EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2017.17006

Original Article

Paradoxical elevation of serum TRACP5b levels despite increase in lumbar spine bone mineral density during anti-TNFα therapy in patients with inflammatory rheumatic disease: a 2-year prospective assessment of bone mass, bone metabolism, and the trabecular bone score

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Abstract

Objective: To examine the impact of long-term anti-TNFα therapy on bone mass, bone metabolism, and the trabecular bone score (TBS) in patients with rheumatoid arthritis (RA) or ankylosing spondylitis (AS).

Material and Methods: In eight patients with RA and 12 with AS, bone mineral densities (BMDs) of the lumbar spine (LS), left and right femoral neck, and total skeleton were measured using dual X-ray absorptiometry at baseline and then at 6, 12, and 24 months after anti TNFα therapy. The TBS was also calculated. At baseline and at 1, 3, 6, 12, 18, and 24 months, bone metabolism was assessed by measurements of pro-collagen-I carboxyterminal propeptide (PICP), osteocalcin, and bone alkaline phosphatase levels in the serum, which are indicative of bone formation and β-isomerized carboxy-terminal telopeptide of type-I collagen (β-CTX-I) and serum isoform 5b of tartrate-resistant acid phosphatase (TRACP5b) levels in the serum, which are indicative of bone resorption.

Results: In patients with RA, the LS T-score increased (3.2%, $p<0.001$) and the TBS progressively decreased (–3.9%, $p=0.03$). In patients with AS, the LS BMD and T-score increased (4.3% and 6.2%, respectively; $p<0.001$) with no significant change in the TBS. Serum TRACP5b levels dramatically increased in both groups (227% in patients with RA and 150% in those with AS, $p<0.001$), while β-CTX-I levels did not change. Serum osteocalcin and PICP levels showed a transitory increase in patients with AS.

Conclusion: Long-term anti-TNFα therapy increased LS bone mass and affected bone quality (TBS) with little impact on bone remodeling. Conversely, TRACP5b levels dramatically increased during anti-TNFα therapy but without any detrimental effect on bone mass.

Keywords: TNFα inhibitors, bone mineral density, trabecular bone score, bone markers, TRACP5b

Cite this article as: Toussirot É, Mourot L, Dehecq B, Michel F, Daniel Wendling D, Grandclément É, et al. Paradoxical elevation of serum TRACP5b levels despite increase in lumbar spine bone mineral density during anti-TNFα therapy in patients with inflammatory rheumatic disease: a 2-year prospective assessment of bone mass, bone metabolism, and the trabecular bone score. Eur J Rheumatol 2017; 4: 189-93.

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Submitted: 10 January 2017
Accepted: 10 April 2017

Introduction

Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are inflammatory rheumatic diseases associated with low bone mass. Osteoporosis is due to systemic inflammation, the use of medications such as corticosteroids, physical disability as well as standard risk factors (1). In inflammatory rheumatic diseases, osteoclasts are highly activated while osteoblasts are suppressed, resulting in a disequilibrium between bone resorption and formation (2). There are numerous studies demonstrating that inflammatory cytokines such as TNFa, IL-1, and IL-6 stimulate bone resorption (2). TNFa is a key driver of inflammation in RA and AS and has the capacity to activate osteoclasts through the RANK/RANK ligand and osteoprotegerin (OPG) system. TNFa inhibits bone formation by increasing osteoblast apoptosis and reducing their differentiation (2). Collectively, these data strongly suggest that bone involvement in inflammatory rheumatic diseases benefits from TNFa inhibition. There are numerous studies showing that bone mineral density (BMD) evaluated by dual X-ray absorptiometry (DXA) increases during anti-TNFa therapy, particularly in patients with RA (1, 3-8). Moreover, studies on the variation of bone turnover markers in RA and AS showed a favorable effect of anti-TNFa agents by restoring the balance between bone formation and resorption (3, 9). However, one limitation is that most of these studies had a relatively short follow-up period (3, 4, 6, 7, 9). Moreover, some included patients were under corticosteroids and/or anti-osteoporotic agents including bisphosphonates, which led to conflicting results (1).

Currently, the diagnosis of osteoporosis is based on the measurement of areal BMD using DXA. In parallel to bone mass, bone microarchitecture is a key factor for bone strength but cannot be measured by DXA. DXA gives only quantitative information on bone mass. The trabecular bone score (TBS) is a new measure that evaluates pixel gray levels in DXA images of the lumbar spine and is assumed to reflect the bone microarchitecture and bone quality (10). To our knowledge, no data are available on changes in TBS during anti-TNFa therapy.

The present study was therefore conducted to better delineate the bone effects of anti-TNFa agents in the long term and the impact they may have on bone mass, bone metabolism, and the TBS.

Material and Methods

Patients

This was a single-center, prospective, observational, open-label study. Patients included were from a cohort of those with RA or AS who underwent repeat DXA over 2 years. The characteristics of this cohort have been previously published (11).

Methods: Clinical and biological data were recorded at baseline and at 1, 3, 6, 12, 18, and 24 months. The erythrocyte sedimentation rate and C-reactive protein levels were used as standard laboratory parameters to evaluate inflammation. Fasting serum samples were collected in the morning and were stored immediately at –80°C for stable dosage and until further analysis. Osteocalcin (OC) and procollagen type-I carboxyterminal propeptide (PICP) levels, which are indicative of bone formation and b-isomerized carboxy-terminal telopeptide of type-I collagen (b-CTX-I) levels, which are indicative of bone resorption, were determined in the serum. Serum isoform 5b of tartrate-resistant acid phosphatase (TRACP5b) (EIA; Quidel Metra) and bone alkaline phosphatase (BAP) were assessed as markers of osteoclast and osteoblast enzymatic activities, respectively. The levels of serum OPG, which is an inhibitor of bone resorption, were also evaluated. At baseline and at 6, 12, and 24 months, BMD was measured in the lumbar spine (LS) (L1–L4, anteroposterior view), left and right femoral neck (FN), and total skeleton by DXA using a Lunar iDXA densitometer (GE Healthcare; Madison, WI, USA). The results are presented as BMD (g/cm^2) and T-score. Quality control scans were performed daily during the study period. Coefficient of variations with the LS, FN, and total body scan were 1.0%, 1.5%, and 0.7%, respectively. The TBS was calculated from an anteroposterior L1–L4 BMD image using TBS iNsight V1.8 (Med-Imaps, Pessac, France). In each measurement region (L1–L4), the TBS was evaluated based on the grey-level analysis of DXA scans, as previously described (10). The coefficient of variation for TBS was 1.5%. The study protocol was approved by our local institutional ethics committee (Comité d'Éthique Clinique du CHU de Besançon). Written informed consent was obtained from all patients.

Statistical analysis

Levels are reported as mean±SEM. The normality distribution of variables was verified using the Shapiro–Wilk test. The mean percentage of change at baseline and 24 months was calculated as follows: (24-month value – baseline value)/baseline value. As our patient series included two disease groups (RA and AS), we separately analyzed each group using repeated measures analysis of variance with Bonferroni correction to detect differences between different assessment points for the variables under study. Relationships between baseline levels of serum bone markers and measurements of bone mass and the TBS were evaluated using the Spearman correlation coefficient.

Table 1. Changes in the bone mineral density, T-score, and trabecular bone score in patients with rheumatoid arthritis (N= 8) or ankylosing spondylitis (N=12) at baseline and at 6, 12 and 24 months after anti-TNFα therapy

	Baseline		Month 6		Month 12		Month 24		Change from baseline (%)		p	
	RA N=8	AS N=12	RA N=8	AS N=12	RA N=8	AS N=12	RA N=8	AS N=12	RA N=8	AS N=12	RA N=8	AS N=1
LS BMD (g/cm^2)	1.21±0.07	1.09±0.08	1.20±0.08	1.14±0.07	1.24±0.07	1.17±0.07	1.26±0.08	1.19±0.07	3.3	4.3	0.25	<0.001
LS T-score	0.14±0.6	-0.99±0.6	0.04±0.7	-0.54±0.6	0.12±0.6	-0.34±0.58	0.475±0.6	-0.11±0.6	3.2	6.2	<0.001	<0.001
FN BMD (g/cm^2)	0.94±0.06	0.93±0.07	0.93±0.06	0.96±0.04	0.93±0.05	0.96±0.03	0.92±0.05	0.98±0.04	-0.6	14.7	0.84	0.2
FNT-score	-0.49±0.4	-0.76±0.5	-0.54±0.45	-0.43±0.3	-0.67±0.37	-0.44±0.24	-0.67±0.44	-0.23±0.27	-13.1	5.3	0.89	0.09
Total body BMD (g/cm^2)	1.14±0.05	1.17±0.03	1.14±0.06	1.18±0.04	1.14±0.06	1.18±0.03	1.14±0.06	1.18±0.03	-0.36	0.9	0.87	0.5
TBS	1.36±0.02	1.26±0.05	1.35±0.02	1.29±0.04	1.33±0.02	1.31±0.03	1.31±0.03	1.3±0.03	-3.9	2.4	0.03	0.29

BMD: bone mineral density; LS: L1–L4 lumbar spine; FN: femoral neck; TBS: trabecular bone score, p values reflect the significance of the difference between assessment points by repeated measures ANOVA

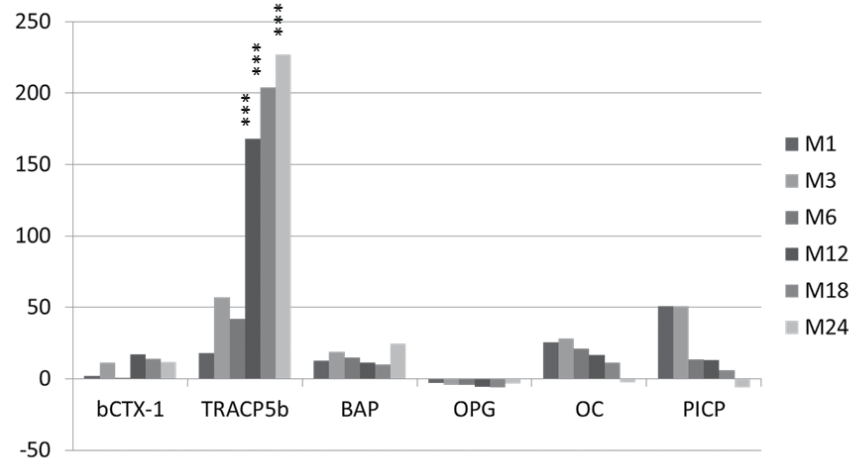

Figure 1. Percentage of changes in the levels of biochemical markers indicative of bone formation (PICP and OC) and bone resorption (β-CTX-I) as well as of the enzymatic activity of osteoclasts (TRACP5b) and osteoblasts (BAP) during the 2-year follow-up during anti-TNFα therapy in patients with rheumatoid arthritis. Assessments were performed at baseline and then at 1, 3, 6, 12, 18, and 24 months. Changes were calculated between each time point and baseline
β-CTX-I: beta C-terminal telopeptide of type-I collagen; TRACP5b: isoform 5b of tartrate-resistant acid phosphatase; BAP: bone alkaline phosphatase; OPG: osteoprotegerin; OC: osteocalcin; PICP: procollagen type-I propeptide
***p<0.001

The same test was used to analyze the association between changes in BMD and changes in acute-phase reactants and disease activity. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using SigmaStat software (SSS Inc.; Chicago, IL, USA).

Results

Eight outpatients with RA and 12 patients with AS participated. At baseline, three patients (AS=3) had osteoporosis (LS or FN T-score below −2.5), eight had osteopenia (RA=3, AS=5), and nine had a normal BMD (RA=5, AS=4). Three patients received infliximab (Merck & Co; Kenilworth NJ, USA), seven received etanercept (Pfizer; New York, USA), and 12 received adalimumab (Abbott; Chicago, USA). Seven patients in the RA group and two in the AS group received low-dose corticosteroids at baseline (mean dose: 8.3±0.8 mg/day), while none were under bisphosphonates. All patients completed the 2-year follow-up with a significant decrease in disease activity and acute-phase reactants (all p<0.005). The corticosteroid dosage was tapered to 3.3±1.2 mg/day (11).

All variables were normally distributed according to the results of Shapiro–Wilk tests. In the RA group, the LS T-score increased from baseline to month 24 (3.2%, p<0.001), while LS and total body BMD and measurements in the FN did not significantly vary (Table 1). The TBS progressively declined in patients with RA (−3.9%, p=0.03). In the AS group, LS BMD and the T-score increased (4.3% and 6.2%, respectively; p<0.001). There were no significant changes in BMD measurements at other sites. The TBS progressively increased in this group (2.4%) but without significant difference.

Serum bone marker levels were also normally distributed. In the RA group, no difference in the serum bone marker levels was observed, except for TRACP5b levels, which markedly increased from month 12 to month 24 (change from baseline: 227%, p<0.001) (Table 2, Figure 1). The same results were observed in the AS group (change from baseline: 150%, p<0.001) (Figure 2). In this group, b-CTX-I and BAP levels did not change over the study period, while OPG levels decreased at month 6 (−10.3%, p=0.02). On the contrary, OC and PICP levels increased between months 1 and 3 and then reached a plateau at month 6 (19.9%, p=0.01 and 26.8%, p=0.025, respectively). In both patient groups, serum TRACP5b levels highly correlated with FN BMD (RA: r=−0.83, p=0.046; AS: r=−0.84, p=0.008) and total body BMD (RA: r=−0.83, p=0.03; AS: r=−0.6, p=0.048). In the AS group, changes in disease activity (as evaluated by Bath Ankylosing Spondylitis Disease activity Index (BASDAI) were correlated to changes in the LS T-score (r=0.61, p=0.04) and changes in the TBS (r=0.84, p=0.018).

Discussion

Our results showed that bone mass increased over 2 years with a significant gain at the LS (BMD in AS or T-score in RA and AS), which

Table 2. Effects of anti-TNFα therapy on serum bone marker levels in patients with rheumatoid arthritis (N= 8) or ankylosing spondylitis (N= 12) at baseline and at 1,3,6, 12, 18, and 24 months after anti-TNFα therapy

RA N=8 AS N=12	Baseline		Month 1		Month 3		Month 6		Month 12		Month 18		Month 24		Change from baseline (%)		p	
	RA	AS	RA	AS	RA	AS	RA	AS	RA	AS	RA	AS	RA	AS	RA	AS	RA	AS
β-CTX-I (ng/mL)	0.3±0.06	0.6±0.1	0.28±0.03	0.61±0.13	0.3±0.05	0.65±0.15	0.31±0.04	0.51±0.1	0.36±0.05	0.54±0.08	0.3±0.03	0.51±0.1	0.38±0.05	0.52±0.12	11.8	- 13.3	0.2	0.4
TRACP5b (U/L)	1.18±0.2	1.13±0.18	1.32±0.3	1.14±0.2	1.93±0.2	1.2±0.2	1.9±0.2	1.2±0.23	1.9±0.3	1.46±0.23	2.3±0.3	1.85±0.3	2.9±0.3	2.17±0.34	227	150	<0.001	<0.001
BAP (mg/L)	8.0±0.8	10.91 ±1.02	8.7±1.3	12.8±1.7	10.1±2.2	13±1.7	9.5±0.8	12.1±1.5	9.0±0.7	11.63±1.17	9.7±0.9	11.1±1.7	9.3±1.5	11.44 ±1.7	24.6	2.3	0.5	0.1
OPG (pmol/L)	4.9±0.6	4.86±0.48	4.5±0.6	4.6±0.4	4.6±0.5	4.4±0.4	4.9±0.6	4.36±0.37	4.9±0.5	4.28±0.37	5.2±0.7	4.2±0.4	4.5±0.6	4.28±0.44	- 3.5	- 10.3	0.6	0.02
OC (ng/ml)	13.0±1.9	20.7±3.2	13±2.4	29.1±5.2	14.6±2.8	27.2±4.7	15.0±2.6	25.67 ±4.5	16.6±3.3	22.64 ±2.6	15±2.4	21.1±4.1	12.7±1.9	22.17±3.3	- 2.3	19.9	0.2	0.01
PICP (n/ml)	74.3±8.1	74.06±10.4	87.6±16.3	119.4±26	80.3±15	126.2±20.7	84.8±14.8	87.73±18.7	80.7±7.9	91.17±14.7	73.6±9.7	81.6±16.5	61.8±7.3	90.62±11.8	-6	26.8	0.45	0.025

β-CTX-I: beta C-terminal telopeptide of type-I collagen; TRACP5b: isoform 5b of tartrate-resistant acid phosphatase; BAP: bone alkaline phosphatase; OPG: osteoprotegerin; OC: osteocalcin; PICP: procollagen type-I propeptide. p values reflect the significance of the difference between assessment points by repeated measures ANOVA

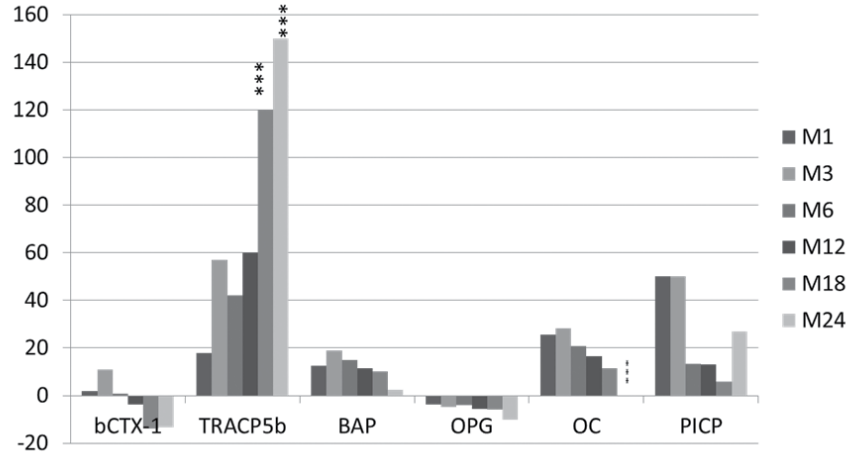

Figure 2. Percentage of changes in the levels of biochemical markers indicative of bone formation (PICP and OC) and bone resorption (β-CTX-I) as well as of the enzymatic activity of osteoclasts (TRACP5b) and osteoblasts (BAP) during the 2-year follow-up during anti-TNFα therapy in patients with ankylosing spondylitis. Assessments were performed at baseline and then at 1, 3, 6, 12, 18, and 24 months. Changes were calculated between each time point and baseline
***p<0.001

confirmed previous findings (2-8). Bone mineral density at the FN and bone mass of the total skeleton slightly increased or remained unchanged. Similar discrepancies in the LS and hip bone changes have been previously reported and explained by the small number of patients included (7). In addition, the results in previous studies vary with regard to the concomitant use of corticosteroids and/or bisphosphonates. For this reason, we selected patients not under anti-osteoporotic drugs. Bisphosphonates were not used for patients under corticosteroids because corticosteroid dosage was expected to be tapered along with time. Finally, previous studies had variable (generally short) follow-up durations (3, 4, 6, 7, 9). Our patients had a long-term follow-up (2 years), and our results on BMD are consistent with those of previous studies of similar duration (5).

The TBS is a new measure giving additional information to DXA on bone strength and predicting fractures (10, 12). The TBS was affected by anti-TNFa therapy in our study, decreasing in patients with RA and increasing in those with AS. However, this variation was weak. By ameliorating bone mass and bone remodeling, one may expect that TBS also improves during anti-TNFa therapy, and this was observed in the AS group, without reaching a significant level. On the contrary, the TBS significantly decreased in the RA group. This seems paradoxical as the T-score in the spine improved. However, seven of our eight patients with RA were under corticosteroids, and this medication is known to have deleterious effect on the cancellous micro-architecture (13). In addition, a previous study demonstrated that the TBS decreased under corticosteroids without parallel changes in BMD, even at a very low dosage (14). As previously performed by others, we measured the serum levels of markers of collagen neosynthesis (PICP) and collagen breakdown (b-CTX-I), together with OC (3, 8, 9). We also evaluated the enzymatic activity of osteoblasts and osteoclasts by means of BAP and TRACP5b, respectively. TRACP5b is a sensitive bone marker that reflects osteoclast number; thus, it is an indicator of bone resorption (15, 16). In general, in patients with RA or AS under anti-TNFa agents, a decrease in bone resorption marker levels (particularly b-CTX-I) and an increase or maintenance in bone formation marker levels (mainly OC or BAP) have been found, even if these changes were not always consistent or moderate and transitory (2, 17). This suggests that equilibrium between bone formation and resorption was restored. We did not find any changes in b-CTX-I and BAP levels, while PICP and OC level showed a transitory increase in the AS group. This indicated a stimulatory effect of anti-TNFa agents on osteoblasts (3). Conversely, TRACP5b levels increased in patients with RA and those with AS to considerable high levels after 24 months of follow- up. TRACP5b was not previously evaluated in patients under anti-TNFa therapy. This dramatic increase seems paradoxical and indicates that the number of osteoclasts increased under the pressure of the TNFa blockade. On the contrary, osteoclast activity did not seem stimulated as b-CTX-I levels remained stable. In transgenic mice with overexpression of the TRAP gene, the animals were mildly osteoporotic, with an increased rate of bone formation that compensated the increased osteoclast activity (18). In our patients, the increase in TRACP5b levels did not have deleterious consequence on BMD, and this may be explained by a compensatory mechanism in bone formation. Accordingly, the levels of markers of bone formation increased at the beginning of follow-up in the AS group. Another explanation is that TRACP5b and b-CTX-I evaluate osteoclast activity via different pathways: enzymatic versus collagen breakdown. Mechanisms explaining this paradoxical TRACP5b level increase are unknown. Paradoxical effects of TNFa on the bone have been described such as osteogenic differentiation effects (19). In our series, changes in LS bone mass was parallel to the decrease in acute-phase reactants, reflecting the fact that reduced inflammation has a favorable effect on bone health.

Compared to previous studies, we performed a full bone evaluation including bone mass, bone metabolism, and bone quality by means of the TBS, with a long-term observation and without missing data. However, a small sample size of patients was considered. Several significant differences were found using appropriate analyses.

In summary, this is the first study to show that the TBS moderately increased in patients with AS, while it decreased in patients with RA under anti-TNFa agents, an effect that may be explained by the concomitant use of corticosteroids in RA. The TNFa blockade was accompanied by a

dramatic increase in TRACP5b levels without deleterious consequence on bone mass. Anti-TNFa agents in patients with RA or AS have different impacts on bone mass, bone remodeling, and the TBS.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Besancon (Comité d'Ethique Clinique du CHU de Besançon).

Informed Consent: Written informed consent was obtained from patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - E.T., G.D.; Design - E.T., G.D.; Supervision - E.T.; Resources - E.T.; Materials - B.D., E.G., G.D.; Data Collection and/or Processing - E.T.; Analysis and/or Interpretation - L.M., E.T.; Literature Search - E.T., G.D.; Writing Manuscript - E.T.; Critical Review - E.T., L.M., B.D., F.M., D.W., E.G., G.D.; Other (patient recruitement) - E.T., D.W., F.M.

Acknowledgements: The authors would like to thank Mrs Fiona Ecarnot MSc, EA3920, Department of Car-

diology, University Hospital Besançon, France for her help in preparing the manuscript.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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