. Anti-TNF therapy has been widely used in the treatment of rheumatoid arthritis (RA) and AS for many years. Anti-TNF therapy having a positive effect on bone loss in RA was reported by many studies[16,17]. This effect was also reported in AS[8,9,10]. Durnez, *et al*[10] found that over an average followup of 6.5 years, the increase in BMD was

11.8% (± 12.8%) at the lumbar spine and 3.6% at the great trochanter (p = 0.0001) in patients with AS treated with anti-TNF therapy. Another study also revealed an improvement in BMD (lumbar spine 6.8%, hip 1.8%) after a 2-year administration of infliximab[17]. Similar effect was also found in our study (lumbar spine 14.9%; femoral neck 4.7%), but the effect was stronger in our study. The possible reason was that more patients with AS in our study had severe low BMD compared with the previous studies.

TNF-α has an obvious effect on osteoclasts, but a limited effect on osteoblasts[16], indicating that bone resorption is significantly influenced by TNF-α, but bone formation may not be. In Chopin, *et al*'s research, sCTX was significantly decreased in patients with RA treated with infliximab, but the PINP was stable before and after treatment[18]. While in patients with AS treated with anti-TNF therapy, the sCTX also decreased as in RA, but the PINP significantly increased in our and other studies[8,9,10]. This suggests that when anti-TNF therapy was used in AS, the effect on bone formation was different compared with RA. AS is a completely different disease from RA, and new bone formation is a feature of AS that causes syndesmophytes and an increased level of bone formation markers. The mechanism of new bone formation is regulated by the bone morphogenetic proteins and the Wnt signaling pathway, which can be influenced by TNF. But whether anti-TNF therapy can slow or promote the rate of new bone formation is still uncertain[19].

It seems that the influence of anti-TNF therapy on BMD may vary with different parts of the body. We found that the influence was stronger in the lumbar spine than hip, although the reason was unclear.

The lumbar spine BMD measured by DEXA in AS can be falsely increased by the presence of lumbar syndesmophytes[20]. Therefore, we used mSASSS to assess the syndesmophytes at the baseline and at the end of the study to ascertain whether the increase of lumbar spine BMD was caused by the increase of syndesmophytes. We found that compared with the baseline, there was no significant increase in mSASSS after 1 year of anti-TNF therapy, indicating that the increase of lumbar spine BMD in the patients treated with anti-TNF therapy was not caused by the presence of syndesmophytes.

There is an ongoing scientific debate on whether these agents can consolidate or prevent spinal osteoproliferation. Data from multiple randomized clinical trials showed that radiographic progression is not inhibited by the usage of various TNF-α blockers for 2–4 years[21,22,23,24,25]. Recently, a retrospective study[26] showed that the use of TNF-α blockers was associated with reduced radiographic progression for patients with AS with a short delay between their first symptoms and the initiation of a longterm TNF-α blocking therapy. In our study, the delay was as short as < 2 years, which may explain why our study group had no radiographic progression.

Although our study found that anti-TNF therapy increased the BMD of the spine and femoral neck, at the end of our study, there was no difference between the study group and the control group in fracture rates. No longitudinal data were available about the effect of TNF-α blocking therapy on the occurrence of new vertebral fractures in AS[8].

A major limitation of our study is the fact that the design is not placebo-controlled and double-blinded. However, a placebo-controlled study is not possible for ethical reasons. Other limitations include a small sample size, short followup period, and measurement error caused by the DEXA machine, which may also influence the results.

Our study suggests that anti-TNF therapy increases the BMD of the spine and femoral neck in patients with active AS with low BMD, indicating that the option of anti-TNF therapy is additionally beneficial for BMD in such patients.

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