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► **To cite this version:**

Manon Peran, Edem Allado, Eliane Albuissou, Marion Couderc, Paul Ornetti, et al.. Performance of ultrasound to assess erosion progression in rheumatoid arthritis. *European Journal of Radiology*, 2021, 136, pp.109536. 10.1016/j.ejrad.2021.109536 . hal-03345209

HAL Id: hal-03345209

<https://hal.science/hal-03345209v1>

Submitted on 3 Feb 2023

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Performance of ultrasound to assess erosion progression in rheumatoid arthritis

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Keywords: Rheumatoid arthritis, Imaging, Ultrasound, Bone erosion, Disease progression

ABSTRACT

Objectives: To analyse the performance of ultrasonography (US) to detect bone erosion progression at the patient level and at the joint level by the US score for erosions (USSe) in early-stage and late-stage rheumatoid arthritis (RA) over a 2-year follow-up.

Methods: Clinical and demographic information was recorded at baseline, and hands and feet RX were scored according to the Sharp erosion score. USSe was performed at baseline and over 2 years of follow-up on six bilateral joints (MCP2, 3, 5; MTP2, 3, 5). Inter-examiner reproducibility was performed on 14 patients, and the smallest detectable change (SDC) was calculated. US progression was defined as a change in USSe > SDC.

Results: 71 patients were included: 22 (31.0%) early RA, and 49 (69.0%) late RA. The intra-class correlation coefficient values of the USSe for intra- and inter-examiner studies were 0.96 (CI95: 0.93-0.98), and 0.92 (CI95: 0.75-0.97), respectively. On US, erosions prevailed at baseline in MTP5 joints followed by MCP2 and MCP5 joints. With an SDC calculated at 2.3, 28 patients (39.4%) were classified as progressors, 30 (42.3%) were stable, and 13 (18.3%) were regressors during the follow-up. At the joint level, erosion progression was significant on the MCP2 and MTP5 joints in early RA ($p < 0.01$) and on the MCP5 and MTP5 joints for all RA ($p < 0.05$).

Conclusions: US is a highly reproducible method that is able to detect erosion progression at the patient level for both early and late RA and at the joint level (MCP2 and MTP5) for only early RA.

INTRODUCTION

Rheumatoid arthritis is the most common chronic inflammatory rheumatism responsible for joint damage and disability, with a prevalence of 0.5% to 1% in European and North American adults. (1,2). Currently, therapeutic strategies involve early pharmacological treatment to block synovial inflammation and prevent joint damage. “Tight control” of RA patients is recommended by EULAR and ACR guidelines until a low disease activity score or clinical remission is obtained, according to a “treat to target” strategy. (3,4)

Delay in treatment is a major cause of irreversible structural damage (joint space narrowing, bone erosions) and important functional impact. In fact, the majority of erosive lesions appear within the first two years, and the rate of progression is more important during the early years of the disease. (5) The modified Sharp/van der Heijde erosion score is widely accepted as the 'gold standard' in assessing radiography (RX) structural joint damage in RA clinical research to determine the percentage of “progressors”, with high reproducibility and sensibility to change. (6–8) Musculoskeletal ultrasound (US) is increasing rapidly in clinical practice for diagnosis and for the follow-up of patients with RA, particularly in detecting inflammatory lesions and infra-radiographic erosions. Indeed, in clinical research, US has shown better sensitivity and specificity to detect erosion than radiography. (9–11) To our knowledge, no information is available concerning the potential of US to evaluate the status of erosion progression at the patient level in RA disease.

The aim of the study was to analyse the ability of ultrasonography to detect erosion progression by the US Score for erosions (USSe), in early-stage (less than 2 years disease duration (DD)) and late-stage (more than 2 years DD) RA over two years of follow-up, at the patient level (progressors or not) and at the joint level.

PATIENTS AND METHODS

Patients

In this longitudinal retrospective monocentric study performed at the Department of Rheumatology between 2005 and 2019, all RA patients ≥ 18 years old fulfilling ACR 1987 and/or ACR/EULAR 2010 were screened. Only patients who underwent RX exams at baseline and US examination at baseline and during follow-up with an interval of at least 6 months and less than 24 months between the two evaluations were selected. The exclusion criteria were the presence of severe joint deformities that could prevent complete appropriate ultrasonography, radiography, and clinical evaluation and incomplete RX or US exams. Demographic variables, such as gender and age, and disease information, such as disease duration, disease activity score (DAS 28), corticosteroid and NSAID consumption, synthetic and biological DMARDS, ACPA and RF status, were collected at baseline. The following measures were collected from computerized medical files: C-reactive protein level (normal value < 5 mg/L), erythrocyte sedimentation rate at the first hour (normal value < 5 mm), rheumatoid factor titres (normal value < 22 UI), and ACPA titres (normal value < 20 UI). A letter of no objection to this research was sent to the patients. The ethical committee of Nancy approved this study in October 2019 (Number of recordings: 2019PI233).

Radiography assessment

Postero-anterior views of wrists and hands and antero-posterior views of feet were performed, according to the usual clinical practice for RA follow-up, to determine the number of erosive diseases at baseline (corresponding to EULAR 2013 definition of erosive RA). (12)

An independent experimented reader (MC) performed the Van der Heidje-modified Sharp score for erosions (SHSe). RX analyses were performed blindly from clinical and US data.

Ultrasound assessment

Standardized US examinations were performed by experimented US analysts (ICV, DL) after several sessions of harmonization for calibration of erosion. The equipment used throughout the study was the same: a Philips HD 11 machine with a multi-frequency linear array transducer (5-12 MHz) with the focal length adjusted to the joint depth. US data were acquired at optimal technical conditions at 12 MHz (spatial resolution 0.1 mm) blinded to clinical, biologic, and radiologic findings. Twelve joints were explored in B mode and with

power Doppler (PD): metacarpophalangeal joints (MCPs) and metatarsophalangeal joints (MTPs) 2, 3 and 5. The dorsal and palmar or plantar facets of each joint and the accessible lateral facet were explored.

Grading of erosions

On each facet, erosion was defined as a cortical defect with an irregular bone surface that was visible in two perpendicular planes (axial and longitudinal). (13,14) Erosions were classified according to a 4-grade semi-quantitative score: grade 0: no erosion; grade 1: single erosion < 2 mm in its largest dimension; grade 2: single erosion \geq 2 mm and < 3 mm in its largest dimension or two erosions < 2 mm; and grade 3: single erosion \geq 3 mm in its largest dimension or multiple erosions ($n \geq 2$). The total US score for erosions (USSe) was the sum of the erosion grades for all eroded joints and ranged from 0 to 90.

Definition of erosive RA on US

For the diagnosis of erosive RA, we recently showed that the presence of at least two eroded joint facets presented a better compromise in terms of sensitivity and specificity (68.0% and 100.0%, respectively) in comparison to a population of patients with hand and feet osteoarthritis. (11) Considering the severity of the erosion at the joint facet level, regardless of its localization, the presence of at least one erosion of grade 2 resulted in the best sensitivity (72.1%) and specificity (89.1%). (11)

Inflammatory parameters on US

Synovitis, defined as the presence of synovial hypertrophy or joint effusion, and tenosynovitis were defined according to the OMERACT definition. (13,15) Tendons explored were the bilateral extensor carpi ulnaris, finger and toe flexor tendons. Synovitis and tenosynovitis were classified on a 4-grade semiquantitative scale: grade 0: absence; grade 1: minimal; grade 2: moderate; grade 3: severe. (16) Synovitis and tenosynovitis scores on B mode were the sum of the grades of all targeted joints. Power Doppler signal was also classified on a 4-grade score: grade 0: no flow; grade 1: single vessel signals; grade 2: confluent vessel signals in less than half of the area; and grade 3: vessel signals in more than half of the area. (17) PD synovitis and tenosynovitis scores were the sum of the grades of all targeted joints.

Intra- and inter-examiner US reproducibility

Intra-examiner reproducibility was assessed in eleven RA patients according to two complete examinations per patient within 24 hours. To evaluate inter-examiner reliability, fourteen patients were scored twice by two independent examiners who performed complete US exams (ICV, DL).

Statistical analyses

Characteristics of patients were described by number and percentage for categorical variables and by means, standard deviations, medians and quartile for continuous variables. For group comparison, the chi-square test or Fisher's exact test was used for qualitative variables, and Student's test or Mann-Whitney test was used for quantitative variables. Inter-reader reliability for ultrasonography was tested using Gwet's AC1 statistic for binary variables and the intraclass correlation coefficient (ICC) for continuous variables. To determine US progression, the smallest detectable change (SDC) was calculated as suggested by Bruynesteyn *et al* (18) by $1.96 \times SD_{\Delta}(\text{CHANGE-SCORES})/(\sqrt{2} \times \sqrt{k})$, in which k represents the number of readings over which one wants to average the analyses of the trial. The US progression was defined as a change in USSe > SDC, as a change score can be considered to represent a real change if it is larger than the minimal detectable change. For comparison of US progression at the joint level, we used the Wilcoxon test. For comparison of US structural progression in relation to baseline characteristics, the chi-square test or Fisher's exact test was used for qualitative variables, and Student's test or Mann-Whitney test was used for quantitative variables. Alpha risk was set at 5% for all analyses. These statistical analyses were performed using SPSS software version 23.0 (IBM Corp.).

RESULTS

Demographic characteristics of the population

In total, 90 patients were screened, and 71 RA patients were included in the final analysis: 19 patients were excluded due to the delay between the two US exams (<6 months (n=2) or > 24 months (n=17)). In the final patient population, 22 patients (31.0%) had early RA, 49 (69.0%) patients had late onset of the disease. The main clinical characteristics are presented in table 1. The mean age was 49.2 (14.9) years, and the mean disease duration was 5.6 (5.0) years. Among them, 26 (36.6%) had low disease activity scores, and 45 (63.4%) had moderate or high disease activity scores at baseline (mean DAS 28 was 3.90 (1.5)). Thirty of the 71

patients (42.3%) presented erosive disease on RX at baseline according to the EULAR 2013 definition. The mean SHSe for these patients was 29.4 (24.7).

US assessment at baseline

Among the 71 patients, 63 (88.7%) met the criteria for erosive RA at baseline. The mean USSe of the population was 10.5 (10.4). At baseline, US erosions prevailed in MTP5 joints (76.1%), followed by MCP2 (62%) and MCP5 (33.8%) joints, on their lateral facets.

Structural progression assessment on US

In the first step, we evaluated intra- and inter-examiner reproducibility to calculate the SDC. For intra-examiner reproducibility, the median value of the total US erosion score was 21 (range: 3-35) for the first exercise and 21 (range: 3-34) for the second one. The intra-class correlation coefficient (ICC) value of the erosion US score for intra-examiner study was 0.96 (CI95: 0.93-0.98) and that for inter-examiner was 0.92 (CI95: 0.75-0.97). The inter-reader reliability for the diagnosis of erosion was excellent (Gwet's AC1: 0.80). The SDC value was calculated at 2.3, defining a threshold of US progression for a change in USSe ≥ 3 (positive erosion change $>$ SDC). Among the 71 patients, 28 (39.4%) were classified as US progressors (corresponding to the definition of a change in USSe ≥ 3), 30 patients (42.3%) were stable, and 13 (18.3%) were considered regressors (Figure 1). At baseline, the mean USSe was 10.5 (10.4) and increased to 11.9 (10.4) during the follow-up.

As shown in Figure 2, the US erosion score progressed significantly in MTP5 joints ($p < 0.01$) and MCP5 joints ($p 0.02$) in all populations.

Structural US assessment in relation to disease duration

In early RA disease, 50% of the patients were considered progressors, one patient (4.5%) regressed, and 10 patients (45.5%) remained stable. The mean USSe score was 4.2 (4.1) at baseline and increased significantly to 7.4 (5.9) during follow-up ($p = 0.001$) (Figure 3).

At the joint level, the US erosion score progressed significantly only on the MCP2 and MTP5 joints ($p=0.008$) (Figure 4). On US, of the four early RA patients without erosive disease, three became eroded.

In late RA disease, 17 patients (34.7%) were considered progressors, 12 patients (24.5%) were regressors, and 20 (40.8%) were stable. The mean USSe score was 13.2 (11.1) at baseline and increased to 13.9 (11.4) (NS). At the joint level, erosion did not significantly

progress on the MCP5 and MTP5 joints (Figure 4). On US, only one of the four non-erosive RA patients became eroded during follow-up. One example of progression and scoring method is presented in figure 5.

Ultrasound structural progression in relation to baseline characteristics

Disease activity on DAS 28, biologic inflammation, immunologic status, and synovitis or tenosynovitis inflammation on ultrasonography (B-mode and PD-mode) were not predictive of USSe progression.

DISCUSSION

The primary focus of this exploratory study was to evaluate erosion joint damage progression by ultrasonography in RA at both the patient and joint levels. We demonstrated through the use of these two approaches that US was efficient in classifying patients as progressors, stable or regressors and that USSe was also able to detect erosion progression at the joint level, especially in the early stage.

As previously reported by Wakefield and Zayat et al., we showed excellent intra- and inter-operator reliabilities at the joint facet level with the same range of values calculated (9,19–21). We also confirmed that US detects more erosive disease than radiography (63 on US versus 30 on X-rays) at baseline (9–11,22,23). In this study, US joint examination was limited at some selected joints because not all the joints evaluated using the modified SHS can be explored in clinical practice. We decided, as other authors, to exclude the wrist because of its anatomic characteristics that make it difficult to localize erosions with precision in axial and longitudinal planes, except for the ulnar styloid process, where detection of these erosion is easier (21). MCP1, MTP1 and PIPs were excluded because these joints may be eroded by other musculoskeletal diseases and especially by osteoarthritis, the most prevalent disease in patients over 50 years old. (24,25). We also excluded MCP4 and MTP4 joints, which are less often affected by the erosion process. (9,19)

The assessment of structural damage progression in RA is crucial since joint damage is associated with poor functional outcome. Currently, radiography remains the conventional modality to measure the structural progression of RA and is routinely performed in clinical practice. (26) Radiography presents many advantages: the views and technical parameters are

well defined, and the structural progression is well evaluated in clinical trials by the modified SHS. It is considered one of the standard methods for assessing the structural effects of RA DMARDs (synthetic and biologic) in clinical trials because it presents excellent intra- and inter-reader reproducibility and good sensitivity to change. (7) Classically, it is reported in active RA patients that 25 to 30% of them progress, while 50 to 60% remain stable and 5 to 15% regress significantly on radiography over two years of follow-up. (27–31) Obviously, the percentage of progressors was lower in RA patients in remission (32).

US also offers many advantages: good accessibility, low cost, lack of irradiation with good intra- and inter-reader reproducibility for assessing structural damage and especially erosion. The medial facet of MCP and MTP joints cannot be assessed because they are not accessible to the probe. However, the dorsal and the ventral facets not accessible to radiography are well examined on US. Then, we can consider that radiography and ultrasonography, did not evaluate the same facets and subsequently these two modalities of imaging may be considered as complementary.

We confirmed on US that the MTP5, MCP2 and MCP5 joints are the most prevalent and the most severely eroded joints, especially on their lateral facets, as previously reported (22,23,27,29). At the patient level, we determined for the first time a structural US progression threshold after calculating the SDC that allowed us to classify patients into progressors (39.4%), stable (42%) and regressors (18.3%), as reported in a clinical trial using RX for structural evaluation. This approach was possible because US exams were performed on every joint facet of USSe by two independent examiners with excellent intra- and inter-examiner reliabilities.

Moreover, we showed that the rate of progressors was higher in early RA patients (50%) than in late RA patients (34.7%), as previously reported in radiography. (5,34) During the follow-up, the diagnosis of erosive RA on US was established in 75% of early RA patients versus 25% of late RA patients. At the joint level, we showed that the progression on USSe was statistically significant on MCP5 and MTP5 joints in all populations and MCP2 and MTP5 joints in early RA patients.

Some remarks should be discussed: joint space assessment, which was not performed in this study and recently validated by Mandl et al., (35) should also be investigated to improve the structural approach by US. This study was performed with a screening time ranged from 6 to 24 months susceptible to introduce several biases. The progression is probably underestimated

for patients followed for a delay <1 year. We showed that RA patients with a short screening time are well balanced between the two groups of patients (early versus late onset) without statistical difference. So this suggests a high level of confidence of the result that progression on ultrasonography had better chance to be observed in patients with early onset. With a variable screening time, we can consider that results at the patient level may be influenced but not at the group level. This study performed by trained sonographers required the development of an external validation process such as the OMERACT filter. This validation could be pertinent in a population of early active RA patients. This study failed to individualize any predictive biomarkers of erosion progression during a two-year follow-up. Several hypotheses are suggested: heterogeneity of disease activity score in RA patients at baseline, a long disease duration (median 4 years) in the majority of patients, and a small sample size. This lack of power is relative to the inclusion criteria: US examination performed by the two senior examiners fulfilling the US exercise reliabilities. Finally, follow-up RX assessment was not performed, and it would be interesting to carry out a future study to compare the performance of both imaging modalities to assess structural progression in RA patients.

To conclude, the USSe is able to detect structural changes (progression, stabilization and regression) in RA patients during a follow-up of two years, especially in RA patients with short disease duration. We showed that progression of US erosion prevailed significantly on MCP5 and MTP5 joints in all RA and in MTP5 and MCP2 joints in only early RA. Moreover, as for radiography, we demonstrated that the percentage of US erosion progression is higher in early RA than in late RA. Further studies are needed to analyse the pertinence of the USSe to evaluate structural progression in RA clinical trials.

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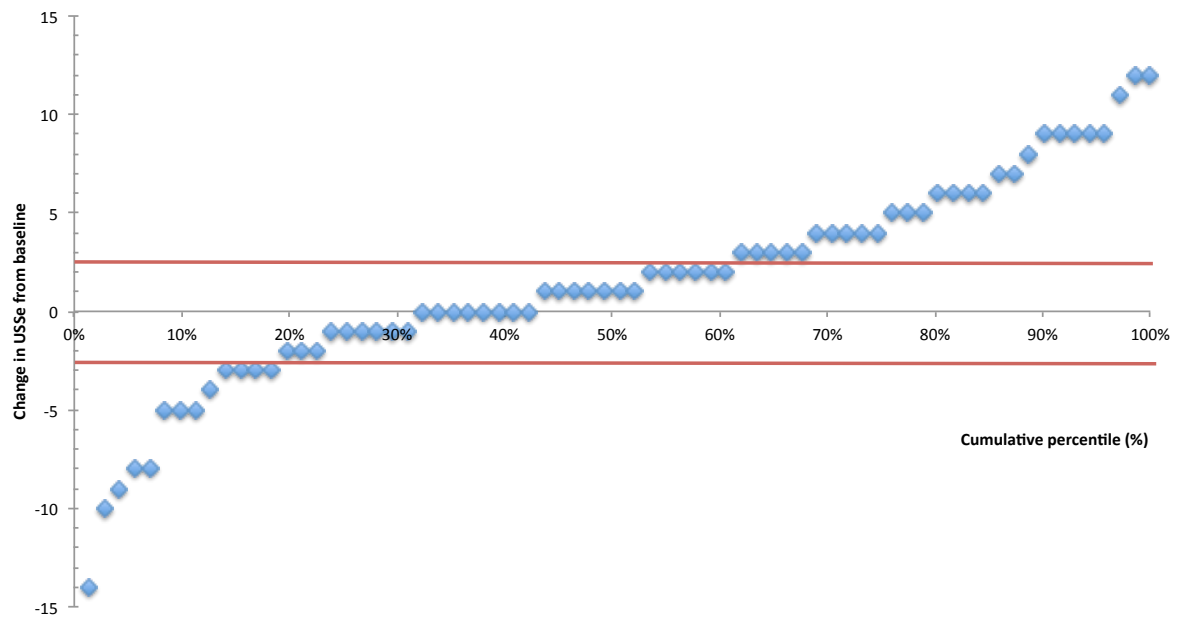
Figure 1: Cumulative progression of structural damage seen on US measured by variation of the USSe; the red lines correspond to the SDC values (+/- 2.3)

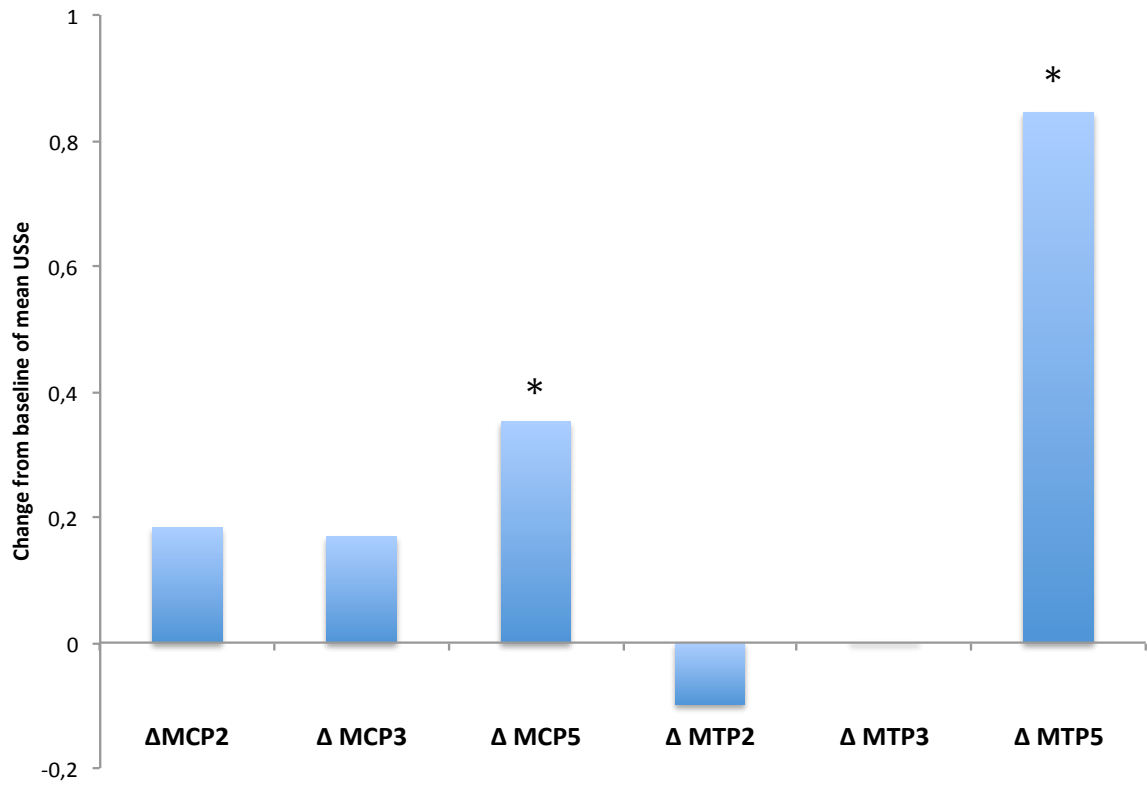
Figure 2: Progression of USSe at the joint level in the total population. Analyses were performed with the Wilcoxon test. * $p < 0,05$

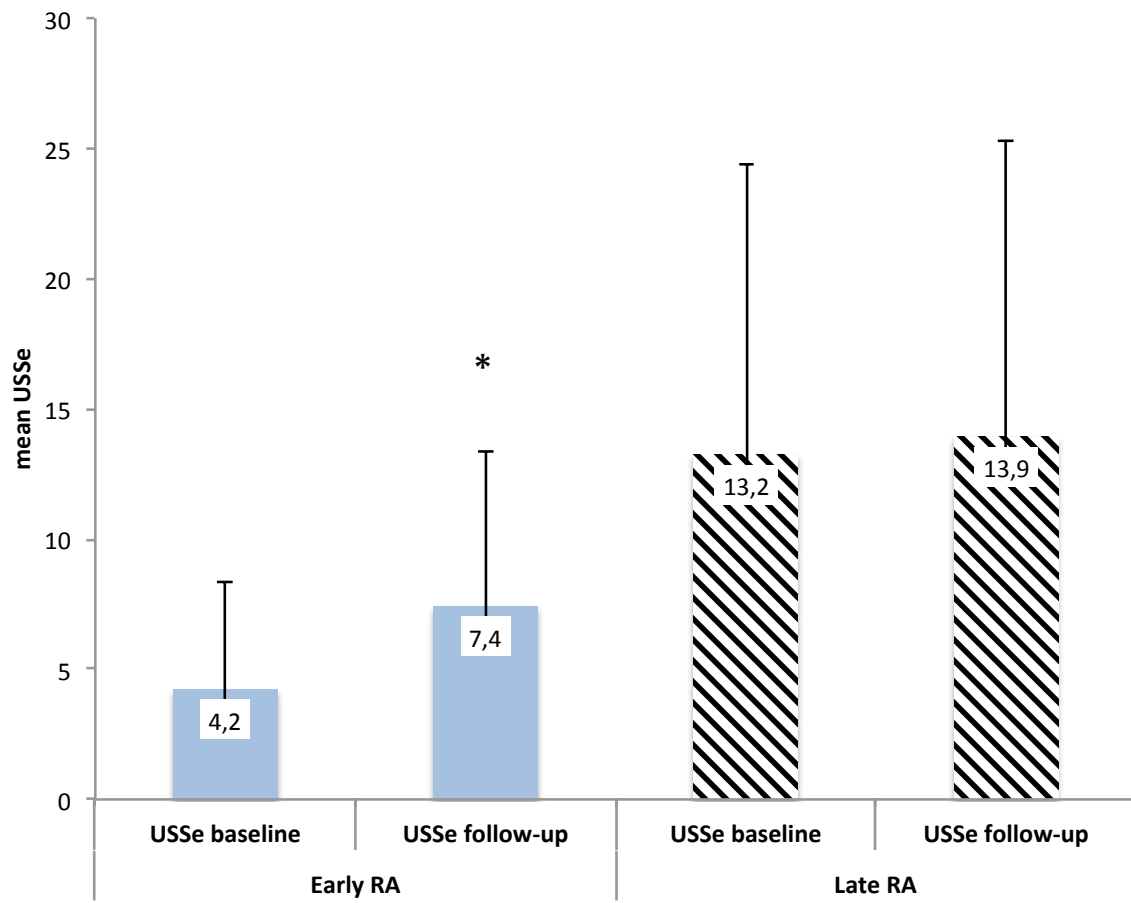
Figure 3: USSe progression for early and late RA (* = $p < 0.001$ on Mann-Whitney test)

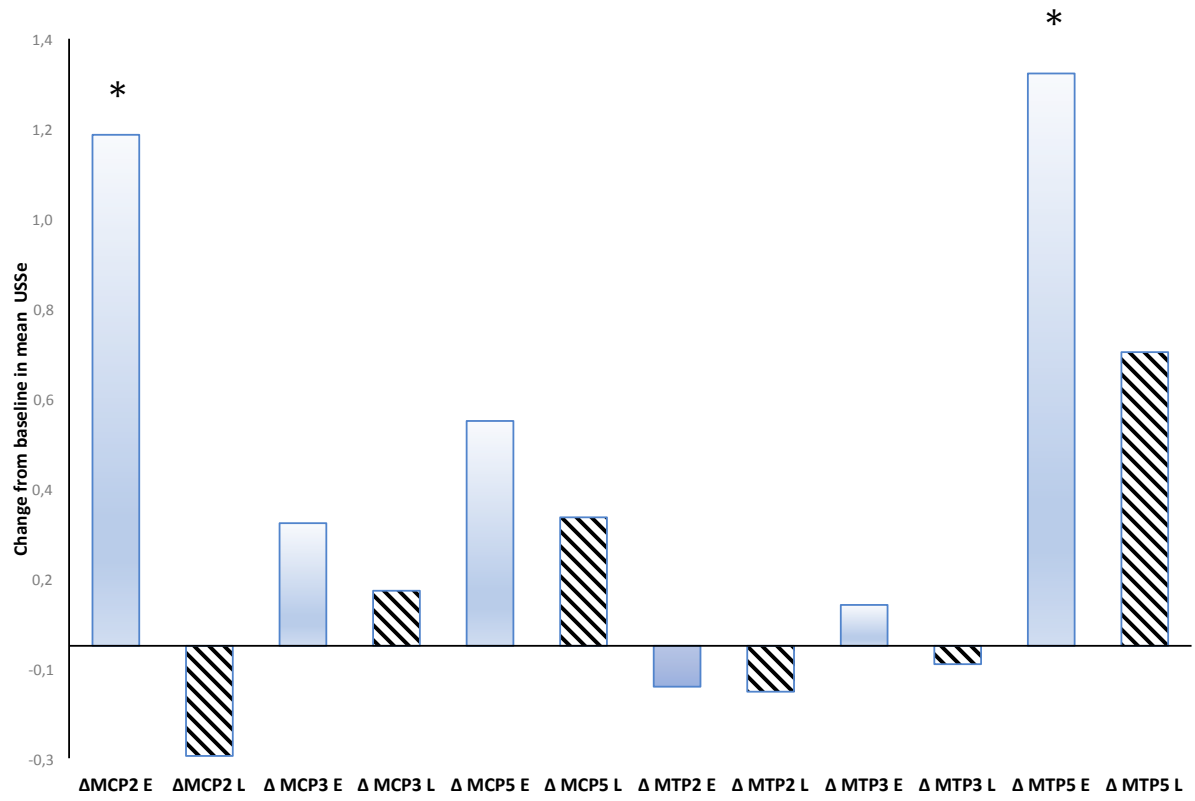
Figure 4: USSe progression at the joint level in early (E) RA (blue columns) and late (L) RA (hatched columns). The Wilcoxon test was used for statistical analyses. * $p < 0.01$

Figure 5 : erosion grading score with erosions of grade 1 to 3 on axial and longitudinal plans. Example of a 45-year-old woman with USSe calculated at 3 at baseline and increasing significantly at 6 one year later.









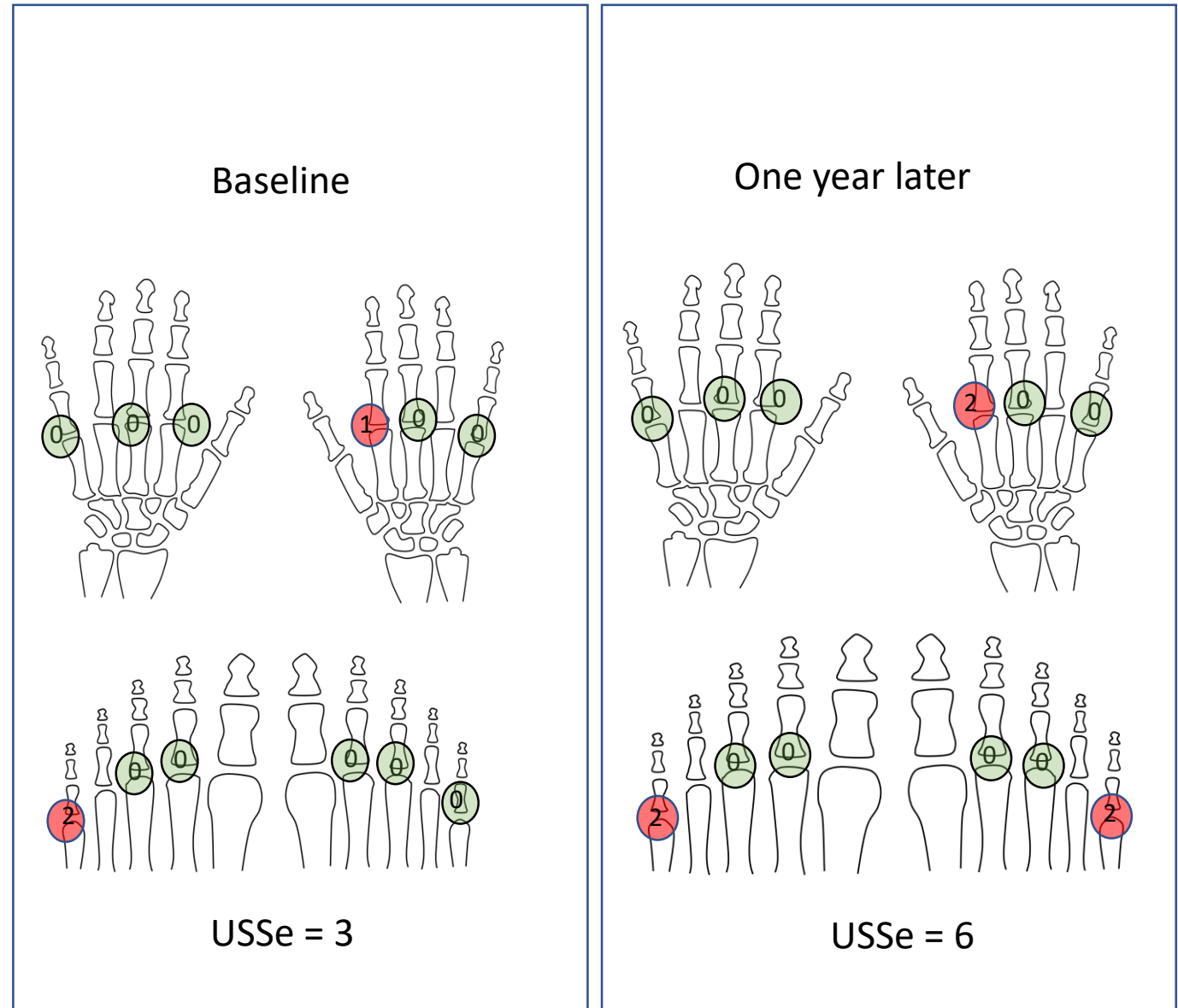
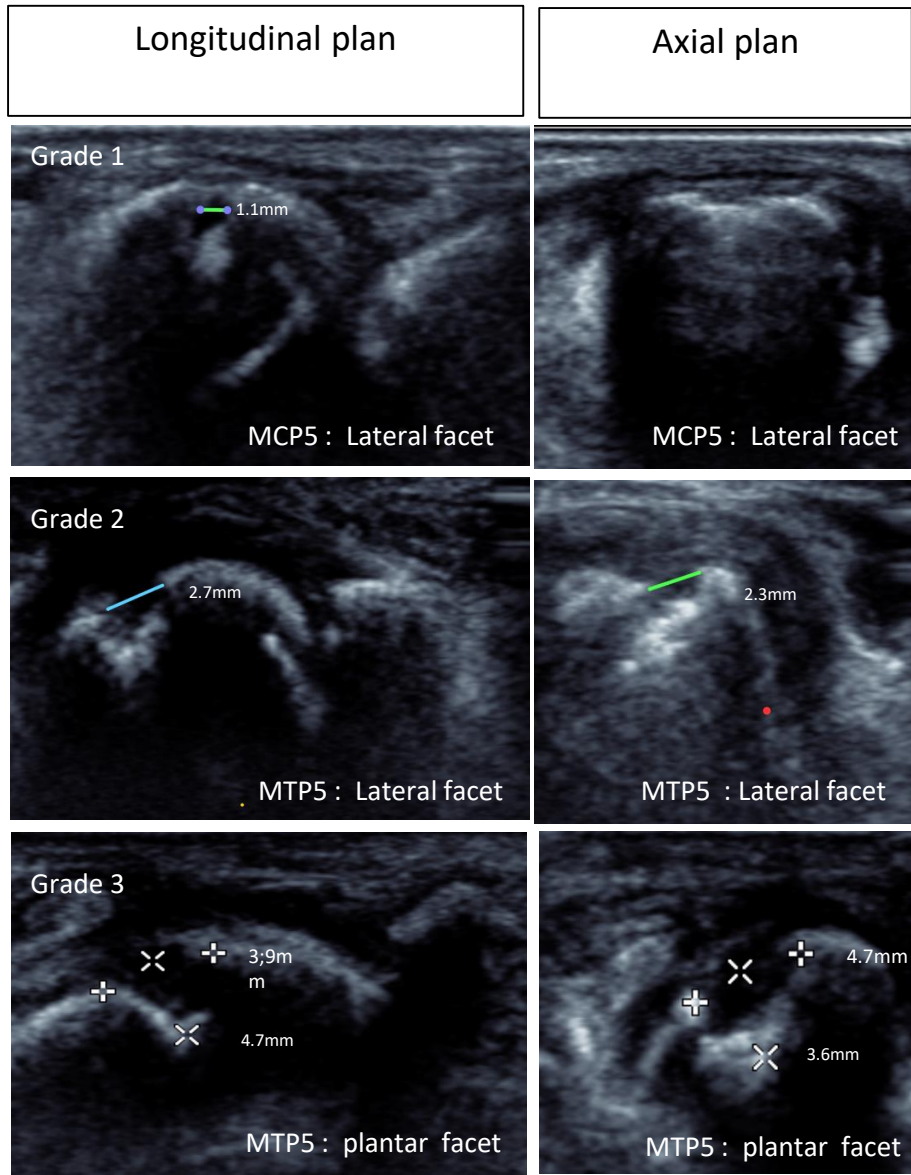


Figure 5 : erosion grading score with erosions of grade 1 to 3 on axial and longitudinal plans. Example of a 45-year-old woman with USSe calculated at 3 at baseline and increasing significantly at 6 one year later.

Table 1 Baseline characteristics of patients

		Total (n = 53)		RA < 2 years (n = 15)		RA ≥ 2 years (n = 38)		p-value
		N (%)	Mean (SD)/median (Q1-Q3)	N (%)	Mean (SD)/median (Q1-Q3)	N (%)	Mean (SD)/median (Q1-Q3)	
Demographic and clinical data								
	Age	53	48.9 (15.5)	15	53.9 (16.2)	38	46.9 (14.9)	0.052
	Female	32 (60.4)		7 (46.7)		25 (65.8)		
	Disease duration (months)	53	71.9 ()	15	8.4 ()	38	96.9 ()	< 0.01
	DAS 28	53	3.90 (1.6)	15	4.6 (1.8)	38	3.61 (1.4)	0.136
	DAS 28 ≤ 3.2	20 (37.7)		4 (26.7)		16 (42.1)		
	DAS 28 > 3.2	33 (62.3)		11 (73.3)		22 (57.9)		0.5
Biology								
	CRP	53	11.8 (-)	15	25.7 ()	38	6.3 ()	0.719
	ESR	53	22.7 (-)		30.4 ()	38	19.6 ()	0.265
	RF +	38 (71.7)		10 (66.7)		28 (73.7)		0.226
	ACPA +	41 (77.4)		10 (66.7)		31 (81.6)		0.221
Treatment								
	NSAIDs	8 (15.1)		2 (13.3)		6 (15.8)		0.985
	Corticosteroids	35 (66.0)		10 (66.7)		25 (65.8)		0.615
	sDMARDs	40 (75.5)		9 (60.0)		31 (81.6)		0.062
	bDMARDs	16 (30.2)		2 (13.3)		14 (36.8)		0.094
Imaging								
	US delay	53	13.0 (5.3)	15	10.7 (3.6)	38	13.9 (5.6)	0.32
	USSe	53	10.4 ()	15	3.2 ()	38	13.3 ()	< 0.01
	SHSe	53	11.8 (0-)	15	1.6 ()	38	15.9 ()	< 0.01
	Erosive RA on RX	24 (45.3)		1 (6.7)		23 (60.5)		
	B mode synovitis	53	8.9 ()	15	8.9 ()	38	8.9 (2-15)	0.857
	PD + synovitis	53	4.9 ()	15	5.6 ()	38	4.7 (0-8)	0.519
	B mode tenosynovitis	53	5.4 ()	15	7.0 ()	38	4.7 (0-8.5)	0.161
	PD + tenosynovitis	53	1.9 (0-)	15	2.7 ()	38	1.6 (0-2.5)	0.080

n : number ; SD : standard deviation ; NSAIDs : non-steroidal anti-inflammatory drugs ; csDMARDs : conventional synthetic DMARDs ; bDMARDs : biologic DMARDs ; RF : rheumatoid factor ; ACPA : Anti citrullinated protein antibody ; CRP : C-reactive protein ; ESR : erythrocyte sedimentation rate ; DAS 28 : disease activity score 28-joint count ; USSe : ultrasonography score for erosions ; SHSe : Sharp erosion score ; RA : rheumatoid arthritis ; RX : radiography ; PD : power doppler