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ORIGINAL ARTICLE

Use of ultrasound in treatment decisions for patients with rheumatoid arthritis: an observational study in Italy

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Abstract In rheumatoid arthritis (RA), treatment response is generally assessed using standard clinical disease activity measures. However, ultrasound has become increasingly popular among rheumatologists to monitor disease activity and response. The purpose of this analysis of ECOgraphic evaluation for STaging ARthritis (ECOSTAR) study data was to determine how ultrasound affects clinicians' decisions about changing treatment in RA. ECOSTAR was an observational, cohort study conducted between March 2010 and December 2012 at nine clinical centers in Italy in RA patients being considered for treatment change. After clinical evaluation of each patient, patients underwent diagnostic ultrasound (US) investigations and each patient was given a total echography score using a combination of scores for joint effusion, synovial hypertrophy, and power Doppler. The US results were provided to the clinicians and the influence of US on the clinicians' treatment choices were recorded. Ninety-five patients screened for study inclusion had confirmed RA (mean age 53.9 years; mean disease duration 8.9 years). Therapy changes were made by clinicians according to the hand and wrist joint US scores: score 0 appeared to have no influence on clinicians' decision to modify treatment, scores >0–3 were associated with a numerically higher estimated probability of not changing therapy than changing therapy, and scores >3 had a greater influence on the clinician to modify therapy and an increased probability of the clinician changing therapy versus not changing therapy. Ultrasonography scores appear to influence treatment decisions in patients with RA, with clinicians appearing less likely to alter treatment regimens in patients with low ultrasound scores and more likely to change treatment regimens when higher scores are obtained. Further research is warranted.

Keywords Clinicians' choice of therapy · Power Doppler · Rheumatoid arthritis · Synovial hypertrophy · Ultrasound

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Introduction

In patients with rheumatoid arthritis (RA), response to treatment is generally assessed using standard clinical disease activity measures, including the 28-joint Disease Activity Score (DAS28) and the Simplified Disease Activity Index (SDAI) [1]. Recently, ultrasound has become increasingly popular among rheumatologists to monitor disease activity and treatment response [2, 3]. Consequently, the ultrasound working group of the OMERACT (Outcome Measures in Rheumatology) group has worked to standardize ultrasound applications and define the typical pathologies in RA that can be detected by musculoskeletal ultrasound, which include joint effusions, synovial hypertrophy, and erosion [4].

Despite reservations regarding the reliability of ultrasound assessment (such as the reliability of acquisition and reading of ultrasounds) [5], ultrasound can be used to detect soft tissue lesions and early erosive changes in bone [2]. Musculoskeletal ultrasound is a sensitive tool which is patient friendly; however, whether data from power Doppler ultrasound monitoring can be used to provide an alternative to disease activity scores and, therefore, be used to monitor response to treatment or in treatment algorithms is not yet clearly established [6].

Findings from a number of studies investigating the use of ultrasound in daily rheumatologic practice have suggested that ultrasound can be used to monitor therapy in real-life clinical practice settings [2, 3, 7–11].

The purpose of this analysis of the ECOSTAR study was to determine how ultrasound is used in daily rheumatologic practice to make decisions about changing treatment in patients with RA. Specifically, we wanted to evaluate what ultrasound scores were most likely to prompt a change in treatment and whether a correlation exists between the choice to modify therapy and the ultrasound score observed.

Materials and methods

Study design and patients

ECOSTAR was an observational, prospective, cohort study conducted between March 2010 and December 2012 at 9 clinical centers (Varese, Venezia, Sacile (PN), Bolzano, Arenzano (GE), Alessandria, Trieste, San Pietro Vernotico (BR), and Barletta) in Italy. Any male and female patient ≥18 years old who was seen in these clinical centers had arthritis, and for whom a change in treatment was not being considered were included. In this analysis, patients with a diagnosis of stable RA made by their clinicians and based on American College of Rheumatology (ACR) 1987 guidelines were assessed. The study protocol was reviewed and approved by the local Ethics Committee at A.O. Ospedale Niguarda Cà Granda Milano prior to patient enrolment and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients received protocol information and either they or their legal representatives provided written informed consent.

Assessments

At baseline, a detailed history of demographic and clinical disease characteristics from each patient was collected. Patient and demographic characteristics included age, disease duration, comorbidities, and previous therapies received. Clinical disease characteristics included results of diagnostic tests (anti-citrullinated protein antibodies and rheumatoid factor), 28-joint disease activity scores (DAS28), and current treatment regimens. Data collection and physical examinations were conducted by the clinicians at each center involved in the study.

After the clinical evaluation, patients underwent diagnostic ultrasound investigations. These assessments were conducted by two qualified sonographers (OE, CS) who traveled to each center involved in the study and were blinded to the clinical data of each patient. These ultrasound investigations were conducted using a MyLab 70 XVG Esaote, which has a linear probe range of 6–18 MHz. The joints assessed included the wrist and hand (metacarpus, phalanges, and proximal intraphalangeal joint). Based on the results of the ultrasound, each patient was given a total echography score using a scoring system first used by Szkudlarek and colleagues [12], which included a combination of scores for joint effusion, synovial hypertrophy (assessed by grey-scale ultrasound), and power Doppler [13]. The data for the hand and wrist ultrasound were provided to the clinician, and decisions regarding each patient's treatment regimen and whether to modify treatment were made by the clinician after evaluation of the results. These decisions were recorded in each patient's clinical chart.

As the majority of patients with RA have synovitis in the hand and wrist (metacarpophalangeal) joints only [2], the correlation analysis between the choice to modify treatment and the observed ultrasound scores was assessed using the ultrasound scores (total echography score, and component joint effusion, synovial hypertrophy, and power Doppler scores) of the hand and wrist joints only. To do this, the hand and wrist correlation analysis began at an ultrasound value of 0 to determine if any ultrasound value observed will influence the clinician's decision. The correlation analysis also assessed for score ranges of 0–3 and 3–8 in the hand and wrist joints. The probability density function (the probability of a therapy change versus no therapy change given a certain total echography score, joint effusion, synovial hypertrophy, or

power Doppler score) for each score range was estimated, applying abnormal kernel smoothing function.

Statistical analyses

Qualitative and quantitative descriptive statistics were used to assess the variables collected and included the usual parameters: mean and standard deviation (SD); median, minimum, and maximum values and 25th–75th percentiles for quantitative variables; and numbers and percentages for qualitative variables. Statistical analyses on the study population were conducted and included chi-squared tests, logistic regression, and non-parametric tests.

Results

Patients

Of the 116 patients screened for inclusion in the study, 95 had a confirmed diagnosis of RA. The baseline demographics and characteristics of patients enrolled are presented in Table 1.

In brief, patients had a mean age of 53.9 years and mean disease duration of 8.9 years. Approximately 60 % of the population had at least one co-morbid disease, with hypertension, respiratory disorders, and thyroid dysfunction being the most common comorbidities.

Treatments

Of the 80 patients for whom prior treatment information was available, all but one had received prior treatment with disease-modifying anti-rheumatic drugs (DMARDs) and most had not previously received biological therapy (59/80). The median number of previously received DMARDs was 2 (range 0–6) and biological therapies 0 (range 0–7).

At baseline, the majority of patients were receiving methotrexate (mean daily dose 8.37 mg) or steroids, while fewer patients were receiving non-steroidal anti-inflammatory drugs (NSAIDs) or biological therapies (Table 1).

Ultrasound scores

In patients with RA, the mean total echography score recorded at baseline was 15.68 ± 17.08 (Table 2): only 12 patients had a total echography score of 0. In the remainder of the patients ($n = 83$), 55 had a total echography score between 0 and 10 (Fig. 1).

Fifteen, 18, and 20 patients had an echography score of 0 in their joint effusion, synovial hypertrophy, and power Doppler assessments, respectively.

Table 1 Baseline patient disease and demographic characteristics in patients with rheumatoid arthritis enrolled in the ECOSTAR study

Characteristic	$N = 95$
Sex, *n*/*N* (%)	
Female	76/93 (81.7)
Male	17/93 (18.3)
Age, years	
Mean ± SD	54.79 ± 14.43
Range	20–89
Disease duration, years	
Mean ± SD	7.93 ± 7.57
Range	0.25–43
Current smokers, *n*/*N* (%)	13/80 (16.3)
Comorbidities, *n* (%)	
None	40 (42.1)
1	36 (37.9)
2	11 (11.6)
3	5 (5.3)
4	3 (3.2)
Positive for anti-CCP antibodies, *n*/*N* (%)	46/80 (57.5)
Positive for RF antibodies, *n*/*N* (%)	35/84 (41.7)
DAS28-ESR	
Mean ± SD	4.34 ± 1.39
Range	1.79–7.67
2.6–5.1[a], *n*/*N* (%)	41/95 (43.2)
DAS28-CRP	
Mean ± SD	3.39 ± 1.32
Range	0.99–6.45
Current anti-rheumatic treatments, *n*/*N* (%)	
NSAIDs	31/95 (32.6)
Steroids	54/90 (60.0)
Biological drugs	22/92 (24.9)
MTX	62/95 (65.3)
Mean ± SD MTX dose, mg	8.37 ± 7.40
Other DMARDs	51/91 (56.0)

CCP cyclic citrullinated peptide, *CRP* C-reactive protein, *DAS28* 28-joint Disease Activity Score, *DMARD* disease-modifying anti-rheumatic drugs, *ERS* erythrocyte sedimentation rate, *MTX* methotrexate, *NSAIDs* non-steroidal anti-inflammatory drugs, *RF* rheumatoid factor, *SD*, standard deviation

[a] A DAS28-ESR score of 2.6–5.1 is considered to be moderate disease activity

Hand and wrist ultrasound scores leading to treatment change

The mean ultrasound scores found in the hand and wrist were 9.93 and 4.04, respectively. Similar to the combined ultrasound results, when only scores from the hand or the wrist joints were analyzed, most patients had a total echography

Table 2 Summary of ultrasound results in patients with rheumatoid arthritis enrolled in the ECOSTAR study ($N = 95$). The total echography scores was calculated using a scoring system first used by Szkudlarek and colleagues [12]

Ultrasound assessment	Scores
Total echography score	
Mean ± SD	15.68 ± 17.08
Median (IQR)	9 (4–22.75)
Range	0–87
Joint effusion score	
Mean ± SD	4.83 ± 4.98
Median (IQR)	3 (2–7)
Range	0–22
Synovial hypertrophy score	
Mean ± SD	6.65 ± 7.35
Median (IQR)	4 (1.25–10)
Range	0–36
Power Doppler score	
Mean ± SD	4.2 ± 5.39
Median (IQR)	2 (0–7)
Range	0–29

IQR interquartile range, *SD* standard deviation

score of >0 (78/95). Scores >0 in the hand and wrist joints were also observed in most patients when assessing the individual joint effusion, synovial hypertrophy, and power Doppler echography scores ($n = 74$, 74, and 63, respectively) (Table 3).

In general, changes to therapy tended to be made by clinicians if hand and wrist joint scores were >0 for each of the total ultrasound, joint effusion, synovial hypertrophy, and power Doppler scores (Table 3). Most changes to therapy were an increase in dose or addition of a biologic or another DMARD, or switching to another biologic.

Using estimated probability density functions, joint effusion, synovial hypertrophy, and power Doppler scores >3 were identified as indicating a likely change in therapy by the clinician. While there was no statistically significant difference between the probability of therapy change versus no therapy change for any given ultrasound score (i.e., chi-squared tests, logistic regression, and non-parametric tests showed no significant difference between the two populations), lower ultrasound scores (0–3) were associated with a numerically higher estimated probability of not changing therapy than changing therapy, whereas scores of 3–8 were associated with a numerically higher estimated probability of changing therapy than not changing therapy (Fig. 2a–c).

Furthermore, there was no significant difference between the type of echographic evaluation used (joint effusion, synovial hypertrophy, or power Doppler scores) and the probability of having a change in treatment: the distributions of patients with and without therapy modification using the three types of echography scores were similar.

Discussion

To our knowledge, this is the first study investigating the effects of ultrasound investigation on the treatment decisions of Italian clinicians in patients with RA. Our study showed that ultrasound scores may be a useful tool in daily rheumatologic practice to help clinicians make decisions about how to treat patients with RA. In particular, ultrasound results may influence the choice of clinicians to modify a patient's treatment regimen. In our study,

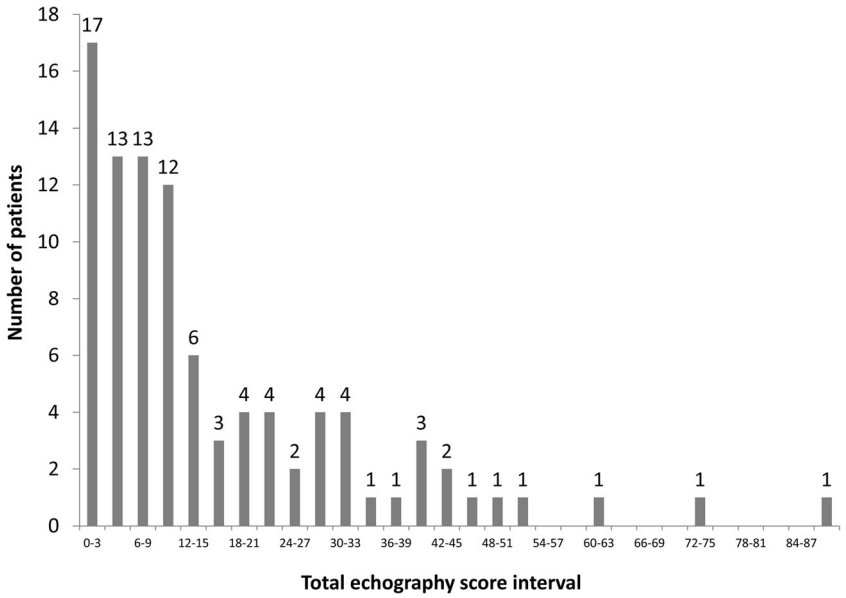

Fig. 1 Distribution of total echography scores in patients with rheumatoid arthritis enrolled in the ECOSTAR study ($N = 95$)

Table 3 Summary of changes (or lack of change) to therapy based on ultrasound scores of hand and wrist in patients with rheumatoid arthritis enrolled in the ECOSTAR study ($N = 95$)

Ultrasound result	Therapy unchanged, *n*	Change in therapy received[a], *n*				
		Increase in DMARD dose or addition of biologic or DMARD therapy	Decrease in DMARD dose or discontinuation of biologic or DMARD therapy	Received one steroid injection	Switched to another biologic agent	Total[b]
Total echography score						
>0 ($n = 78$)	28	38	3	3	8	50
0 ($n = 17$)	11	2	3	1	0	6
Joint effusion score						
>0 ($n = 74$)	25	37	3	3	8	49
0 ($n = 21$)	14	3	3	1	0	7
Synovial hypertrophy score						
>0 ($n = 74$)	27	35	3	3	8	47
0 ($n = 21$)	12	5	3	1	0	9
Power Doppler score						
>0 ($n = 63$)	22	31	2	3	7	41
0 ($n = 32$)	17	9	4	1	1	15

[a] Each patient could have more than one type of therapy change type (e.g., increased therapy and injection)

[b] Total number of patients who were selected for therapy change is calculated without duplicates

when assessing the ultrasound results of the hand and wrist, a total echography score, joint effusion, synovial hypertrophy, or power Doppler score of 0 appeared to have no influence on a clinician's decision to modify treatment, whereas an ultrasound score between 0 and 3 appeared to place the decision for modifying treatments upon the clinician (i.e., the probability for the clinician to modify or maintain the existing RA therapy the patient is receiving is the same). In contrast, an ultrasound score of >3 had a greater influence on the clinician to modify therapy and the likelihood of the clinician changing therapy was higher than the likelihood of not changing therapy. As expected, in most of the cases in this study, the clinician modified a patient's therapy by increasing the dosage of DMARD the patients were already receiving or by adding a second therapy to their treatment regimen.

While the majority of clinicians modified therapy in patients with high ultrasound scores, there were a few patients where the clinicians decided to not change treatment. This may have occurred for many reasons. The first reason could be that clinicians were not given any advice on how to interpret the ultrasound results. If the clinician was less experienced, they may not have sufficient knowledge to understand the ultrasound results. Furthermore, the clinicians may have already done an ultrasound previously and the scores provided in this study, while still high, were lower than the initial ultrasound score. This would indicate that the therapy the patient was receiving was effective and the clinician may decide not to change therapy. Finally, there may be differences between the centers included in terms the weight ultrasound was given in treatment decisions.

Interestingly, there was no difference between the type of echography assessed (joint effusion, synovial hypertrophy, or power Doppler score) and the probability of the clinician switching treatment. This was unexpected because the power Doppler score is known to be more informative on providing inflammation status. Indeed, it indicates active inflammation and, therefore, active disease. For this reason, it would be expected to be the main factor influencing clinicians in their decision. However, clinicians were not influenced by these data and did not consider power Doppler data to be more relevant than the other ultrasound data. Furthermore, there was no limit above which patients had their therapy changed. In fact, patients with higher echography scores appeared more likely to not change therapy. This was unexpected as it was anticipated that a higher score would be associated with a higher likelihood of changing therapy, but this may be due to the final therapy decision by the clinician being influenced to a greater extent by individual evaluation than by the echographic scores.

The results of this study suggest that ultrasound is an important tool in helping clinicians make therapeutic decisions for their RA patients. This is in line with the results of a few studies which suggest that adding an ultrasound assessment to the clinical management of RA patients can predict an improvement in clinical outcomes [14]. However, it has yet to be determined if making clinical decisions based on ultrasound imaging is better for patients with RA than amending therapy based on other measures of disease activity (such as DAS28 or SDAI scores). Three multicenter, randomized

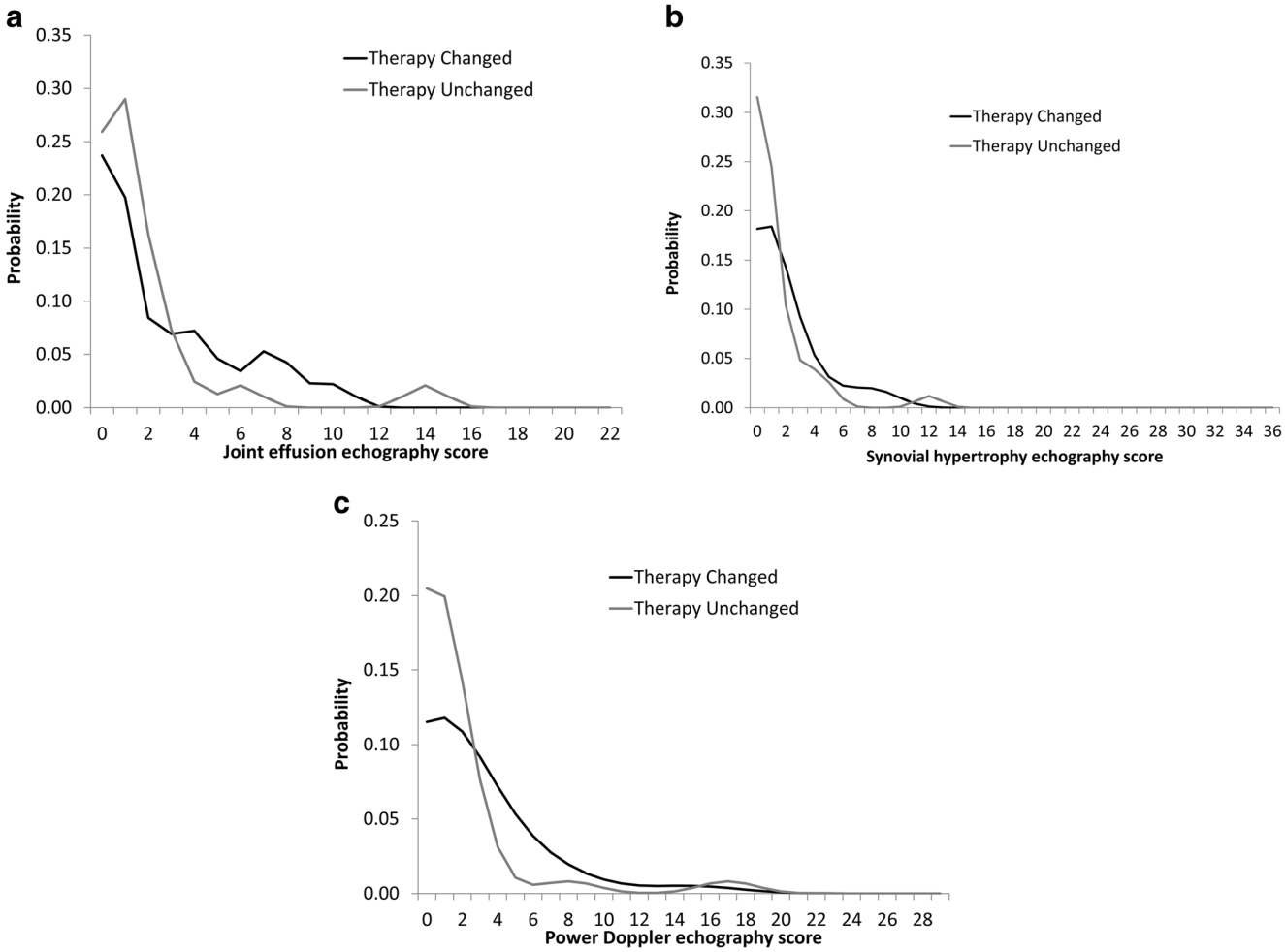

Fig. 2 Probability of changing therapy given the hand and wrist echography scores for **a** joint effusion, **b** synovial hypertrophy, and **c** power Doppler ultrasound in patients with rheumatoid arthritis enrolled in the ECOSTAR study ($N = 95$)

studies are currently underway to address this issue [14], the results of which will likely change clinical practice.

There is also still some debate about the most appropriate musculoskeletal ultrasound scoring system to use in the assessment of RA disease activity [4]. However, since this study was conducted, the OMERACT working group has initiated the development of a scoring system for synovitis in RA that combines grey-scale ultrasound and power Doppler ultrasound findings into a semi quantitative (0–3) scale (GLOSS) [15]. Initial assessments of the GLOSS assessment scale as an outcome measure for responsiveness have been evaluated in a multicenter, open-label, phase IIIb study [16] and show that the ultrasound-GLOSS is highly responsive (data not yet published).

Furthermore, consensus regarding what joint regions to include and the optimal (minimal) number of joints that should be used for a composite ultrasound score on joint level has not yet been reached. Different sum/composite scores have been published, which show high variation in the number of joints assessed and the responsive index used [2, 17–21]. Despite the variation observed in these studies, a European League Against Rheumatism (EULAR) task force has recently published the first guidelines on the use of imaging in the clinical management of RA which emphasizes the importance of ultrasound [22]. It concludes that while 10 general recommendations encompassing the role of imaging in RA have been provided, there is still a large amount of research required to optimize the use of imaging tools in routine clinical practice [22]. In particular, research on which joints should be used for monitoring and disease assessment, and consideration of the feasibility, cost and appropriate training required to use ultrasound in clinical practice should be conducted.

There are a few limitations to this study. In particular, due to the small sample size, the statistical significance was unable to be calculated. Also, in this study only the

hands and wrists were evaluated using ultrasound as these are the joints most commonly affected by rheumatoid arthritis [2]. However, we do acknowledge that only including these joints could influence a clinician to not change therapy and may have an impact on the results of this study.

However, despite the limitations, we believe that results of this study provide reasonable evidence that ultrasound scores are a useful tool in daily rheumatologic practice to make decisions about treatment choice for patients with RA and that clinicians are less likely to alter a treatment regimen in patients with low ultrasound scores but are likely to change a treatment regimen if higher scores are obtained. Further research is warranted.

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Compliance with ethical standards

Disclosures None.

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