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Effect of abatacept treatment on serum osteoclast-related biomarkers in patients with rheumatoid arthritis (RA)

A multicenter RA ultrasound prospective cohort in Japan

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Abstract

We evaluated the effect of abatacept treatment on osteoclast-related biomarkers and explored whether the biomarkers are associated with the therapeutic response in rheumatoid arthritis (RA) patients treated with abatacept.

We enrolled 44 RA patients treated with abatacept from a multicenter prospective ultrasound cohort study of patients who received biologic or targeted synthetic disease-modifying antirheumatic drug therapy. We evaluated the disease activity score (DAS) 28-CRP (C-reactive protein), musculoskeletal ultrasound scores including the total grayscale score (GS)/power Doppler (PD) score and the serum concentrations of isoform 5b of tartrate-resistant acid phosphate (TRACP-5b) and soluble receptor activator of nuclear factor-κB ligand (sRANKL) at baseline and at 3 and 6 months of treatment. "PD responder" was defined as a patient whose Δtotal PD score over 6 months was greater than the median change of that.

Abatacept significantly improved DAS28-CRP as well as the total GS/PD score over 6 months. Serum TRACP-5b was significantly elevated and serum sRANKL was significantly decreased at 6 months ($P < .0001$ and $P < .01$, respectively). At 6 months, serum sRANKL was significantly decreased in the patients who achieved DAS28-CRP remission and the PD responders but not in those who did not. However, serum TRACP-5b rose regardless of the therapeutic response.

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Among RA patients treated with abatacept, serum sRANKL decreased in the patients with a good therapeutic response, but serum TRACP-5b elevated paradoxically regardless of the therapeutic response.

Abbreviations: ACPA = anti-cyclic citrullinated peptide antibody, bDMARD = biologic disease-modifying antirheumatic drug, CRP = C-reactive protein, CTLA-4 = cytotoxic T lymphocyte-associated antigen-4, DAS = Disease Activity Score, DMARD = disease-modifying antirheumatic drug, GS = grayscale, IL = interleukin, IQR = interquartile range, JCR = Japan College of Rheumatology, KUDOS = Kyushu Multicenter Rheumatoid Arthritis Ultrasound Prospective Observational Cohort Study, MSUS = musculoskeletal ultrasound, MTX = methotrexate, PD = power Doppler, RA = rheumatoid arthritis, sRANKL = soluble receptor activator of nuclear factor-κB ligand, TNF = tumor necrosis factor, TRACP-5b = isoform 5b of tartrate-resistant acid phosphate, tsDMARD = targeted synthetic DMARD.

Keywords: abatacept, musculoskeletal ultrasound, rheumatoid arthritis, sRANKL, TRACP-5b

1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease characterized by persistent inflammation that leads to bone and cartilage destruction, deformation, disability, and loss of quality of life.[1,2] RA-associated bone loss is characterized by 3 different manifestations: (i) local erosions in the inflamed joints, where bone and cartilage are in direct contact with the inflamed synovium, (ii) periarticular bone loss of trabecular and cortical bone close to sites of inflammation, and (iii) systemic osteopenia and osteoporosis.[3–5] All 3 forms of bone loss are caused by altered bone homeostasis with increased osteoclast generation and activity resulting in accelerated bone resorption, whereas osteoblast-mediated bone formation is suppressed.[4]

The tight control of the disease activity of RA according to the treat-to-target strategy is recommended for better clinical outcomes.[6,7] Advances in the treatment of RA such as biological disease-modifying anti-rheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) have provided clinical remission, the prevention of joint damage, and the preservation of function for individuals with RA. Abatacept, a fusion protein of cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and immunoglobulin G1, selectively modulates the CD80/CD86: CD28 costimulatory signal required for full T-cell activation.[8] Abatacept is an effective treatment for patients with RA, according to both clinical trials[9–12] and practice.[13,14] Abatacept is thus recommended as one of the first-line bDMARDs for RA.[7]

Several studies indicated that abatacept strongly inhibits radiographic progression in patients with RA.[9–12] CTLA-4/CTLA-4-Ig is effective in inhibiting receptor activator of nuclear factor-κB ligand (RANKL)/tumor necrosis factor (TNF)-mediated osteoclastogenesis independently of T-cell activation.[15–18] CTLA-4/CTLA-4-Ig is thus suggested to be an anti-osteoclastogenic molecule that directly binds osteoclast precursor cells and inhibits their differentiation.[15–18] This fact is an attractive explanation for the anti-erosive effect of abatacept.[15]

Several inflammatory cytokines involved in the pathogenesis of RA such as TNFα, interleukin (IL)-6, IL-1β, and IL-17 have been shown to exert pro-osteoclastogenic effects and to simultaneously suppress bone formation in part.[3] These effects are mediated by a direct cytokine stimulation of osteoclast differentiation or indirectly by the induction of RANKL expression in the joints.[3] As a biomarker reflecting osteoclast activity, isoform 5b of tartrate-resistant acid phosphate (TRACP-5b) is a commonly used surrogate marker for bone resorption.[19] Although the serum concentration of TRACP-5b is measured as an indicator of treatment for osteoporosis in daily clinical practice, the effect of abatacept on these osteoclast-related markers in patients with RA has not been investigated.

To achieve the goal of the treat-to-target strategy, the adequate management of disease activity requires a sensitive and accurate assessment of arthritis. The addition of a musculoskeletal ultrasound (MSUS) assessment help improves the management of RA in daily clinical practice.[20,21] Compared to clinical and radiographic examinations, MSUS provides a straightforward and more accurate detection of both inflammation and damage at the joint level.[20] We have conducted a multicenter prospective observational cohort study of patients with active RA who received bDMARD or tsDMARD therapy at 27 participating rheumatology centers in the Kyushu region of Japan since June 2013 [Kyushu Multicenter Rheumatoid Arthritis Ultrasound Prospective Observational Cohort Study (KUDOS)].[22–24] We evaluated the therapeutic efficacy of the bDMARDs and tsDMARDs by clinical measurements, MSUS, and biomarker assessments. A multicenter collaborative study that prospectively evaluates disease activity using MSUS standardized at a high level is rare, even worldwide.

In the present study, we evaluated the effect of abatacept treatment on osteoclast-related biomarkers (ie, TRACP-5b and sRANKL) and explored whether the biomarkers are associated with the therapeutic response assessed by clinical disease activity indices as well as the MSUS score in RA patients treated with abatacept using the KUDOS cohort.

2. Methods

2.1. Patients

This study is part of an ongoing non-randomized multicenter prospective observational cohort study [KUDOS] of patients with active RA who received bDMARD or tsDMARD therapy at 27 participating rheumatology centers in Japan's Kyushu region since June 2013.[22–24] In that study, we have been evaluating the therapeutic efficacy by determining the patients' clinical disease activity, MSUS score, and serum biomarkers at baseline and at 3, 6, 9, 12, 18, and 24 months starting from the initiation of treatment with a new bDMARD or tsDMARD.

For the present study, we enrolled the 44 consecutive Japanese patients with active RA who were treated with abatacept and had continued the treatment for >6 months at 10 participating rheumatology centers during the period from June 2013 to March 2016. For their enrollment in this study, all patients were required to satisfy the 1987 American College of Rheumatology[25] and/or 2010 American College of Rheumatology/European

League Against Rheumatism criteria for RA.[26] Abatacept was administered as recommended by the manufacturers: 125 mg via subcutaneous injection weekly or 500 to 750 mg via intravenous infusion every 4 weeks. We excluded patients who have newly introduced an oral bisphosphonate during the study period or treated with intravenous bisphosphonates, anti-RANKL antibodies, or parathyroid hormone agents.

The study is registered with the University Hospital Medical Information Network Clinical Trials Registry (http://www.umin.ac.jp/ctr/, #UMIN 000012524) and was approved by the Institutional Review Board of Nagasaki University (approval no. 13102866). All patients gave their signed informed consent to participate in accordance with the Helsinki Declaration.

2.2. Clinical and laboratory assessments

Disease activity was evaluated by each of the attending physicians (Japan College of Rheumatology [JCR]-certified rheumatologists) according to the Disease Activity Score (DAS) 28-CRP (C-reactive protein) value at baseline and every 3 months after the introduction of abatacept. The treating physicians were different from the MSUS evaluators. The baseline MSUS scores were evaluated after the decision regarding the introduction of b/tsDMARD therapy.

2.3. Musculoskeletal ultrasound assessment

The MSUS examination of each patient was performed by JCR-certified sonographers. At all of the participating institutions, a trained MSUS expert examined the patient in a situation recommended by the JCR guidelines, paying attention to factors that can affect power Doppler (PD) results, including the room temperature, the last use of a nonsteroidal anti-inflammatory drug, and hand position. Medium-level to high-level ultrasound machines were used (Toshiba AplioXG and Aplio300, GE Logic series 7 and 8 or Hitachi Ascendus, Avius, Noblus, and Hi Vision Preirus) with high-frequency (12–18.5 MHz) linear transducers. The Doppler parameters were adjusted according to the device used (range of pulse repetition frequency 500–1000 Hz; Doppler frequency 6.1–10.0 MHz). There was no change in MSUS settings during the study.

Twenty-two joints including the metacarpophalangeal, proximal interphalangeal, and wrist joints of the bilateral hands were assessed by MSUS at baseline and at 3 and 6 months of treatment. The 22 joints were scanned on the dorsal aspect. Standardized joint and probe positions were used, based on a guideline published by the JCR. Each grayscale (GS) synovial hypertrophy and PD signal was scored semi-quantitatively on a scale from 0 to 3.[27] The sum of the GS or PD scores was used as the indicator of US disease activity, described as the total GS score or total PD score. The total scores ranged from 0 to 66.

We defined a "PD responder" at 6 months as a patient whose change in total PD score (Δtotal PD score) over 6 months was greater than the median change (ie, a Δtotal PD score over 6 months less than or equal to −4) in all patients. We defined PD remission as a total PD score of 0 at 6 months. Interobserver reliability was confirmed in a previous investigation.[22]

2.4. Bone biomarker measurements

We measured the concentrations of the following biomarkers using serum stored on the same day as the patient's clinical evaluation. Rheumatoid factor (RF) was measured by a latex agglutination turbidimetric immunoassay (LZ test "Eiken" RF, Eiken, Tochigi, Japan). Anti-cyclic citrullinated peptide antibody was measured by a chemiluminescent immunoassay (STACIA MEBLux test CCP, MBL, Nagoya, Japan). The patients' serum concentrations of TRACP-5b were measured by an enzyme immunoassay (Osteolinks "TRAP-5b," DS Pharma Biomedical, Osaka, Japan). Serum concentrations of sRANKL were measured by an enzyme-linked immunosorbent assay (FREE soluble RANKL High Sensitivity; Biomedica, Vienna, Austria).

2.5. Statistical analyses

Categorical quantitative variables are presented as medians and interquartile ranges (IQRs). Categorical variables are presented as percentages. Missing data for serum concentration of TRACP-5b/sRANKL in 3 patients at 3 months due to lack of stored serum were treated as missing values. We used the Mann–Whitney *U* test for comparisons between independent medians, and we used the Chi-square test for the evaluation of the associations between categorical variables. Correlations were assessed with Spearman correlation coefficient. The changes in clinical disease activity indices, MSUS scores, or serum concentrations of bone biomarkers over 6 months were analyzed using the Wilcoxon signed-rank test. P values $<.05$ were considered significant. Statistical analyses were performed using JMP Pro statistical software, ver. 15.0 (SAS, Cary, NC, USA).

3. Results

3.1. Demographic, clinical, and laboratory characteristics of the 44 RA patients

Forty-four RA patients were enrolled in this study. The patient's characteristics at baseline are summarized in Table 1. The median (IQR) age of the patients was 72 (65–77) years: >55 years except for 1 patient, and the median (IQR) of the RA disease duration was 52 (14–210) months. The median (IQR) of the DAS28-CRP was 4.33 (2.85–5.30). The median (IQR) of the total GS and PD scores were 14 (7–22) and 7 (4–14), respectively. Methotrexate (median dose: 8 mg weekly) and low-dose oral glucocorticoids (median dose: 5 mg daily) were concomitant in 18 (40.9%) and 27 (61.4%) patients, respectively. Nineteen (43.2%) patients had a history of previous use of a bDMARD.

3.2. Improvement of clinical and MSUS activities over 6 months

Overall, the patients' DAS28-CRP (Fig. 1A) value was significantly improved at 3 and 6 months compared to the baseline ($P<.001$, respectively). At 6 months, 25 patients (56.8%) had achieved DAS28-CRP remission, and the other 19 patients (43.2%) had not (non-remission). The median (IQR) of the total GS scores decreased from 14 (7–22) at baseline to 10 (5–18) at 3 months ($P=.0008$) and 9 (4–19) at 6 months ($P=.0018$) (Fig. 1B). In addition, the median (IQR) of the PD scores decreased from 7 (4–14) at baseline to 6 (1–12) at 3 months ($P=.0006$) and 3 (0–10) at 6 months ($P<.0001$) (Fig. 1C).

3.3. Changes in the serum concentrations of osteoclast-related biomarkers

Serum TRACP-5b was significantly elevated at 3 and 6 months (both, $P<.0001$) after the introduction of abatacept (Fig. 2A).

Table 1

Demographic, clinical, and laboratory characteristics of the 44 patients with RA.

Age (yrs)	72 (65–77)
Male (n)	11 (25.0)
Disease duration (months)	52 (14–210)
csDMARD use (n)	36 (81.8)
MTX use (n)	18 (40.9)
Corticosteroid use (n)	27 (61.4)
Previous use of bDMARD	19 (43.2)
Oral bisphosphonate use	19 (43.8)
Positive RF (n)	33 (75.0)
Positive ACPA (n)	38 (86.4)
Tender joint count (28) (n)	6 (3–13)
Swollen joint count (28) (n)	6 (2–13)
PtGA (mm)	40 (20–75)
EGA (mm)	43 (30–55)
CRP (mg/dL)	0.78 (0.11–2.16)
MMP-3 (ng/mL)	120 (60–291)
DAS28-CRP	4.33 (2.85–5.30)
Total GS score	14 (7–22)
Total PD score	7 (4–14)

The data are median (interquartile range, Q_{1-4}–$Q_{3/4}$) or number (percentage).
ACPA = anti-cyclic citrullinated peptide antibody, bDMARDs = biologic disease-modifying antirheumatic drugs, CRP = C-reactive protein, DAS = disease activity score, csDMARD = conventional synthetic disease-modifying antirheumatic drug, EGA = evaluator's global assessment, ESR = erythrocyte sedimentation rate, GS = grayscale, MTX = methotrexate, PD = power Doppler, PtGA = patient's global assessment, RA = rheumatoid arthritis, RF = rheumatoid factor.

On the other hand, serum sRANKL was significantly decreased at 6 months ($P = .0086$) after the introduction of abatacept (Fig. 2B).

We evaluated the association between the changes of serum TRACP-5b/sRANKL and the therapeutic response to abatacept. We compared the changes of serum TRACP-5b/sRANKL between the DAS28-CRP remission patients and DAS28-CRP non-remission patients and between the PD responders and PD non-responders at 6 months. Serum TRACP-5b/sRANKL at baseline was not significantly different between the remission and non-remission patients or between the PD responders and non-responders. Serum TRACP-5b elevated significantly after the introduction of abatacept regardless of therapeutic responses (DAS28-CRP remission patients: Fig. 3A and B; PD responders: Fig. 4A and B). Serum sRANKL decreased significantly after the introduction of abatacept in the remission patients and the PD responders but did not change significantly in the non-remission patients and the PD non-responders (DAS28-CRP remission patients: Fig. 3C and D, PD responders: Fig. 4Cand D).

Serum TRACP-5b and sRANKL were not associated with age or disease duration. Although serum sRANKL was not associated with gender, serum TRACP-5b was significantly higher in females than males ($P = .016$). Serum TRACP-5b was significantly elevated after the introduction of abatacept regardless of gender (Figure S1, Supplemental Digital Content, http://links.lww.com/MD/G245). The oral corticosteroids and bisphosphonates did not affect the serum concentrations of biomarkers at baseline or their changes (data not shown). Serum TRACP-5b and sRANKL did not have a significant correlation with clinical disease activity or with each other at baseline (Table S1, Supplemental Digital Content, http://links.lww.com/MD/G246).

4. Discussion

We evaluated the association between the serum concentrations of osteoclast-related biomarkers (TRACP-5b and sRANKL) and the therapeutic response to abatacept in RA patients, using our multicenter prospective ultrasound cohort study [KUDOS]. In the present investigation, since abatacept significantly improved the patients' clinical disease activity as well as their MSUS score over the 6-month treatment, bone destruction was expected to be prevented in this population. As new knowledge, we observed that in RA patients treated with abatacept, the serum sRANKL values decreased in the patients with a good therapeutic response, but the serum TRACP-5b values were paradoxically elevated regardless of therapeutic response.

RA-associated bone loss is caused by increasing osteoclast differentiation and activity leading to rapid bone resorption.[4] Two essential mechanisms trigger enhanced osteoclast differentiation during autoimmune inflammatory diseases such as RA.[3,4] Traditionally, pro-inflammatory cytokines mediate osteoclast differentiation by binding to cytokine receptors on osteoclasts or via the stimulation of RANKL expression.[3,4]

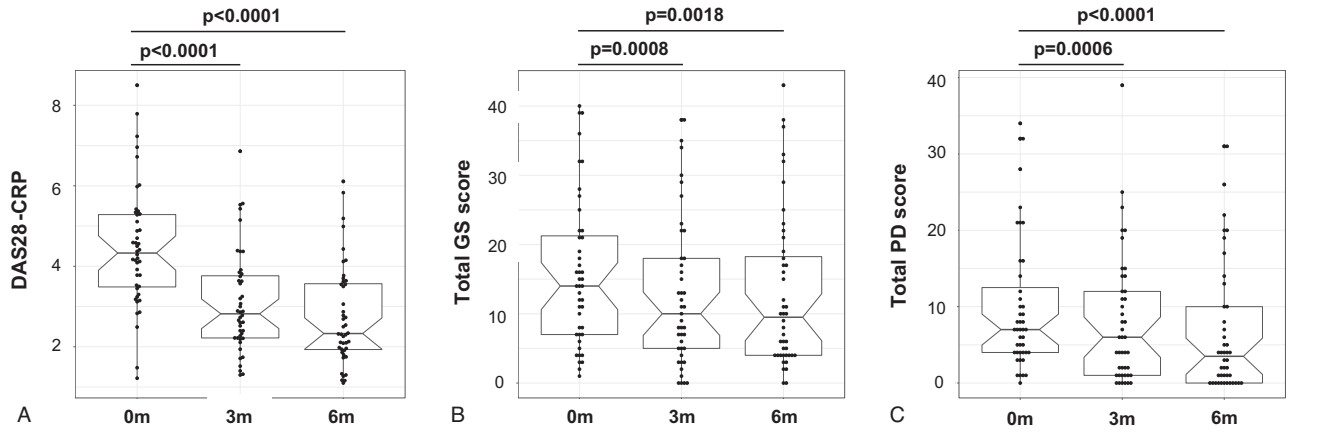

Figure 1. Changes in the patients' clinical disease activity and MSUS scores over the 6-month abatacept treatment period. The (A) DAS28-CRP, (B) total GS score, and (C) total PD score were significantly improved at 3 and 6 months compared to the baseline. Wilcoxon signed-rank test. DAS28-CRP = disease activity score 28-C-reactive protein, GS = grayscale, PD = power Doppler.

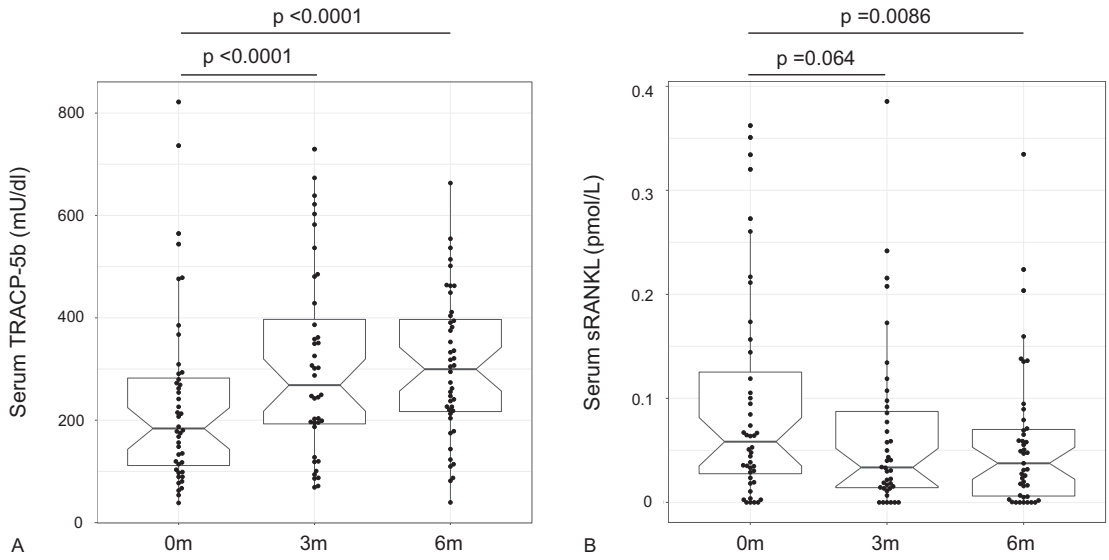

Figure 2. Changes in serum TRACP-5b and sRANKL over the 6-month abatacept treatment period. (A) Serum TRACP-5b was significantly elevated at 3 and 6 months compared to the baseline. (B) Serum RANKL was significantly decreased at 6 months compared to the baseline. Wilcoxon signed-rank test.

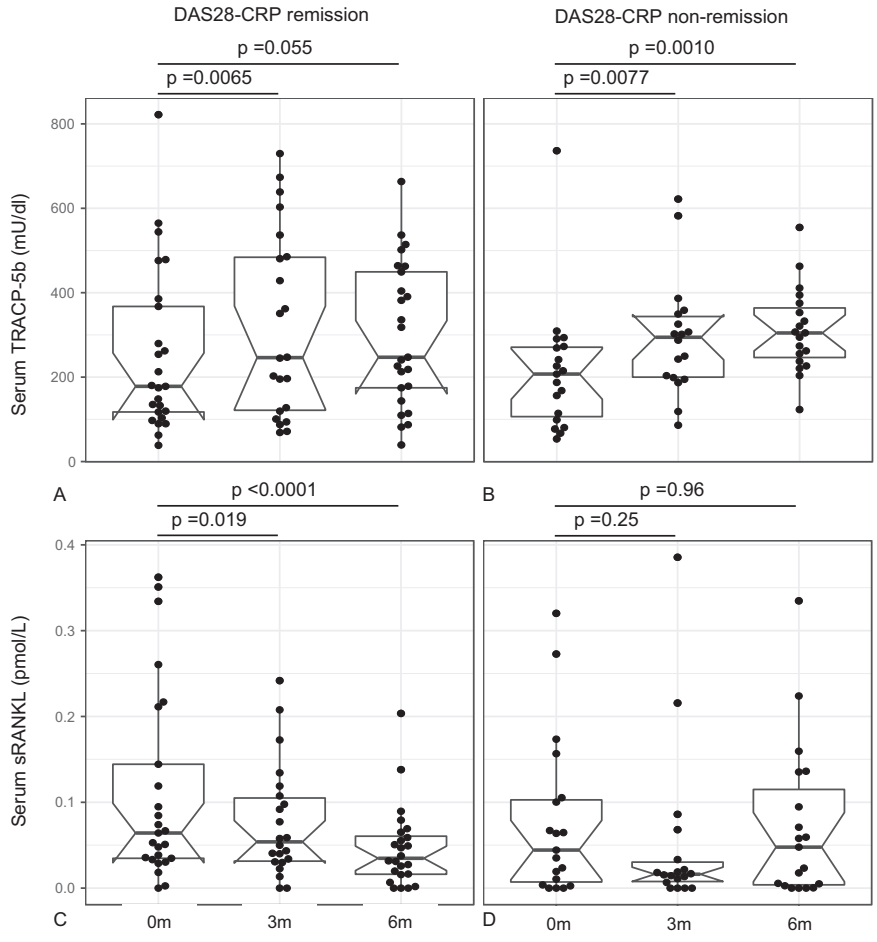

Figure 3. Changes in serum TRACP-5b and sRANKL in DAS28-CRP remission patients and non-remission patients over the 6-month abatacept treatment period. Serum TRACP-5b was significantly elevated at 3 months and tended to be elevated at 6 months compared to the baseline in both (A) DAS28-CRP remission and (B) non-remission patients. Serum RANKL was significantly decreased at 6 months compared to the baseline in the (C) DAS28-CRP remission patients but did not change significantly in the (D) DAS28-CRP non-remission patients. Wilcoxon signed-rank test. DAS28-CRP = disease activity score 28-C-reactive protein, sRANKL = soluble receptor activator of nuclear factor-κB ligand, TRACP-5b = isoform 5b of tartrate-resistant acid phosphate.

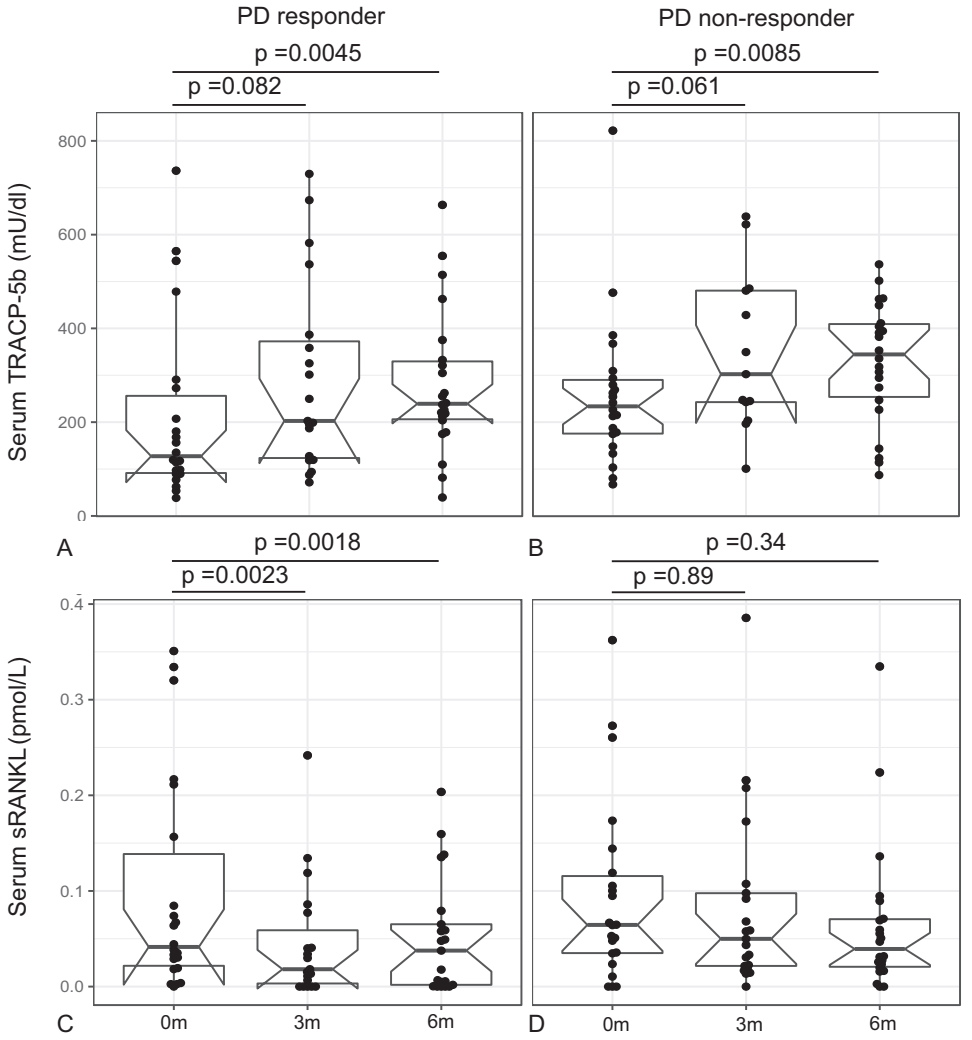

Figure 4. Changes in serum TRACP-5b and sRANKL in the PD responders and PD non-responders over the 6-month abatacept treatment period. Serum TRACP-5b was significantly elevated at 3 and 6 months compared to the baseline in both the PD responders (A) and PD non-responders (B). Serum RANKL was significantly decreased at 3 and 6 months compared to the baseline in the PD responders (C) but did not change significantly in the PD non-responders (D). Wilcoxon signed-rank test. PD = power Doppler, sRANKL = soluble receptor activator of nuclear factor-κB ligand, TRACP-5b = isoform 5b of tartrate-resistant acid phosphate.

More recent evidence suggests that autoantibodies such as RF and ACPA mediate osteoclast differentiation by binding to the citrullinated protein of Fc-receptors on osteoclast precursors.[3,4]

Abatacept blockades the costimulation that is essential for T-cell activation.[8] Abatacept may not only suppress osteoclastogenesis indirectly by inhibiting the production of pro-inflammatory cytokines via modulation of the T-cell costimulation but also directly by binding osteoclast precursors.[15,16] Abatacept may inhibit autoantibody production by inhibiting T cell-dependent B-cell differentiation to autoantibody-producing cells.[28] In a post hoc analysis of the AGREE study, treatment with abatacept in combination with methotrexate led to a decrease in autoantibody titers, resulting in some patients undergoing conversion to ACPA and RF seronegative status in patients with early RA.[28] Thus, abatacept may also suppress autoantibody-mediated osteoclastogenesis.

The RANK-RANKL system is the major driver of bone destruction in inflammatory arthritis.[29] TNFα (a cytokine that plays a central role in synovial inflammation) is indirectly responsible for inducing bone loss via the induction of osteoclast differentiation from monocyte lineage precursor cells exposed to RANKL.[29] TNFα stimulates RANKL expression by osteoblasts, T cells, B cells, and synovial fibroblasts.[29] Other pro-inflammatory cytokines such as IL-1, IL-6, and IL-17 also exert similar actions.[29] We observed that the serum sRANKL level decreased in the patients with a good clinical and ultrasonographic response to abatacept. We propose that the inhibition of T-cell activation and the subsequent improvement of synovitis by treatment with abatacept suppressed the production of RANKL.

Serum TRACP-5b is secreted by osteoclasts and its activity can be used as a clinically relevant bone resorption marker[30] because it reflects the osteoclast number.[30] Serum TRACP-5b declines during treatment with an anti-osteoclastic agent such as anti-RANKL and bisphosphonate.[31,32] TRACP-expressing osteoclast precursors are abundant in the invasive RA synovium and are ultimately responsible as differentiated osteoclasts for bone

erosions.[30,33] Few studies have investigated the effect of anti-rheumatic therapy on serum TRACP-5b in RA patients.[19] A recent report demonstrated that serum TRACP-5b paradoxically elevated despite an increase in bone mineral density during anti-TNFα therapy.[19]

Serum TRACP-5b had not been evaluated previously in RA patients under abatacept therapy. It was reported that CTLA4-Ig induces the enzyme indoleamine 2,3-dioxygenase in osteoclast precursors via CD80/86, which degrades tryptophan and promotes apoptosis in osteoclast precursors.[16] As a result, CTLA-4-Ig suppresses osteoblast differentiation and proliferation.[16] In the present study, unexpectedly, the patients' serum TRACP-5b also rose during abatacept therapy. The mechanisms underlying an increase in the TRACP-5b level are unknown.

CTLA-4-Ig was reported to promote Wnt-10b and bone formation in a mouse model.[34] A recent report suggested that abatacept might improve bone metabolism (increase bone mineral density) better than other bDMARDs in RA patients.[35] The increase in TRACP-5b regardless of therapeutic response under abatacept therapy may be explained by a compensatory mechanism against bone formation accompanied by an improvement of the systemic bone metabolism balance.

Among the available bDMARDs, abatacept is often used for elderly patients in Japan, based on its safety observed in clinical settings.[36,37] The median age of the patients enrolled in the present study was 72 years, and almost all of the females were expected to be postmenopausal. Although serum TRACP-5b does not vary with age in men, it is significantly higher in postmenopausal women compared to premenopausal women.[38] In the present study, serum TRACP-5b was significantly higher in the female patients compared to the male patients.

Some limitations of our study should be mentioned. The limited sample size (n = 44) does not allow for subanalyses of differences due to the patients' heterogeneous characteristics. However, our results are valuable as a part of a multicenter collaborative study that prospectively and closely evaluates disease activity using MSUS. Second, we could not evaluate structural changes in the patients' joints. In the cohort study, we evaluated the patients' X-ray images at baseline and 6, 12, 18, and 24 months of treatment. We will explore whether bone biomarkers are associated with radiographic progression in RA patients treated with abatacept. Third, we could not also evaluate systemic osteoporosis. However, the patients' use of oral corticosteroids and bisphosphonates was not associated with their serum TRACP-5b and sRANKL values at baseline or the changes in these values.

In conclusion, this is the first study to evaluate the effects of abatacept treatment on serum TRACP-5b and sRANKL levels in RA patients and to explore whether bone biomarkers are associated with the patients' therapeutic response using the KUDOS cohort. The reduction of serum sRANKL under abatacept therapy was associated with the improvement of the patients' clinical disease activity as well as their MSUS score. However, the elevation of serum TRACP-5b under abatacept therapy was not associated with the therapeutic response. Further studies are needed to elucidate the mechanisms of these effects of abatacept.

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