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Original Article

Clinical and ultrasonographic enthesitis assessment before and after anti-tumor necrosis factor treatment in patients with spondyloarthritis

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ABSTRACT

Objectives: This study aimed to clinically and ultrasonographically evaluate enthesitis in patients with spondyloarthritis (SpA) and to determine enthesitis response to anti-tumor necrosis factor (TNF) treatment.

Patients and methods: Thirty-one SpA patients (22 males, 9 females; mean age: 39.4±10.9 years; range, 22 to 60 years) who started anti-TNF treatment due to their high disease activity were included in the cross-sectional prospective study between May 2017 and January 2018. Ankylosing Spondylitis Disease Activity Score, Bath Ankylosing Spondylitis Disease Activity Index, Ankylosing Spondylitis Quality of Life Questionnaire, Bath Ankylosing Spondylitis Functional Index, and Bath Ankylosing Spondylitis Metrology Index were recorded. Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) and Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Score were utilized for clinical enthesitis evaluation. Patients were ultrasonographically evaluated in accordance with the Madrid Sonographic Enthesitis Index (MASEI) by a blinded sonographer. Patients were clinically and ultrasonographically assessed at baseline and in the third month after the treatment.

Results: In the initial evaluation, 24 (77.42%) of the patients had clinical enthesitis, and 30 (96.77%) of the patients had ultrasonographic enthesitis. After anti-TNF treatment, MASES, SPARCC, MASEI-structure, MASEI-thickness, MASEI-bursitis, MASEI-Doppler, MASEI-inflammatory, and MASEI-total scores significantly decreased ($p<0.05$). There was no significant change in MASEI-damage, MASEI-erosion, and MASEI-calcification scores following the therapy ($p>0.05$).

Conclusion: Anti-TNF treatment may improve clinical and ultrasonographic enthesitis, particularly inflammatory changes. Erosions and calcifications may not ameliorate after three months of anti-TNF treatment.

Keywords: Anti-TNF, enthesitis, MASEI, spondyloarthritis, ultrasonography.

The enthesis is the site where the tendon, ligament, fascia, or joint capsules adhere to the bone. There are two enthesis types: fibrous and fibrocartilaginous. Spondyloarthritis (SpA) is limited to fibrocartilaginous enthesis.[1] Enthesitis, which is the chronic inflammation of the entheseal region, is a characteristic feature of SpA. It has been shown that inflammation begins in the enthesis region in SpA.[2]

Insufficiency of clinical evaluation of enthesitis causes a delay in diagnosis and initiation of effective treatment. Imaging methods are believed to facilitate diagnosis. The entheseal changes in asymptomatic patients lead to the need to examine the enthesis sites by imaging methods.[3] However, entheseal bone changes can be seen late on the radiographs, and mechanical changes may accompany them.[4] Magnetic resonance imaging (MRI) has the ability to evaluate changes in the bone (bone marrow edema, erosion, calcification, and enthesophyte), as well as in the soft tissue (tendon structure change, increase in thickness, and bursitis). There are several disadvantages of MRI; it is expensive, difficult to access, and time-consuming, and each enthesitis region requires separate imaging.[4]

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In the last decade, the usage of ultrasonography (US) has become widespread in the evaluation of peripheral enthesitis. Ultrasonography is a preferred method of enthesitis assessment thanks to real-time and high-resolution images, the possibility of evaluating multiple regions, excellent security profile, ease to reach, and low cost. Several ultrasonographical scores have been developed to evaluate enthesitis. These scores have been used for early diagnosis and classification of SpA, and there are studies investigating whether US may be used for response to treatment.[5-9]

Ultrasonographically, enthesopathy is defined as tendon hypoechogenicity or increase in tendon thickness at its bony insertion; calcifications inside tendon; enthesophytes; bony erosions or cortex irregularities and accompanying Doppler signal at the enthesis based on the OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials).[10] Bursitis, hypoechogenicity, and increase in thickness in grayscale US and signal presence in Doppler US are considered as signs of inflammation; calcification, enthesophyte, erosion, and cortical bone irregularities are evaluated as structural damage findings.[11]

In the treatment of SpA, nonsteroidal anti-inflammatory drugs (NSAIDs) have been recommended as the first option. Following NSAID treatment, biological agents should be considered in patients with high or very high disease activity. The first-line drugs among biological agents are anti-tumor necrosis factor (TNF) drugs.[12] It has been known that anti-TNF drugs improve disease activity, quality of life, and acute phase reactants. In recent years, the efficacy of anti-TNF treatments on clinical and ultrasonographical enthesitis has been a matter of curiosity.[13,14] In this prospective study, we aimed to evaluate enthesitis and detect changes in the clinical and ultrasonographic evaluation before and after anti-TNF treatment.

PATIENTS AND METHODS

The cross-sectional prospective study was conducted at the rheumatology clinic of Istanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty, Physical Medicine and Rehabilitation Department between May 2017 and January 2018. Thirty-one SpA patients (22 males, 9 females; mean age: 39.4±10.9 years; range, 22 to 60 years) who were not previously treated with anti-TNF agents were enrolled in the study. All patients were diagnosed according to the Assessment of Spondyloarthritis International Society (ASAS) criteria. Anti-TNF treatment was initiated according to the 2016 ASAS/EULAR (European League Against Rheumatism) management recommendations for SpA and expert opinion.[15] Anti-TNFs (golimumab [n=6], adalimumab [n=5], certolizumab [n=8], etanercept [n=12]) were used in standard doses in all patients. Patients were told that they could use NSAIDs if needed. Having severe systemic disease, such as cardiovascular, respiratory, liver, and kidney disease, pregnancy and lactation, infection, malignancy, peripheral neuropathy, demyelinating diseases, concomitant rheumatologic disease, fluoroquinolone, retinoid, and fluoride use, and a history of local corticosteroid injection within the six weeks before evaluation or surgery at the examination sites were considered exclusion criteria.

Age, age of onset, diagnostic delay, disease duration, and body mass index (BMI) were recorded. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), human leukocyte antigen-B27 (HLA-B27), and grade of radiographic sacroiliitis results were recorded. Sacroiliac radiographs of the patients were evaluated according to Modified New York criteria by a researcher who has 20 years of experience blinded to the clinical evaluation. Patients were described as having ankylosing spondylitis (AS) or nonradiographic axial SpA (nr-axSpA) based on radiographic sacroiliitis.

To evaluate disease activity, Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP, ASDAS-ESR, and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) were applied. In BASDAI, pain, tenderness, and swelling in the axial and peripheral joints, as well as the duration and severity of morning stiffness in the last week, were questioned. In ASDAS, there are four questions related to spinal pain, joint pain/swelling, duration of morning stiffness, and patient global assessment. Afterward, by adding the CRP or ESR value, ASDAS-CRP or ASDAS-ESR were calculated through the calculator on the website of the ASAS.

Bath Ankylosing Spondylitis Functional Index (BASFI), developed to show the functional condition of the patient, is an index that evaluates the answers to 10 questions to determine functions in daily life. The questions are answered by placing a mark on a 10-cm numerical scale. The average of the answers to the questions gives the BASFI score. To evaluate spinal mobility, a total Bath Ankylosing Spondylitis Metrology Index (BASMI) score ranging from 0 to 10 was calculated by points (0=mild, 1=moderate,

2=severe) given to lateral lumbar flexion distance, modified Schober result, cervical rotation angle, maximal intermalleolar distance, and tragus wall distance. Ankylosing Spondylitis Quality of Life (ASQoL) Questionnaire assesses the quality of life with 18 questions for the last week. The questions are answered yes or no, and the score is obtained by summing up the questions answered yes. All scales were used in the native language of the patients (Turkish). Turkish validity and reliability studies of all scales are available.[16-18] The Spondyloarthritis Research Consortium of Canada (SPARCC) score and the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) were used to clinically evaluate enthesitis sites. The MASES is calculated by palpating 13 enthesis regions: right and left first and seventh costochondral joint, spina iliaca posterior superior, spina iliaca anterior superior, iliac crest, Achilles tendon's proximal insertion, and fifth lumbar spinous process. The SPARCC score is only based on the bilateral evaluation of peripheral joints: the supraspinatus tendon insertion site, medial epicondyle, lateral epicondyle, greater trochanter, quadriceps tendon, patellar tendon, Achilles tendon, and plantar fascia. Clinical enthesitis scores were evaluated with 4 kg/cm² pressure by Baseline® algometer (Jamar Hand Evaluation Kit, Sammons Preston Inc., Bolingbrook, IL, USA). Evaluations were performed just before anti-TNF treatment and in the third month after treatment. Patients were asked to apply to the hospital in case of increased pain or morning stiffness or swelling in their joints despite drug treatment.

On the same day as the clinical evaluation, all patients underwent ultrasonographic enthesitis evaluation by a researcher who had 10 years of experience in US blinded to clinical evaluation. Patients were evaluated in a dark room after resting for 30 min. Patients were asked not to give information about their global health situation to the researcher who performed the ultrasonographic evaluation. Esaote MyLab × 70 brand US device (Esaote S.p.A., Genoa, Italy) with a 4-13 MHz linear probe was used in the evaluation. Power Doppler (PD) settings were adjusted to a pulse repetition frequency of 750 Hz and a wall filter of 3. The gain adjustment was achieved by removing background signals.

Ultrasonographic evaluation of enthesitis was performed with the assessment of the bilateral six entheseal regions. Five of them (distal insertion of the quadriceps tendon, distal and proximal insertions of the patellar tendon, Achilles tendon and plantar aponeuroses at their insertion at the calcaneus) were located at the lower limb, and one of them was located at the upper limb (distal triceps brachii tendon at its insertion at the olecranon). Each tendon was evaluated in two planes (longitudinal and transverse planes) and the assessment was performed in standardized patient positions. All grayscale and Doppler findings that have been seen at the entheseal regions in accordance with the Madrid Sonographic Enthesitis Index (MASEI) were recorded. The MASEI score evaluates five elemental lesions and PD findings: structure (0 or 1), thickness (0 or 1), erosions (0 or 3), calcifications (0, 1, 2, or 3), bursitis (only at the distal patellar tendon and Achilles tendon; 0 or 1), PD signal (0 or 3). Calcifications were scored as 0 if it was absent, 1 if it was <5 mm, 2 if it was 5-10 mm, or 3 if it was >10 mm calcifications. Bursitis is evaluated anatomically in four enthesis sites (bilateral distal patellar and distal Achilles tendon).[5] The total score ranges from 0 to 136. The MASEI-inflammatory score was recorded as entheseal thickness, structural changes, bursitis, and PD findings, and the MASEI-damage score was recorded as calcifications and erosions.[19]

Statistical analysis

Data were analyzed by IBM SPSS version 29.0 software (IBM Corp., Armonk, NY, USA). Normality distribution was assessed by histogram graphics and the Kolmogorov-Smirnov test. Descriptive analyses were presented as mean ± standard deviation or median (min-max). The Wilcoxon test and the paired samples t-test were used for the comparison of repeated measures. Nonrepeated measures were analyzed by the Mann-Whitney U test. The Spearman correlation analysis was used for the analysis of the measured data with each other. Wilcoxon test was utilized to compare pre-treatment and post-treatment results and the effect size was calculated based on the statistical test used for comparisons. A p-value <0.05 was considered statistically significant.

RESULTS

Twenty-eight of the patients had AS, and three had nr-axSpA. Sixteen HLA-B27-positive patients were identified, and 15 patients were HLA-B27 negative. The mean BMI was 26.13±4.36 kg/cm². The median age of onset, mean disease duration, and median diagnostic delay was 26 (14-47), 11.42±7.58, and 5 (1-27) years, respectively. In the initial evaluation, 24 (77.42%) of the patients had clinical enthesitis, and 30 (96.77%) of the patients had ultrasonographical enthesitis.

TABLE 1
Clinical values at baseline and three months after treatment

	Baseline		3rd month			
	Median	Min-Max	Median	Min-Max	Effect size	*p*
CRP (mg/L)	9.91	0.39-109.00	1.93	0.08-26.30	-0.594	<0.001
ESR	18	2-49	4	1-20	-0.581	<0.001
BASDAI	6.00	1.00-8.40	1.80	0.20-6.80	-0.617	<0.001
BASFI	4.60	0.10-8.20	1.90	0-6.20	-0.613	<0.001
PGA	7	3-10	3	0-9	-0.608	<0.001
ASDAS-CRP	3.90	1.30-5.70	1.50	0.80-3.50	-0.617	<0.001
ASDAS-ESR	3.70	1.10-5.30	1.20	0.40-3.00	-0.617	<0.001
ASQoL	15	3-18	3	0-18	-0.598	<0.001
MASES	5	0-13	0	0-12	-0.422	0.001
SPARCC	2	0-14	0	0-15	-0.387	0.002

CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; PGA: Patient global assessment; ASDAS: Ankylosing Spondylitis Disease Activity Score; ASQoL: Ankylosing Spondylitis Quality of Life Questionnaire; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; SPARCC: Spondyloarthritis Research Consortium of Canada; Pre- and posttreatment comparisons were performed with the Wilcoxon test.

The clinical values at baseline and after three months of treatment are presented in Table 1. A statistically significant decrease was observed in all clinical values in the third month ($p<0.05$). In addition, there was no modification or discontinuation of anti-TNF due to ineffectiveness or intolerance in any patient during the treatment process.

Madrid Sonographic Enthesitis Index values at baseline and after three months of treatment are shown in Table 2. Madrid Sonographic Enthesitis Index-total, MASEI-Doppler, and MASEI-inflammatory, the sonographic score of structure, thickness, and bursitis were significantly decreased in the third month ($p<0.05$). There was no significant change in the sonographic score of erosion and calcification and MASEI-damage ($p>0.05$).

No difference was found between sexes for all ultrasonographic values ($p>0.05$; data not shown). No difference was found between AS and nr-axSpA for all ultrasonographic enthesitis scores ($p>0.05$; data not shown). When MASEI baseline values were compared according to HLA-B27 results, MASEI-damage, -bursitis, and -erosion scores were higher in HLA-B27-positive patients than negative ones ($p<0.05$; data not shown).

TABLE 2
Ultrasonographic enthesitis values at baseline and three months after treatment

	Baseline			3rd month				
	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	Effect size	*p*
MASEI-total		30	0-70		22	3-64	-0.527	**<0.001**
MASEI-inflammatory	22.52±11.22			13.81±8.21			0.811*	**<0.001***
MASEI-damage		9	0-38		9	0-27	-0.167	0.187
MASEI-Doppler		15	0-30		6	0-18	-0.439	**0.001**
MASEI-structure		4	0-10		3	0-9	-0.345	**0.006**
MASEI-thickness		4	0-9		3	0-8	-0.425	**0.001**
MASEI-bursitis		1	0-3		0	0-2	-0.362	**0.004**
MASEI-erosion		3	0-24		3	0-15	-0.248	0.051
MASEI-calcification		5	0-21		6	0-21	-0.026	0.832

SD: Standard deviation; MASEI: Madrid Sonographic Enthesitis Index; Pre- and posttreatment comparisons were performed with the Wilcoxon test. * Pre- and posttreatment comparison was performed with Paired Sample t-test.

TABLE 3
Correlations among baseline MASEI scores and demographic, clinical, and radiographic values

	Age	BMI	Age of onset	Duration of diagnostic delay	Disease duration	Sacroiliitis grade	BASMI 2-step
MASEI-total							
r	0.420	0.096	0.199	0.343	0.436	0.296	0.361
p	**0.019**	0.607	0.282	0.059	**0.014**	0.106	**0.046**
MASEI-inflammatory							
r	0.399	0.205	0.219	0.293	0.362	0.187	0.292
p	**0.026**	0.269	0.236	0.109	**0.045**	0.313	0.111
MASEI-damage							
r	0.326	-0.082	0.212	0.183	0.337	0.373	0.363
p	0.073	0.662	0.252	0.325	0.064	**0.039**	**0.045**

MASEI: Madrid Sonographic Enthesitis Index; The r values show the Spearman correlation coefficient. Sacroiliitis grade has been evaluated as ordinal data.

Correlations among baseline MASEI scores and demographic, clinical, and radiographic values are shown in Table 3. There was no correlation between MASEI-total, MASEI-inflammatory, MASEI-damage, and clinical values (CRP, ESR, BASDAI, BASFI, patient global assessment, ASDAS-CRP, ASDAS-ESR, ASQoL, MASES, and SPARCC) at both baseline and three months (data not shown).

DISCUSSION

Mechanical stress, activation of the natural immune system, proliferation of mesenchymal tissue, and remodeling, guided by molecules such as prostaglandin E2, interleukin (IL)-17, IL-23, TNF, IL-22, and bone morphogenic proteins, take place at the pathogenesis of enthesitis. This can explain the response of enthesitis to NSAIDs and biological drugs. It has been shown that anti-TNFs provide a weaker control over the new bone formation phase than the inflammatory-erosive phase.[20] In support of these, we found that findings of inflammation in US, including MASEI-structure, MASEI-thickness, MASEI-bursitis, MASEI-Doppler, and MASEI-inflammatory, decreased but findings of chronic damage, including MASEI-erosion, MASEI-calcification, and MASEI-damage, did not change after three months of anti-TNF therapy. In addition, the total MASEI score and clinical enthesitis score (MASES and SPARCC) decreased significantly after treatment.

Our study showed that anti-TNF drugs significantly reduced ultrasonographic findings after three months of anti-TNF treatment. Aydin et al.[21] have also shown significant decreases in grayscale and total US scores at Achilles enthesis region after two months of anti-TNF treatment. Wang et al.[13] evaluated the treatment response of enthesis with 100 AS patients. Seventy-five of the patients were given anti-TNF treatment, and 25 of them had disease-modifying anti-rheumatic drugs (DMARDs). At the end of three-month treatment, significant improvements in the US scores and MASES scores in the anti-TNF group were found. In addition, there were no differences between the three different anti-TNF types in terms of US scores. Naredo et al.[14] evaluated 14 peripheric entheseal sites of 197 SpA patients at baseline and at the end of six months of anti-TNF treatment. After six months of treatment, total US scores significantly decreased. Ruta et al.[22] evaluated 10 enthesis sites of each 34 SpA patients who started DMARDs or anti-TNF treatment or changed the type of treatment. Ten out of 34 patients started treatment with a DMARD, nine of them switched to another DMARD, seven patients added a second DMARD, and the rest of the patients initiated anti-TNF inhibitors. Total US scores decreased during the three-month follow-up, and no statistical difference in score change between treatment groups was found in the study. Although inflammatory changes were susceptible to change, erosions and calcifications did not improve during treatment.[22] These results in the study are consistent with our results. The decrease in ultrasonographic enthesitis scores after treatment with anti-TNFs indicates that these drugs are effective on inflammatory changes at the entheseal sites.

Anti-TNF drugs may not be effective on new bone formation, although it is known that these drugs are

effective on inflammatory changes. Naredo et al.[14] showed that structural changes (hypoechogenicity and increase in thickness), PD, and bursitis significantly decreased after six months of treatment, but a statistically insignificant increase in calcific deposits was observed. Ruta et al.[22] found a decrease in soft tissue abnormalities (thickening, hypoechogenicity, and bursitis) and PD scores. However, there were no significant improvements in bone changes (calcification, erosion, and enthesophytes). In our study, we found no change in MASEI-damage and erosion scores and a statistically insignificant increase in calcification scores. The three-month treatment period may not be sufficient to state that anti-TNF drugs did not change the findings about chronic damage. Our study found that even in a short time, these drugs are effective on the findings of inflammatory changes but not on the findings of chronic damage. Long-term studies may be needed to see the effects, if any, on chronic damage.

In previous studies, no difference was found according to disease subgroup (AS, SpA, psoriatic arthritis, undifferentiated SpA, enteropathic SpA, and reactive arthritis) and involvement pattern (axial, peripheral, and mixed).[9,23,24] In our study, there was no difference between MASEI scores of AS and nr-axSpA patients. However, the small number of patients (n=3) in the nr-axSpA group is an important limitation in making this assessment.

In studies evaluating the Glasgow Ultrasound Enthesitis Scoring System (GUESS) and MASEI, no correlation was found between HLA-B27 and US scores.[24,25] Patients positive for HLA-B27 had higher Doppler scores in Achilles enthesitis.[26] In our study, pretreatment MASEI-damage, MASEI-bursitis, and MASEI-erosion scores were found higher in HLA-B27-positive patients. This can be partially clarified by the fact that HLA-B27 is a triggering factor in disease pathogenesis.[27] Human leukocyte antigen-B27 may have an effect on enthesitis progression as well as be a triggering factor in enthesitis pathogenesis, hence the current results may be notable. However, the small number of patients and the absence of randomization are the limitations of our study in evaluating this difference.

In the study of Ezzat et al.,[25] a relationship was found between the GUESS score and disease duration. Two other studies have found a relationship between US scores and age.[28,29] Two separate studies showed no relation between age, disease duration, and ultrasonographic enthesitis.[30,31] Our study found a positive correlation between MASEI-total, MASEI-inflammatory scores, age, and disease duration. Increasing age and duration of the disease can be expected to result in ultrasonographic findings of damage, such as erosion and calcification, due to increased exposure to the disease. Furthermore, an increase in inflammatory findings reveals that the inflammatory process continues despite the advancing age and disease duration.

In a study, a relationship was found between radiographic sacroiliitis and MASEI-total and MASEI-damage.[32] In our study, there was a positive correlation between the radiographic sacroiliitis and MASEI-damage, as well as between BASMI and MASEI-total and MASEI-damage. Radiographic sacroiliitis shows signs of damage, such as erosion, sclerosis, and joint narrowing, and also erosion is a sign of damage that can be evaluated by US. The correlation between radiographic sacroiliitis and MASEI-total and MASEI-damage may demonstrate that ultrasonographic enthesitis evaluation may be a radiation-free way to estimate radiographic sacroiliitis. The correlation between spinal mobility (BASMI) and both MASEI-total and MASEI-damage scores may indicate that spinal mobility may be affected not only by damage but also by acute inflammation.

In many studies analyzing ultrasonographic enthesitis scores, acute phase reactants, and clinical scores, such as BASDAI, BASFI, and MASES, no correlation was found between them.[8,14,33] In the follow-up study of Wang et al.,[13] a relationship was found between the decrease in US scores and the decrease in MASES and BASDAI at three months after anti-TNF treatment. In the follow-up study of Aydın et al.,[21] a correlation was found between the decrease in US scores and the decrease in acute phase reactants but not with BASDAI after two months of anti-TNF treatment. In a previous study, a significant correlation was found between US scores and CRP, ESR, and very high disease activity (ASDAS >3.5).[29] In our study, no correlation was found between ultrasonographic scores and clinical values (CRP, ESR, BASDAI, BASFI, patient global assessment, ASDAS-CRP, ASDAS-ESR, ASQoL, MASES, and SPARCC) at baseline and after the three-month treatment. Spondyloarthritis is a group of diseases that are characterized by involvements in the axial skeleton, peripheral joints, and extra-articular systems, including enthesitis. The ultrasonographic evaluation of only entheseal sites may be insufficient in the assessment of the whole disease. Therefore, ultrasonographic enthesitis scores may not correlate with clinical scores.

This study has some limitations. The duration of follow-up was relatively short (three months) to assess the influences of anti-TNFs on chronic changes. Erosion and Doppler scores in MASEI were graded as no-yes (0-3) regardless of their magnitude and severity. Ultrasonography evaluation of the plantar fascia was suboptimal in particular patients who had thick footpad skin. Another limitation of our study is the lack of a control group or a placebo treatment group. The low sample size is also a limitation of our study, and the effect size was calculated based on the statistical analysis previously used in another study.

In conclusion, although ultrasonographic scores were correlated with the radiographic assessment of sacroiliitis and spinal mobility, no correlation was found with other clinical scores. It can be said that the ultrasonographic evaluation of only entheseal sites may be insufficient in the assessment of the whole disease. The study showed that anti-TNF therapy improves clinical and ultrasonographic enthesitis. Anti-TNF drugs are effective on inflammatory entheseal changes but not effective on new bone formation, such as calcification, enthesophytes, and erosion. Long-term follow-up studies are required to assess the influences of anti-TNF on bone changes.

Ethics Committee Approval: The study protocol was approved by the Cerrahpaşa Medical Faculty Clinical Research Ethics Committee (date: 18.04.2017, no: 89403766-604.01.02-147611). The study recorded to clinicaltrials.gov (NCT04953871). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Conception and design of the study: I.A., D.P., K.A., H.S.; Acquisition of data, analysis, interpretation of data: I.A., D.P., K.A.; Drafting the article: G.E., D.P.; Final approval of the version to be submitted: I.A., D.P., K.A., G.E., H.S.

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