Bakırköy Tıp Dergisi 2018;14:155-64
DOI: 10.5350/BTDMJB.20161219035358

Clinical and Ultrasonographic Findings in Patients with Early Rheumatoid Arthritis: An 18-Month Follow-Up Cohort Study

Halil Harman[1], Ibrahim Tekeoglu[2]

[1]Bolu Abant Izzet Baysal University, Faculty of Medicine, Deparment of Rheumatology, Bolu, Turkey
[2]Sakarya University, Faculty of Medicine, Department of Pysical Medicine and Rehabilitation, Division of Rheumatology, Adapazari, Turkey

ABSTRACT

Objectives: The aim of our study is to perform the clinical, functional and ultrasonographic (US) follow-up of the early and very early RA patient who are naive among the disease modifying antirheumatic drugs (DMARDs) for 18 months and evaluate the relationship of these parameters with the radiological final state.

Material and Methods: This prospective study included 48 early RA (15 very early RA) patients. Gray scale US (GSUS), Power Doppler US (PDUS) examinations, Disease Activity Score 28 (DAS 28), Health Assessment Questionnaire (HAQ), Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP) were evaluated repeatedly at each visit (baseline, 1, 3, 6, 9, 12, 18 months). Hand, wrist, elbow, shoulder, knee joints and hand, wrist tendon structures were evaluated via GSUS and PDUS.

Results: During the follow-up period of the patients, the ESR and CRP levels started to decrease statistically significantly from the 1st month (p=0.006). Statistically significant improvement in HAQ, DAS 28 scores, total GSUS synovitis scores, total PDUS tenosynovitis scores, total GSUS tenosynovitis scores, total PDUS tenosynovitis scores started at 3th months (p=0.007, p=0.003, p=0.001, p=0.009, p=0.002, p=0.004 respectively). In follow-up of very early RA patients; laboratory, US findings were similar to early RA patients. In multiple linear regression analysis, only the GSUS and PDUS scores at 0 and 1, could have an effect on the radiographic progression scores (ß=0.417, p=0011, ß=0.549, p=0.028, ß=0.476, p=0015; ß=0.358, p=0.017, respectively).

Conclusions: Radiographic damage progresses at the similar severity in early and very early RA patients. The most important factor affecting the radiographic damage progression is the severity of US synovitis at the baseline and in the 1st month, independently of the disease activity.

Keywords: Inflammation, rheumatoid arthritis, synovitis, ultrasonography

ÖZ

Erken romatoid artrit hastalarının klinik ve ultrasonografik bulguları: 18 aylık takip çalışması

Amaç: Çalışmamızın amacı erken ve çok erken tanı konulmuş hastalık modifiye edici ajanlardan naif olan romatoid artrit (RA) hasta grubunun, 18 ay boyunca klinik, fonksiyonel, ultrasonografi (US) takibini yapmak ve bu parametrelerin radyolojik son durum ile ilişkilerini değerlendirmektir.

Gereç ve Yöntemler: Çalışmamıza 48 erken RA (15'i çok erken RA) tanılı hasta dahil edildi. Gri skala US (GSUS) ve Power Doppler US (PDUS) muayenesi, 28 eklem hastalık aktivite skoru (DAS28), sağlık değerlendirme anketi (HAQ), eritrosit sedimantasyon hızı (ESH), C reaktif protein (CRP) düzeyleri başlangıçta, 1, 3, 6, 9, 12, 18 aylarda tüm hastalarda yapıldı. Elbilek, metokarpofalangeal, proksimal interfalangeal, dirsek, omuz ve diz eklemleri ve elbilek çevresi tendon yapıları GSUS ve PDUS ile değerlendirildi.

Bulgular: Hastaların takibinde ESH, CRP seviyelerinde 1. aydan itibaren istatistiksel olarak anlamlı bir şekilde azalma başladı (p=0.006). HAQ, DAS 28 skorları, toplam GSUS sinovit skorları, toplam PDUS tenosinovit skorları, toplam GSUS tenosinovit skorları, toplam PDUS tenosinovit skorlarında istatistiksel olarak anlamlı düzelme ise ancak 3. ayda başlamaktadır (sırasıyla; p=0.007, p=0.003, p=0.001, p=0.009, p=0.002, p=0.004). Çok erken RA hastalarının izleminde laboratuar, US bulguları erken RA hastalarına benzer bulundu. Çoklu lineer regresyon analizinde, sadece 0 ve 1. Aydaki toplam GSUS ve PDUS skorları radyografik ilerleme skorları üzerine etkisini devam ettirebilmiştir (sırasıyla, ß=0.417, p=0011; ß=0.549, p=0.028; ß=0.476, p=0015; ß=0.358, p=0.017).

Sonuç: Radyografik hasarda ilerleme erken ve çok erken RA hastalarında benzer şiddette olmaktadır. Radyografik hasarın ilerlemesini etkileyen en önemli faktör, hastalık aktivitesinden bağımsız olarak, başlangıçtaki ve 1. aydaki US sinovitinin şiddetidir.

Anahtar kelimeler: İnflamasyon, romatoid artrit, sinovit, ultrasonografi

Received/Geliş tarihi: 19.12.2016 **Accepted/Kabul tarihi:** 01.05.2017

Address for Correspondence/Yazışma Adresi: Halil Harman, Bolu Abant İzzet Baysal University Faculty of Medicine, Deparment of Rheumatology, Bolu, Turkey
Phone/Telefon: +90-374-253-5363 **E-mail/E-posta:** drhharman@yahoo.com

Citation/Atıf: Harman H, Tekeoglu I. Clinical and ultrasonographic findings in patients with early rheumatoid arthritis: an 18-month follow-up cohort study. Bakırköy Tıp Dergisi 2018;14:155-64. https://doi.org/10.5350/BTDMJB.20161219035358

INTRODUCTION

The evaluation of the disease activity in rheumatoid arthritis (RA) is quite important in determining the treatment strategy, prognosis assay, and final state prediction. Clinical examination, laboratory, and sensitive radiological methods are used in determining the disease activity. Nowadays, the treatment goals in RA are low disease activity and clinical remission. The advancement in the imaging technology brought forward evaluating with sensitive radiological methods such as ultrasonography (US) and magnetic resonance (MR). Hence, it has been shown radiologically that erosions develop in the following years even in the patients who are clinically in remission nowadays (1,2). These observations change the treatment goals in RA to the radiological remission along with the clinical remission.

US is a method which is quite practical and repeatable to be applied clinically in RA. Grey-scale US (GSUS) detects synovitis and differently from GSUS, Power Doppler (PD) signal is a quite effective method of distinguishing the early and active disease. It was shown that PDUS distinguishes the acute and chronic disease more precisely in synovium (3,4). In cross-sectional studies, subclinical synovitis in US in the patients who were clinically in remission was elaborated much more (5,6). These are some studies in the literature in which joint US was used for the long-term follow-up in early RA patients (7,8). While the disease follow-up periods were short and the US follow-up intervals were long in the studies, the disease groups also consisted of rather established RA patients. Thus, evaluating the US response to the treatment does not seem sound.

The purpose of our study is to perform the clinical, functional and US follow-up of the early and very early-diagnosed RA patient group which is naive among the disease modifying antirheumatic drugs (DMARDs) for 18 months and evaluate the relationship of these parameters with the radiological final state.

MATERIAL AND METHODS

This prospective study included 48 early RA (15 very early RA) patients according to the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) RA 2010 classification criteria between January 2013 and August 2015. Patients were recruited from the rheumatology outpatient clinics at the same center. All patients evaluated by ACR/EULAR 2010 RA classification criteria feature; (a) joint involvement, (b) rheumatoid factor (RF) and anti-citrullinated protein antibody (anti-cyclic citrullinated peptide (CCP)) levels, (c) acute phase reactant levels, and (d) duration of symptoms, consecutively included in the study (9). The early RA term definition based on the onset of RA symptoms. The threshold of symptom duration is 6 months for early RA and 3rd months for very early RA. The study protocol was approved by our local ethics committee, and informed consent was obtained from all patients. Patients who have any kind of cancer, or hematological abnormality, those who were pregnant or in the post-partum period (6 months), and those who had previously taken low-dose corticosteroids or synthetic DMARDs were excluded.

Gender, age, DMARD type, body mass index (BMI), the number of tender and swollen joints, and the patient's assessment of disease activity (0–10 scale) were recorded. Initially, patients received synthetic DMARDs or corticosteroids (<10 mg/day). Disease activity was assessed by calculating the Disease Activity Score (DAS 28).

DAS 28 remission criteria, involving C reactive protein (CRP), swollen and tender joint counts and patient's global health assessment were used to determine whether the disease in remission. A score of DAS28 between 2.6-3.2 indicates low disease activity, 3.2-5.1 moderate and > 5.1 high disease activity (10). If the clinical response was inadequate (improvement of the 28-joint disease activity score [DAS28] <0.6) at 3rd months, another synthetic or biologic DMARD was added to the therapy.

To evaluate quality of life, the Health Assessment Questionnaire (HAQ) disability index (consisting of 20 questions) was applied (11).

Laboratory assessment included measurement of erythrocyte sedimentation rate (ESR), level of C-reactive protein (CRP), rheumatoid factor (RF), and anti-cyclic citrullinated peptide (anti-CCP) antibody.

The ESR was measured immediately after blood collection by using a Greiner SRS 20/II instrument (Vacuette Greiner, Austria). RF and CRP levels were measured by nephelometric methods, using an IMAGE 800 analyzer (Beckman Coulter Inc., USA). Anti-CCP antibodies were

measured via enzyme-linked immunosorbent assay (ELISA), and a result was considered positive if the level was above a cutoff of five arbitrary units (as suggested by Abbott ARCHITECT i1000SR).

Ultrasonographic assessment Hand, wrist, elbow, shoulder, knee joints were evaluated via GSUS and PDUS. Fourteen joint regions (thus, 28 in both extremities) were evaluated. These included the first through to the fifth metacarpophalangeal (MCP), first through to the fifth proximal interphalangeal (PIP), the radiocarpal, ulnocarpal, and intercarpal compartments of the wrist; the humeroradial and humeroulnar compartments of the elbow; the posterior joint region of shoulder, the suprapatellar and medial and lateral parapatellar recesses of the knee joints.

The MCP and PIP joints were scanned at palmar/plantar and dorsal sites; wrist joints were scanned at dorsal sites. All of the patients were examined by a trained ultrasonographer with 4 years of experience. US examinations were repeated at each visit (baseline, 1, 3, 6, 9, 12, 18 months). The settings for the GSUS and PDUS were the same for all patients. US examinations were completed in 30 min, and all of the images were stored. A US platform featuring a 5–13-MHz linear array transducer was employed to this end (LOGIQ P5; General Electric, New York, NY).

Synovitis was classified on gray-scale images using a semiquantitative scoring method. We considered only synovial proliferation as a sign of synovitis (not synovial effusion). The approach features use of a 0–3 scale, in which 0 corresponds to no synovitis, 1 to mild synovitis, 2 to moderate synovitis, and 3 to severe synovitis. Grade 1 synovitis may occur in normal populations, and for this reason, patients of grades 2 and 3 (only) were considered to have abnormal synovitis (12) Semiquantitative scoring method was evaluated for each of 28 joints, and total synovial scores were calculated by summing grade 2 and 3 synovitis. The range of total GSUS synovitis score was 0–84. Also, GSUS synovitis score was calculated for each joint.

The maximal area of augmentation on PDUS was recorded using a previously described semiquantitative technique featuring use of a 0–3 scale, in which 0 corresponds to normal/ minimal vascularity, 1 to mild hyperemia (single vessel signal), 2 to moderate hyperemia (confluent vessels), and 3 to marked hyperemia (vessel signals in >50 % of the joint area) (13).

Semiquantitative scoring method was evaluated for each of 28 joints, and total synovial scores were calculated by summing each semiquantitative grade. The range of total PDUS synovitis score was 0–84. Figure 1 shows PDUS and GSUS synovitis at wrist joints.

Tenosynovitis was recorded in the extensor digitorum carpi, the extensor carpi ulnaris, in each of the five flexor digitorum tendons of the hand, (thus a total of 14 tendons in both extremities). A four-grade semiquantitative scoring system (i.e., grade 0, normal; grade 1, minimal; grade 2, moderate; grade 3, severe) was used to score tenosynovitis revealed on GSUS. Semiquantitative scoring method was evaluated for each of 14 tendon regions, and total tenosynovitis scores were calculated by summing each semiquantitative grade. The range of total GSUS tenosynovitis score was 0–42. Figure 2 shows PDUS tenosynovitis at finger joints with longitudinal and transverse images.

A four-grade semiquantitative scoring system (i.e., grade 0, no Doppler signal; grade 1, minimal signal; grade 2,

Figure 1: PDUS and GSUS synovitis at wrist joints

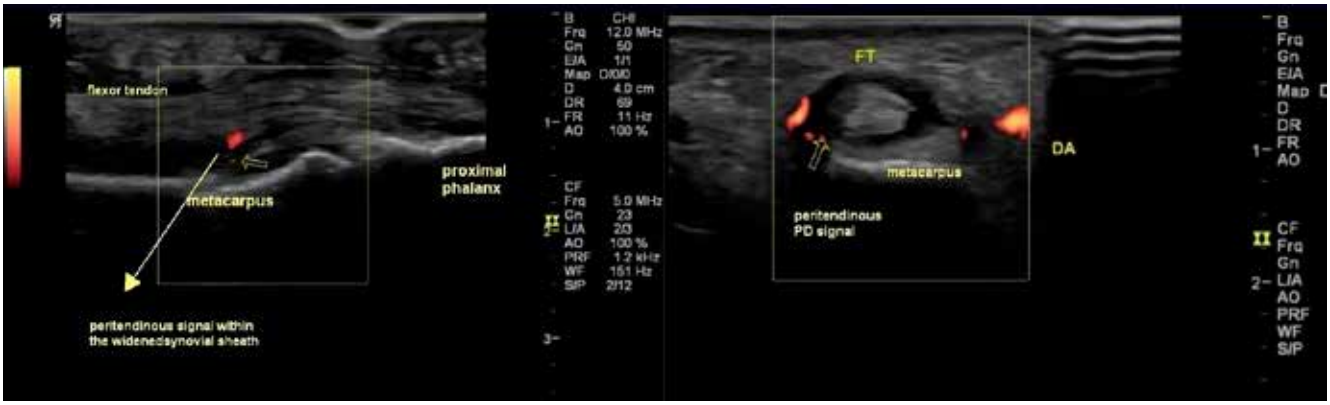

Figure 2: tenosynovitis at finger joints with longitudinal and transverse images

moderate signal; grade 3, severe signal) was used to score pathological peritendinous PD signals within the synovial sheath (14). Semiquantitative scoring method was evaluated for each of 14 tendon regions, and total PD tenosynovitis scores were calculated by summing each semiquantitative grade. The range of total PDUS tenosynovitis score was 0–42.

Radiographic Assessment

Posteroanterior radiographs of the patients' wrists were obtained at baseline and at the 18. month follow-up. The radiographs were read by an independent radiologist, who was blinded regarding the clinical, laboratory, and PDUS findings. Radiologic damage was assessed according to the van der Heijde modified Sharp method for only hands (15). This method measures erosions and joint space narrowing in 32 different joints. Maximal total erosion score of the hands is thus 160. Maximal total narrowing score in the hands is 120. For only hands, the van der Heijde modified Sharp score is 280.

Radiographic progression scores were defined as the difference between modified Sharp score at baseline and at 18th. months.

Statistical Analysis

The SPSS software (IBM SPSS statistics version 20.0) was used in statistical analysis. Quantitative variables (clinical, laboratory, and US parameters) are given as means with standard deviations (SD) and ranges. Upon univariate analysis, the Mann-Whitney U test was used to compare continuous variables and the chi-square test to compare categorical variables. Spearman's correlation coefficients between radiographic and US findings were calculated. To determine independent predictors of radiographic progression scores independence of variables was determined by entering any significant variables from the univariate analysis into multiple linear regression analysis. AP value less than 0.05 was considered to indicate statistical significance.

RESULTS

Baseline Clinical and Laboratory Findings

We included 48 early RA patients aged 18–68 years into the study. Among the 48 included patients, all had an 18th month visit, but 2 patients had no visit at 12th months. The principal demographic and clinical features were summarized in Table 1. In total, 68% were RF-positive and 75% were anti-CCP positive. The average ESR and CRP values for all of the patients were 44.04 mm/h and 24.84 mg/dL at baseline, respectively. (ESR 0–20 mm/h, CRP 0–5 mg/dL, normal range).

Of a total of 1344 examined joint regions, 22.3% (n=300) of all examined joints had tender joints and 15.9% (n=215) had swollen joints. On clinical examination, tenderness was predominantly observed in the wrist, MCP2, and MCP3 joints (30.2, 21.3, and 13.5%, respectively); swelling was predominantly observed in the wrist, MCP2, and MCP3 joints (26.5, 16.5, and 13.5%, respectively).

At inclusion, all patients were administered methotrexate (10–15 mg/week) and low-dose prednisone or methylprednisolone. After the 18-month follow-up, 23

Table 1. Clinical characteristics of 48 study patients with rheumatoid arthritis

	Early RA (n=48)	Very early RA (n=15)	p values
Age, mean±SD (years)	55.56±15.54	57.00±20.45	0.063
Sex (% women)	68.7	60	0.383
BMI, mean±SD (kg/cm^2)	27.39±3.11	25.17±3.81	0.075
Time elapsed from first clinical symptoms, mean±SD (months)	3.12±1.33	2.45±0.31	0.752
DAS28 scores at baseline, mean±SD	4.37±0.64	4.27±0.63	0.824
Swollen joint counts at baseline, mean±SD	3.69±2.31	2.87±1.76	0.083
Tender joint counts at baseline, mean±SD	5.65±2.65	5.20±2.88	0.752
HAQ total scores at baseline, mean±SD	39.67±12.70	34.87±13.53	0.074
Receiving synthetic DMARD monotherapy after 18 months (% patients)	48.0	46.6	0.376
Receiving two or more synthetic DMARD therapy after 18 months (% patients)	52.0	53.4	0.798
Receiving biologic DMARDs during after 18 months (% patients)	16.6	13.3	0.041

*BMI: body mass index, DAS28: Disease activity score -28, DMARD: disease-modifying anti-rheumatic drugs, HAQ: Health assessment questionnaire, SD: standard deviation.
**p values versus early RA and very early RA

(48.0%) patients were taking one DMARD and 25 (52.0%) were taking two or more synthetic DMARDs. Six patients (12.5%) had started therapy with adalimumab, and 2 (4.1%) had started therapy with etanercept. Two of the patients who started tumor necrosis factor (TNF) blocker therapy were very early RA. One patient had pulmonary rheumatoid nodül at 18th month follow-up.

According to the DAS28 score, 12.5% (n=6) of patients exhibited low-level disease activity, 66.6% (n=32) exhibited moderate disease activity, and 20.9% (n=10) exhibited highlevel disease activity at baseline. According to the DAS28 score, 47.9% (n=23) of patients were in remission (DAS28 <2.6), 47.9% (n=23) exhibited low-level disease activity, and 4.2% (n=2) exhibited moderate disease activity at the 18- month follow-up.

Baseline Ultrasonography Findings

A total of 1344 joints were examined by US in all of the RA patients. Of these joints, GSUS synovitis was detected in 26.4% (n=356) of joints and PDUS synovitis was detected in 24.1% (n=325) of joints. GSUS synovitis was predominantly observed in the wrist, MCP2, and MCP3 joints (25.6, 18.2, and 12.5%, respectively); PDUS synovitis was predominantly observed in the wrist, MCP2, and MCP3 joints (21.5, 15.5, and 10.3%, respectively).

A total of 672 tendons from all of the RA patients were examined by US. Of these tendons, GSUS tenosynovitis was detected in 12.6% (n=85) of tendons and PDUS tenosynovitis was detected in 8.9% (n=60) of tendons. The extensor carpi ulnaris, second flexor digitorum were the most common affected tendons in GSUS and PDUS (24.0, 13.5%, respectively).

Baseline and Follow up Radiographic Findings

Baseline and 18th month radiographs were available for 44 patients. The total mean (±standard deviation [SD]) modified Sharp score was 11.62±4.90 at baseline in early RA patients. The total mean (±standard deviation [SD]) modified Sharp score was 8.26±3.76 at baseline in very early RA patients. There was statistically significant difference between very early RA and early RA group about radiographic score at baseline (p=0.001).

Laboratory, Ultrasonographic, and Radiographic Course

In the laboratory, ultrasonographic monitoring of the early RA patients, the parameters which improved statistically the earliest were the ESR and CRP levels. The improvement in the ESR and CRP levels is observed in the 1st month of the treatment (p=0.007). The statistically significant improvement in the HAQ, DAS 28 scores, total GSUS synovitis score, total PDUS tenosynovitis score, total GSUS tenosynovitis score, and total PDUS tenosynovitis score begins only in the 3rd month (p=0.007, p=0.003, p=0.001, p=0.009, respectively). In the VAS evaluation of the patients, while a statistically significant difference was not observed when compared to the previous control, a statistically significant difference was found between baseline and 18th month of the treatment (p=0.001) (Table 2).

Table 2. Clinical, laboratory and ultrasonographic course in patients with very early rheumatoid arthritis (n=15)

Parameter	Baseline	1.month	3.months	6 months	9 months	12 months	18 months
Pain, 0–10-mm VAS	4.07±2.70	4,13±0.99	4.00±1.13	3.40±0.72	2.80±0.86	2.40±0.50	1.87±0.64
ESR (mm/h)	47.47±20.45	29.54±21.45**	20.93±19.44*	14.00±8.87*	13.23±9.13	12.08±8.77	8.79±4.26
CRP (mg/dL)	24.84±26.98	12.31±9.97**	4.87±6.10*	6.54±8.89	6.00±4.04	4.77±2.35	3.64±3.64
DAS28 score	4.27±0.62	3.95±0.40	3.56±0.34*	3.21±0.39	2.93±0.30	2.78±0.39	2.69±0.31
HAQ score	34.87±13.52	32.65±12.12	24.01±10.52**	17.33±13.57**	20.13±6.76	22.00±7.29	14.00±5.18*
Total GSUS synovitis score	4.73±2.91	4.57±3.18	2.71±2.33**	2.36±1.90	1.92±1.55	0.50±1.09*	0.64±1.08
Total PDUS synovitis score	4.40±2.82	3.86±2.65	1.36±1.90**	0.43±1.08*	0.43±1.08	0.29±0.75	0.36±0.74
Total GSUS tenosynovitis score	1.40±1.45	1.36±1.49	0.64±1.44 **	0.57±1.45	0.42±1.05	0.29±0.72	0.33±0.65
Total PDUS tenosynovitis score	1.40±1.45	1.21±1.57	0.29±0.72**	0.00±0.00*	0.00±0.00	0.00±0.00	0.00±0.00

CRP C-reactive protein, DAS28 28-joint disease activity score, ESR erythrocyte sedimentation rate, GSUS gray-scale ultrasonography, HAQ. Health assessment questionnairre, PDUS power Doppler ultrasound, VAS visual analog scale, *p<0.05 versus the preceding visit, by pairwise comparison; **p<0.01 versus the preceding visit, by pairwise comparison; ***p<0.001 versus the preceding visit, by pairwise comparison

Table 3. Clinical, laboratory and ultrasonographic course in patients with early rheumatoid arthritis (n=48)

Parameter	Baseline	1.month	3.months	6 months	9 months	12 months	18months
Pain, 0–10-mm VAS	6.34±2.40	5.54±1.22	4.21±1.20	3.67±0.93	2.90±1.18	2.44±0.76	2.25±0.97
ESR (mm/h)	44.04±25.89	25.39±15.13**	18.42±13.46*	14.50±8.10	13.13±7.58	11.65±7.26	10.06±8.16
CRP (mg/dL)	29.62±28.75	13.50±12.50**	8.69±7.83	8.96±13.58	7.13±11.29	4.15±1.92	3.47±2.71
DAS28 score	4.37±0.64	4.01±0.51	3.55±0.47*	3.05±0.49*	2.81±0.43	2.69±0.37	2.63±0.35
HAQ score	39.67±12.70	37.54±10.43	27.58±9.12 **	21.58±10.24*	19.76±5.76	17.71±6.84	14.21±5.23
Total GSUS synovitis score	4.60±2.28	4.54±2.33	2.91±2.40 **	1.61±1.52*	1.09±1.23	0.48± 0.86	0.59±0.90
Total PDUS synovitis score	3.71±2.24	3.33±2.20	1.20±1.70 ***	0.35±0.84*	0.24±0.67	0.15±0.47	0.22±0.55
Total GSUS tenosynovitis score	1.88±2.48	1.80±2.52	0.70±1.65**	0.57±1.66	0.39±1.14	0.22±0.62	0.26±0.64
Total PDUS tenosynovitis score	1.56±2.27	1.24±2.32	0.52±1.53**	0.13±0.49*	0.07±0.25	0.00±0.00	0.11±0.06

CRP C-reactive protein, DAS28 28-joint disease activity score, ESR erythrocyte sedimentation rate, GSUS gray-scale ultrasonography, HAQ. Health assessment questionnairre, PDUS power Doppler ultrasound, VAS visual analog scale, *p<0.05 versus the preceding visit, by pairwise comparison; **p<0.01 versus the preceding visit, by pairwise comparison; ***p<0.001 versus the preceding visit, by pairwise comparison

The laboratory, US monitoring of very early RA patients, is similar to early RA patients. However, different from the early RA group, a statically significant found in the HAQ scores of the very early RA group, even in the 18th month (Table 3).

The total mean (±standard deviation [SD]) modified Sharp scores increased from 11.62±4.90 at baseline to 26.35±8.43 at 18th. months in early RA patients. The total mean (±standard deviation [SD]) modified Sharp scores increased from 8.26±3.76 at baseline to 23.27±7.58 at 18th. months in very early RA patients. A statistically significant difference was seen in modified Sharp scores between 0-18 months in early and very early RA patients (p=0.002, p=0.001). There was not a statistically significant difference between early and very early RA patients about radiographic scores at 18th. months and radiographic progression scores (p=0.071, p=0.885).

Correlation Between Radiography or US and Clinical Variables

Diagnosis duration, age, BMI did not correlate with radiographic progression scores in the RA patients (p>0.05).

Significant correlations were found between ESR, CRP values at baseline, ESR values at 1st month and 3rd months visit and radiographic progression scores (respectively, r=0.402, p=0.005; r=0.370, p=0.01; r=0.306, p=0.039, r=0.303, p=0.036). There were no correlations between RF, Anti-CCP positivity and radiographic progression scores (p>0.05).

Significant correlation was found between DAS28 scores at baseline, 1st month, 3rd months and radiographic progression scores (respectively, r=0.388, p=0.006; r=0.438, p=0.002; r=0.500, p=0.001). DAS 28 scores at other visits did not correlate with radiographic progression scores (p>0.05).

There were positive and significant correlations between total GSUS synovitis scores at baseline, 1st month, 3rd

Table 4. Multivariate analysis of the factors associated with radiographic progression scores.

Dependent variable	R^2 (adjusted)	Independent variables	B	ß	p value
Radiographic progression scores	0.384	Constant	8.275		0.558
		ESR at baseline	-0.054	-0.236	0.611
		CRP at baseline	0.216	0.154	0.502
		ESR at 1. month	0.127	0.138	0.556
		ESR at 3. months	0.054	0.236	0.611
		DAS28 scores at baseline	4.646	4.324	0.293
		DAS28 scores at 1.month	-1.190	-0.096	0.453
		DAS28 scores at 3.months	-4.852	-0.366	0.453
		total GSUS synovitis scores at baseline	0.091	0.417	0.011
		total GSUS synovitis scores at 1.month	0.518	0.549	0.028
		total GSUS synovitis scores at 3.months	2.261	1.110	0.278
		total PDUS synovitis scores at baseline	0.057	0.476	0.015
		total PDUS synovitis scores at 1.month	0.075	0.358	0.017
		total PDUS synovitis scores at 3.months	1.154	0.214	0.507

months, total PDUS synovitis scores at baseline, 1. month, 3. months visits and radiographic progresion scores (respectively, r=0.515, p=0.001; r=0.508, p=0.001, r=0.431, p=0.01; r=0.503, p=0.001; r=0.501, p=0.001, r=0.411, p=0.007). Other US parameters did not correlate with radiographic progression scores (p>0.05).

To establish an optimal model identifying variables influencing radiographic progression scores, we performed multipl lineer regression analysis on variables associated with p values of ≤0.2 upon univariate analysis (Spearman's correlations). The dependent variable was the radiographic progression scores, and the independent variables were ESR, CRP values at baseline, ESR values at 1st month and 3rd months visit, DAS28 scores at baseline, 1st month, 3rd months, total GSUS synovitis scores at baseline, 1st month, 3rd months, total PDUS synovitis scores at baseline, 1st month, 3rd months visits.

In the multiple linear regression model, only total GSUS synovitis scores, total PDUS synovitis scores at baseline and 1st month continued to show an effect on the radiographic progression scores in the early RA patients. Associations between other parameters and radiographic progression scores was not observed in the sample in early RA patients (Table 4).

DISCUSSION

According to the main results of our study, US observed synovitis is more common in patients with RA than tenosynovitis. When the patients are evaluated longitudinally, the ESR and CRP values stand out as the parameters which indicated the response first in the DMARD treatment. The ultrasonographically and clinically significant improvements emerge in the 3rd month follow-ups. This state of well-being continues as long as the DMARD treatment continues. In the very early RA group which is a subgroup in the early RA, a similar improvement process is observed in the ultrasonographic, clinical and laboratory improvement parameters. A difference was not found in this group in the radiological damage progression when compared to the early RA group. Even observing an improvement in only the life quality in the late term in the very early RA group is a remarkable result. One of the original findings of our study, that the most important factor affecting the radiographic damage progression scores is that the total GSUS, PDUS synovitis scores obtained at baseline and 1st month is high.

US brings a new perspective on the disease follow-up in RA and has begun to affect the clinical decisions more than the physical examination. Hence, there are studies which demonstrate that US has the permanent disease activity even in the RA patients with a low disease activity and who are in remission and it changes the treatment decisions. According to the study of Dale et al. (16), although clinically moderate disease activity, minimal US synovitis can be found. Our study emerged out of the need to eliminate the contradictions regarding when and how US affects our treatment decisions. One of the main purposes is to conduct

complete follow-ups for 18 months ultrasonographically in the early RA cases and associate the findings with the radiographic final state and progression. Although there are many studies carried out on this subject, there is not a study in which such a complete US follow-up as in our study is carried out. In the study of Naredo et al. (17), in which 12-month US follow-up was carried out, it was concluded that PDUS is a sensitive and reliable method for the longitudinal evaluation in the early RA patients. It was stated that PDUS findings could be used in the estimation of the disease activity and radiologic final state prognosis. In this study, like in our study, 28 joint evaluations were employed. While the 1st-month follow-up of the patients was not performed, ultrasonographic follow-ups were carried out at 3-month intervals. A statistically significant relationship was reached between the increase in the GSUS and PDUS findings and radiological total scores. In this study, the advancement in the radiographic scores was not elaborated on.

Damjanov et al. (8) forecasted the radiographic erosion in his 6-month follow-up study and arrived at the conclusion that the DAS scores combined with US were more successful than only the DAS scores. The presence of PD positive synovitis in another 1-year follow-up study was associated with a more rapid radiographic progression. This study which is an early arthritis study is the largest study in terms of the patient group with the group of 127 patients. However, while it is reliable in terms of the erosion results since only MKF and MTF joints are evaluated in US, the results are contradictory in terms of the clinical and functional parameters and correlation results (18). In another study which 38 patients were followed for 2 years, it was determined that erosion developed at the end of 2 years in the PD synovitis cases who has excessed values at the onset and it did not develop in the PD-negative patients. This study is an effective study since it has complete US follow-ups and follow-up periods (19). In the study carried out by Ikeda et al (20) in 2013, the late-term patients the US follow-ups of whom were performed in 0-12-24 months were compared as patient groups receiving methotrexate, anti-TNF, and tocilizumab treatment. It was determined that the radiographic erosion scores at the end of 2 years, that the outset PD synovitis scores were an independent risk factor for the erosion development in the group receiving methotrexate. As for the group receiving anti-TNF and tocilizumab treatment, it was demonstrated that the fact that PD synovitis scores were high did not lead to radiographic erosion. Different from our study, it is possible that the fact that the treatment was administered to the established patients may have caused the encounter with such a result. The studies in which early RA patients are included and in which a follow-up study can be carried out after the use of methotrexate, biologic agent in a naive fashion at the onset may give similar results to the study of Ikeda et al. However, performing such a study design does not seem possible in many countries in regards to the conditions of starting the biologic agent of the repayment institution.

While the results of our study are parallel with the study of Pascual-Ramos et al. (19), it prominently demonstrates that a radiologic damage develops in the patients with the high baseline and 1 month PDUS and GSUS total scores. This case is the indirect proof of how much neovascularisation increases the disease morbidity in RA. The importance of the persistence of PD synovitis on the erosion development is known but more importantly, the fact that the high baseline PD synovitis severity develops erosion even in the early RA patients emerges as a new finding. Thus, based on these results, it will not be wrong to say that the own burden of the disease determines the fate of the disease. Applying more aggressive treatment protocols apart from the standard treatments in patients with high PD synovitis scores at the onset can be offered as a recommendation.

When the clinical and laboratory follow-ups of the early RA patients are examined, the most striking parameters which improve with the treatment are acute phase reactants being ESR and CRP. For the decrease in the disease activity and the significant increase in the daily life activities, although the patients are diagnosed very early, it is necessary to wait for the 3rd month. In parallel with the results of our study, the improvement in the laboratory findings occurs in the 1st month in the similar studies (21,22).

The important advantage of our study, differently from other studies, is having included early RA patients and having carried out US follow-ups very completely. Having included the very early RA diagnosed patients as a subgroup in the early RA group in the follow-up is another advantage.

The fact that the interobserver and intraobserver reliability tests of the use of single ultrasonography were not carried in the US examination is one of the limitations of our study. Another limitation is the fact that carrying out the US evaluation in line with DAS 28 leads to not evaluating ankle and MTF joints.

As a result, our study has shown to clinicians and US applicators that the similar US findings are present in the early RA and very early RA patients and the ultrasonographic response to the treatment occurs in the similar periods. Although the baseline radiographic damage scores are different, the radiographic damage progresses are similar in these patient groups. The most important factor affecting the radiographic damage progression is the severity of ultrasonographic synovitis at the baseline and in the 1st month, independently of the disease activity. The studies in which the follow-up periods are longer and the patient groups are more diverse will shed light on explaining different development reasons of the radiographic damage.

Ethics Committee Approval: Ethics committee approval was received for this study from the local ethics committee.

Informed Consent: Informed consent was obtained.

Author contributions: Conception/Design of study -H.H., I.T.; Data acquisition - H.H.; Data analysis/Interpretation - H.H.; Drafting manuscript - H.H., I.T.; Critical revision of manuscript - H.H, I.T.; Final approval and accountability - H.H., I.T.; Technical or material support - H.H.; Supervision -H.H., I.T.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: Authors declared no financial support.

REFERENCES

1. Brown AK, Quinn MA, Karim Z, Conaghan PG, Peterfy CG, Hensor E, et al. Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression. Arthritis Rheum 2006;54:3761-73. [CrossRef]

2. Yan Geng, Jingjing Han, Xuerong Deng, Zhuoli Zhang. Presence of power Doppler synovitis in rheumatoid arthritis patients with synthetic and/or biological disease-modifying anti-rheumatic drug-induced clinical remission: experience from a Chinese cohort. Clin Rheumatol 2014;33:1061-6. [CrossRef]

3. Brown AK. Using ultrasonography to facilitate best practice in diagnosis and management of RA. Nat Rev Rheumatol 2009;5:698-706. [CrossRef]

4. Hama M, Uehara T, Takase K, Ihata A, Ueda A, Takeno M, et al. Power Doppler ultrasonography is useful for assessing disease activity and predicting joint destruction in rheumatoid arthritis patients receiving tocilizumab--preliminary data. Rheumatol Int 2012;32:1327-33. [CrossRef]

5. Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum 2008;58:2958-67. [CrossRef]

6. Witt M, Mueller F, Nigg A, Reindl C, Leipe J, Proft F, et al. Relevance of grade 1 gray-scale ultrasound findings in wrists and small joints to the assessment of subclinicalsynovitis in rheumatoid arthritis. Arthritis Rheum 2013;65:1694-701. [CrossRef]

7. Filer A, de Pablo P, Allen G, Nightingale P, Jordan A, Jobanputra P, Bowman S, et al. Utility of ultrasound joint counts in the prediction of rheumatoid arthritis in patients with very early synovitis. Ann Rheum Dis 2011;70:500-7. [CrossRef]

8. Damjanov N, Radunovic G, Prodanovic S, Vukovic V, Milic V, Simic Pasalic K, Jablanovic D, et al. Construct validity and reliability of ultrasound disease activity score in assessing joint inflammation in RA: comparison with DAS-28. Rheumatology (Oxford). 2012;51:120-8. [CrossRef]

9. Neogi T, Aletaha D, Silman AJ, Naden RL, Felson DT, Aggarwal R, Bingham CO, et al. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: phase 2 methodological report. Arthritis Rheum 2010;62:2582-91. [CrossRef]

10. Wells G, Becker JC, Teng J, Dougados M, Schiff M, Smolen J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis 2009;68:954-60. [CrossRef]

11. Cohen JD, Dougados M, Goupille P, Cantagrel A, Meyer O, Sibilia J, et al. Health assessment questionnaire score is the best predictor of 5-year quality of life in early rheumatoid arthritis. J Rheumatol 2006;33:1936-41.

12. Witt M, Mueller F, Nigg A, Reindl C, Leipe J, Proft F, Stein N, et al. Relevance of grade 1 gray-scale ultrasound findings in wrists and small joints to the assessment of subclinical synovitis in rheumatoid arthritis. Arthritis Rheum 2013;65:1694-701. [CrossRef]

13. Szkudlarek M, Court-Payen M, Strandberg C, Klarlund M, Klausen T, OstergaardM. Power Doppler ultrasonography for assessment of synovitis in the metacarpophalangeal joints of patients with rheumatoid arthritis: a comparison with dynamic magnetic resonance imaging. Arthritis Rheum 2001;44:2018-23. [CrossRef]

14. Naredo E, D'Agostino MA, Wakefield RJ, Möller I, Balint PV, Filippucci E, et al. Reliability of a consensus-based ultrasound score for tenosynovitis in rheumatoid arthritis. Ann Rheum Dis 2013;72:1328-34. [CrossRef]

15. Sokka T. Radiographic scoring in rheumatoid arthritis: a short introduction to the methods. Bull NYU Hosp Jt Dis 2008;66:166–8.

16. Dale J, Purves D, McConnachie A, et al. Tightening up? Impact of musculoskeletal ultrasound disease activity assessment on early rheumatoid arthritis patients treated using a treat to target strategy. Arthritis Care Res 2014;66:19-26. [CrossRef]

17. Naredo E, Collado P, Cruz A, Palop MJ, Cabero F, Richi P, et al. Longitudinal power Doppler ultrasonographic assessment of joint inflammatory activity in early rheumatoid arthritis: predictive value in disease activity and radiologic progression. Arthritis Rheum 2007;57:116-24. [CrossRef]

18. Funck-Brentano T, Gandjbakhch F, Etchepare F, Jousse-Joulin S, Miquel A, Cyteval C, Lukas C, et al. Prediction of radiographic damage in early arthritis by sonographic erosions and power Doppler signal: a longitudinal observational study. Arthritis Care Res (Hoboken) 2013;65:896-902. [CrossRef]

19. Pascual-Ramos V, Contreras-Ya-ez I, Cabiedes-Contreras J, Rull-Gabayet M, Villa AR, Vázquez-Lamadrid J, Mendoza-Ruiz JJ. et al. Hypervascular synovitis and American College of Rheumatology Classification Criteria as predictors of radiographic damage in early rheumatoid arthritis. Ultrasound Q 2009;25:31-8. [CrossRef]

20. Ikeda K, Nakagomi D, Sanayama Y, Yamagata M, Okubo A, Iwamoto T, et al. Correlation of radiographic progression with the cumulative activity of synovitis estimated by power Doppler ultrasound in rheumatoid arthritis: difference between patients treated with methotrexate and those treated with biological agents. J Rheumatol 2013;40:1967-76. [CrossRef]

21. Naredo E, Möller I, Cruz A, Carmona L, Garrido J. Power Doppler ultrasonographic monitoring of response to anti-tumor necrosis factor therapy in patients with rheumatoid arthritis. Arthritis Rheum 2008;58:2248-56. [CrossRef]

22. HartungW, Kellner H, Strunk J, Sattler H, SchmidtWA, Ehrenstein B, et al. Development and evaluation of novel ultrasound score for large joints in rheumatoid arthritis: one year of experience in daily clinical practice. Arthritis Care Res (Hoboken) 2012;64:675-82. [CrossRef]