RHEUMATOLOGY

Rheumatology 2017;56:1276–1281
doi:10.1093/rheumatology/kex080
Advance Access publication 11 April 2017

Original article

No clear association between ultrasound remission and health status in rheumatoid arthritis patients in clinical remission

Myrthe van der Ven[1], T. Martijn Kuijper[1], Andreas H. Gerards[2], Ilja Tchetverikov[3], Angelique E. Weel[1,4], Jendé van Zeben[5], Johanna M. Hazes[1] and Jolanda J. Luime[1]

Abstract

Objectives. Although RA patients achieve clinical remission, risk of flare still exists. Given the association between US synovitis and increased risk of flare, it is of clinical interest whether these patients report a different health status. Therefore, our aim was to evaluate the frequency of US remission in RA patients in clinical remission and to compare the health status of RA patients in clinical remission with those who were also in US remission.

Methods. In a prospective study, we included 89 RA patients (aged >17 years) treated with a synthetic DMARD and a TNF inhibitor who were in remission (DAS in 44 joints ⩽2.4 and swollen joint count ⩽1). Demographic characteristics, swollen and tender joints, laboratory variables, US (MCP2–5, PIP2–5, wrists and MTP2–5) and patient-reported outcomes (general health, functional ability, fatigue, depression and anxiety, pain and morning stiffness) were recorded at two consecutive visits (3 months apart). US remission was defined as grey scale grade ⩽1 and power Doppler = 0.

Results. At visit 1, 39% of patients were in US remission. At visit 2, 32% of patients were in US remission. At visit 1, functional ability (HAQ) was scored lower by patients in US remission (P = 0.029). At visit 2, HAQ scores were similar (P = 0.928). At visit 2, Hospital Anxiety and Depression Scale anxiety score and visual analog scale pain were significantly higher in patients in US remission. Similar levels were found for the other patient-reported outcomes.

Conclusion. One-third of RA patients in clinical remission were in US remission. In our study population, we could not find a clear association between health status of RA patients and being in US remission.

Key words: rheumatoid arthritis, ultrasound, patient-reported outcomes, health status, remission

CLINICAL SCIENCE

Rheumatology key messages

- Only one-third of RA patients in clinical remission were also in US remission.
- In RA patients in clinical remission, health status was not associated with being in US remission.

Introduction

Owing to the effectiveness of synthetic and biological DMARDs, and tight-controlled treatment, many RA patients are able to reach a state of clinical remission [1]. Although patients achieve clinical remission, studies have reported that risk of flare still exists in these patients while DMARD treatment is continued [2, 3]. This might indicate that underlying inflammation is still present. Such subclinical inflammation could be detected with US. Previous studies found ongoing active US synovitis in 48–73% of

[1]Department of Rheumatology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, [2]Department of Rheumatology, Vlietland Hospital, Schiedam, [3]Department of Rheumatology, Albert Schweitzer Hospital, Dordrecht, [4]Department of Rheumatology, Maasstad Hospital and [5]Department of Rheumatology, Sint Franciscus Gasthuis, Rotterdam, The Netherlands

Submitted 16 March 2016; revised version accepted 27 February 2017

Correspondence to: Myrthe van der Ven, Department of Rheumatology, Erasmus MC, University Medical Center Rotterdam, PO Box 2040, 3000 CA Rotterdam, The Netherlands.
E-mail: myrthe.vanderven@erasmusmc.nl

RA patients who were clinically in remission [3–7]. Furthermore, previous research indicated that US synovitis (especially power Doppler positive) predicts short-term relapse in RA patients in clinical remission [3, 8, 9].

Given the association between US synovitis and increased risk of flare, it is of clinical interest whether these patients with US synovitis report a different health status regarding pain, fatigue and general health. Subtle changes in health status may precede clinical flare [9, 10]. This could be used by physicians to adapt their treatment in these patients compared with patients who are in both clinical and US remission. However, the association between health status and clinical remission or US remission has not been investigated thoroughly. If a better health status is associated with US remission, regular measurement of the self-reported health of RA patients would help to monitor patients at risk of flare. This relates to the aim of the OMERACT RA Flare Group, working on a validated outcome measure to identify flare including both the patient and the physician perspective [11, 12].

In this study, we evaluated the frequency of US remission in RA patients who were in clinical sustained remission while they were continuing their synthetic and biological DMARD treatment. Our second objective was to compare the health status of RA patients in clinical remission with RA patients who were also in US remission.

Methods

Patients

We used consecutive RA patients (aged >17 years) who were included in the ongoing TARA (TApering strategies in RA) study. Patients were treated with the combination of a synthetic DMARD and a TNF inhibitor and were in remission defined as DAS in 44 joints (DAS44) $\leqslant$2.4 and swollen joint count $\leqslant$1 (TARA remission). According to the Boolean remission definition, we permitted one swollen joint [13]. This study focuses on the first two visits (baseline and 3 months follow-up) of the TARA study. During these 3 months of follow-up, patients continued their medication. The use of concomitant NSAIDs was allowed. Patients were asked to refrain from CSs, but there were no restrictions on the use of intra-articular injections with glucocorticosteroids. At baseline (visit 1), demographic characteristics, medication use, swollen and tender joint count (44 joint count), laboratory variables (ESR and serology), US and patient-reported outcomes were recorded for each patient. After 3 months (visit 2), if the patient was still in TARA remission, laboratory variables, swollen and tender joint count, US and patient-reported outcomes were recorded again.

Patients had to be able to understand, speak and write in Dutch. Written informed consent was obtained from the participants according to the Declaration of Helsinki. The study was approved by the local medical ethic committee of Erasmus MC, University Medical Centre Rotterdam, The Netherlands.

US examination

A trained US examiner blinded for the clinical details performed US, following the EULAR guidelines concerning patient position and scanning planes [14]. Twenty-six joints were evaluated with the Esaote Mylab60 (probe LA435, Genoa, Italy) using grey scale (GS) and power Doppler imaging. We scanned MTP2–5 (dorsal aspect), MCP2–5 and PIP2–5 (dorsal and palmar aspects) and wrist (radiocarpal and intercarpal joints) bilaterally. A single midline (longitudinal 12 o'clock position) scan perpendicular to the bone surface was used, as advised by the OMERACT US working group [15]. The following power Doppler settings were used: colour gain was set at the disappearance of colour noise. The pulse repetition frequency was set as low as possible to yield maximal sensitivity, which resulted in a frequency of 750 Hz. We adjusted the size and position of the colour box to include the s.c. tissue to recognize artefacts caused by superficial vessels [16]. Power Doppler signals were measured only in joints with GS $\geqslant$1. The total scanning time was 0.5 h per patient per session. The treating rheumatologist was unaware of the results from the US examination.

US evaluation

Image evaluation followed the recommendations of the Spanish society for Rheumatology. This is a modified version of the previously developed OMERACT definitions of sonographic pathology [17]. Joints were graded according to a semi-quantitative scoring system (0–3) for both GS and power Doppler. For GS, all joints were graded according to Szkudlarek *et al.* [18], as follows: 0 = no synovial thickening; 1 = minimal synovial thickening, filling the angle between the periarticular bones without bulging over the line linking the bone diaphyses of the periarticular bone regions; 2 = synovial thickening without extension over the bone diaphyses; and 3 = synovial thickening over at least one of the bone diaphyses.

Synovial vascularization was measured using power Doppler. Power Doppler was graded according to Naredo *et al.* [19], as follows: 0 = absent; 1 = mild, with single vessel signal or isolated signal; 2 = moderate, confluent vessel signals in the intra-articular area; and 3 = marked, with vessel signals in more than half of the intra-articular area. US remission was defined as GS grade 0 or 1 and absence of power Doppler.

Health status

Patients completed questionnaires regarding their health status before each visit. General health and functional ability were assessed at baseline and after 3 months. Fatigue, morning stiffness, pain, depression and anxiety were evaluated after 3 months.

General health

Physical and mental health were assessed by the Medical Outcomes Study Short Form 36 health survey. The Study Short Form 36 includes eight scales that assess pain, physical functioning, general health, fatigue/vitality, mental health, social functioning and role limitations

attributable to either physical or emotional problems. Two summary scores, the physical component summary and mental component summary, were computed [20, 21]. The scores range from 0 to 100, where a higher score indicates a better physical or mental health.

Functional ability

Functional ability was assessed by the HAQ [22]. The HAQ comprises 20 questions on eight dimensions of functional ability (e.g. dressing, arising, eating). The score ranges from 0 to 3, where higher scores indicate more disability.

Fatigue

Fatigue was measured by two questionnaires: the Fatigue Assessment Scale (FAS) and the Bristol RA Fatigue Multi-Dimensional Questionnaire. The FAS asks about fatigue on an average day and has two dimensions (physical and mental). Scores range from 10 to 50, with scores >21 being regarded as fatigued and scores >34 as severely fatigued [23]. The Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire asks about how fatigue has affected the patient in the past 7 days and has four dimensions (i.e. physical, living, cognition and emotion). Scores range from 0 to 70 [24]. For both the FAS and the Bristol RA Fatigue, higher scores indicate higher levels of fatigue.

Depression and anxiety

The Hospital Anxiety and Depression Scale (HADS) was used to assess anxiety and depression status. A HADS score $\geqslant 8$ (range: 0–21) is indicative of the presence of symptoms of mild, moderate or severe depression or anxiety [25].

Pain

Pain was measured by tender joint count and by the visual analog scale (VAS) for pain. Tender joint count was measured during physical examination and included 44 joints. For the VAS pain, patients were asked to self-assess the joint pain they have because of their arthritis. VAS pain ranges from 0 to 10 cm. The level of pain increases with higher scores.

Morning stiffness

Patients were asked if they encountered morning stiffness, for how long the morning stiffness was present (in minutes), and they were asked to self-assess the severity of the morning stiffness by a score ranging from 0 to 10. The severity of morning stiffness increases with higher scores.

Statistical analysis

Our primary outcome was US remission. US remission was defined as GS grade $\leqslant 1$ and absence of power Doppler signal. Simple descriptive techniques were used to describe the study sample. We analysed differences in health status between patients who were and who were not in US remission cross-sectionally for both baseline (visit 1) and after 3 months (visit 2). As the data were not normally distributed, we used the Wilcoxon-Mann–Whitney test. Frequencies were compared using a χ^2 test. Analyses were done using STATA 13.0 (College Station, Texas, USA), using a value of $P \leqslant 0.05$ as the level of statistical significance.

Table 1 Baseline characteristics of patients in tapering strategies in RA remission (n = 89)

Characteristic	
Age, mean (S.D.), years	55 (12)
Women, n (%)	59 (66)
Time since diagnosis, mean (S.D.), years	5 (3.4)
DAS44, mean (S.D.)	1.1 (0.5)
DAS44 remission, DAS44 <1.6, n (%)	73 (82)
SJC = 1, n (%)	12 (14)
ESR, median (interquartile range)	8 (3–16)
RF positive, n (%)	45 (55)
ACCP positive, n (%)	56 (69)

RA remission was defined as DAS44 $\leqslant 2.4$ and swollen joint count $\leqslant 1$. DAS44: disease activity score in 44 joints; SJC: swollen joint count; ACCP: anti-cyclic citrullinated peptide.

Results

For this analysis, we included 89 patients. Table 1 shows the baseline characteristics of all patients. According to the DAS44, 82% of the patients were in clinical remission (DAS44 <1.6). Eighteen per cent of the patients had low disease activity ($1.6 <$ DAS44 $\leqslant 2.4$). After 3 months (visit 2), we had data of 71 patients. Seven patients had a flare (DAS44 $\geqslant 2.4$ or $\geqslant 1$ swollen joint) while continuing their combination treatment of synthetic and biological DMARDs. Of these seven patients, four patients had US synovitis at visit 1. At joint level, there was no concordance between the clinical findings (swollen joint count) and US synovitis. Eleven patients were lost to follow-up at visit 2.

US examination

In total, 39% of the patients in TARA remission were in US remission at visit 1. At visit 2, after 3 months, 32% of the patients were in US remission. Eighteen per cent of the patients were in US remission at both visits. In the patients who were not in US remission, US synovitis was found most often in the wrists (visit 1: 39%; visit 2: 45%) and in the MTP joints (visit 1: 27%; visit 2: 30%). US synovitis was found in 3% (visit 1) and 6% (visit 2) of the patients in the PIP joints. When we focused on the absence of power Doppler signal, the number of patients in US remission increased to 54% (visit 1) and 42% (visit 2). Table 2 shows the US findings for visits 1 and 2.

Health status and US remission

Table 3 shows the health status at baseline and at 3 months. No clear pattern emerged on health status between patients who were in US remission and who were not in US remission. At visit 1, functional ability (HAQ) was

scored lower by patients who were in US remission than by patients who were not in remission (P = 0.029), whereas general health (Short Form 36) and tender joint count were similar. At visit 2, similar levels in both US groups were observed for functional ability, general health, tender joint count, depressive symptoms and fatigue. In general, we found low scores for HADS anxiety, HADS depression and VAS pain. Nonetheless, the HADS anxiety score and VAS pain were significantly higher in patients who were in US remission than in patients who were not in US remission at visit 2 (HADS anxiety: P < 0.001; VAS pain: P = 0.014).

We conducted the same analysis on health status and the presence or absence of power Doppler signal. The results were not analogous with the results we found with US remission. At visit 1, Short Form 36 physical scale was significantly lower in patients with the presence of power Doppler signal (no power Doppler US remission; P = 0.015). At visit 2, we could not find any association between health status and the presence or absence of power Doppler signal.

Table 2 US findings at baseline and at 3 months

US characteristic	Visit 1 (n = 89)	Visit 2 (n = 71)
GS, n positive joints, median (IQR)	0 (0–2)	0 (0–1)
Power Doppler, n positive joints, median (IQR)	0 (0–1)	1 (0–1)
US synovitis, %		
MCP	12	10
PIP	6	3
Wrists	39	45
MTP	30	27
US remission, %	39	32
Power Doppler remission, %	54	42

GS: grey scale (GS ⩾2); IQR: interquartile range; power Doppler remission: absence of power Doppler signal; US remission: GS ⩽1 and absence of power Doppler signal; US synovitis: GS ⩾2 and/or presence of power Doppler signal.

Discussion

Thirty-nine per cent of the RA patients in TARA remission were in US remission (GS grade ⩽1 and absence of power Doppler signal) at baseline. This indicates that the remaining two-thirds of the patients had US synovitis (GS grade 2 or 3 and/or power Doppler grade 1, 2 or 3) while they were in TARA remission and continued their synthetic and biological DMARDs. This is comparable to previous studies, which found active US synovitis in 48–73% of RA patients who were clinically in remission [3–7, 26]. After 3 months of follow-up, patients returned to the outpatient clinic; at this visit, 32% of the RA patients were in US remission. Comparing the US results at both visits, 18% of the patients were in US remission at visit 1 and at visit 2. If we focused on the absence of power Doppler signal, 31% of the patients had no power Doppler signal at both visits. According to the Boolean remission criteria for RA, we allowed one clinically swollen joint. At the joint level, however, the US findings were not consistent with the clinically swollen joints.

In our study population, we could not find a clear association between health status and being in US remission. Overall, patients reported good health, with low scores for pain, functional disability, anxiety, depression and fatigue and higher scores for general health. These self-reported patient outcomes were expected, because all patients were in clinical remission or had low disease activity.

Table 3 Patient-reported outcomes at baseline and at 3 months[a]

Patient-reported outcome	Visit 1			Visit 2		
	US remission (n = 35)	non-US remission (n = 54)	P-value[b]	US remission (n = 23)	non-US remission (n = 48)	P-value[b]
HAQ, range 0–3, median (IQR)	0.3 (0-0.9)	0.6 (0.1-1.4)	0.029	0.3 (0-0.6)	0.3 (0-0.6)	0.928
Short Form 36, range 0–100, median (IQR)						
PCS	49 (44–52)	44 (38–50)	0.084	48 (44–52)	46 (40–52)	0.780
MCS	54 (49–59)	57 (54–59)	0.134	55 (41–59)	58 (54–61)	0.054
TJC, range 0–44, median (IQR)	0 (0–2)	0 (0–1)	0.528	0 (0–2)	0 (0–1)	0.478
VAS pain, range 0–10, median (IQR)				3 (2–4)	1 (1–3)	0.014
Morning stiffness severity, range 0–10, median (IQR)				3 (0–4)	1 (0–2)	0.084
HADS anxiety, range 0–21, median (IQR)				5 (3–7)	3 (1–5)	<0.001
HADS depression, range 0–21, median (IQR)				2 (1–3)	1 (0–3)	0.250
BRAF, range 0–70, median (IQR)				21 (13–26)	14 (6–23)	0.070
Fatigue, FAS range 10–50, median (IQR)				21 (18–23)	18 (14–23)	0.160

[a]All patients were in TARA remission, defined as DAS44 ⩽2.4 and swollen joint count ⩽1. [b]Wilcoxon–Mann–Whitney test for continuous scales, χ^2 test for binary scales, P ⩽ 0.05. BRAF: Bristol RA Fatigue Multi-Dimensional Questionnaire; DAS44: DAS in 44 joints; FAS: Fatigue Assessment Scale; HADS: Hospital Anxiety and Depression Scale; IQR: interquartile range; MCS: mental component summary; PCCL: Pain Coping and Cognition Scale; PCS: physical component summary; TJC: tender joint count; VAS: visual analog scale; PCS: physical component summary; MCS: mental component summary.

A study by Sakellariou *et al.* [27] showed that being in clinical remission was associated with low disability (low HAQ score) and absence of power Doppler signal. We found low HAQ scores overall, but we did find positive power Doppler signals in half of our population while they were in clinical remission.

In our definition of US synovitis, we combined GS abnormalities with power Doppler signal. GS abnormalities in RA patients could also be explained as hypertrophy of the synovium after inflammation [28]. Other studies showed that GS abnormalities also occur in non-arthritic individuals, and in particular, the discriminative value of GS score 1 is debatable [29, 30]. In addition, it has been shown that the presence of power Doppler signal is associated with increased risk of flare [3, 8, 9]. We found a positive power Doppler signal in 46% (visit 1) and 58% (visit 2). These percentages are comparable to other studies evaluating the presence of power Doppler signal in RA patients in clinical remission [3–7, 26]. After analysis of health status and the presence or absence of power Doppler signal, the results were not analogous with the results we found with US remission. This indicates that using a different definition for US remission is not helpful to distinguish between patients by their health status. We chose to include 26 joints (MCP2-5, PIP2-5, wrists and MTP2-5), because these joints are most frequently involved in RA [31]. Based on a review by Ten Cate *et al.* [28], it also seemed that it is not necessary to include large joints in the US assessment.

We found significantly higher scores on the HADS anxiety score and VAS pain in patients who were in US remission than in patients who were not in US remission. Although the median score for both outcomes was low, these were still unexpected findings because one might expect an association in the opposite direction. It might be explained by the fact that patients who were not in US remission were less sensitive to pain or could cope better, or these results might be spurious findings. Another explanation could be related to a drop-out bias, because seven patients had a flare and 11 patients were lost to follow-up at visit 2. The majority (n = 13) of these patients were in the non-US remission group at visit 1, which might imply that they had worse health status. However, we do not have data for HADS anxiety and VAS pain at visit 1, which made it not possible to say whether this explanation holds.

There are limitations to monitoring patients only with self-reported health status. Previous studies showed that changes in self-reported health status were of limited value to predict disease activity in individual patients [32, 33]. We know from previous research in RA patients in clinical remission that clinically swollen or tender joints and US synovitis can predict disease relapse. Our results indicate that US remission does not distinguish between patients with different health status. Therefore, it might be desirable to combine physical examination, self-reported health status and US examination to optimize patient care.

Our study has some limitations. At 3 months of follow-up (visit 2), only 8% (n = 7) of the patients in TARA remission had a flare, which was captured by DAS44 $\geqslant$2.4 or $\geqslant$1 swollen joint. This low flare rate might be explained by selection bias by the rheumatologists who included the patients. Rheumatologists could be tempted to refer only RA patients who achieved remission easily and who had less severe disease.

In this study, we included patients with a mean disease duration of 5 years. These patients were treated according to a tight treatment protocol and with the availability of biologicals. Our study population possibly consisted of patients with less severe disease, because they had no longstanding disease and were in clinical remission on combination therapy of a synthetic and a biological DMARD.

In conclusion, one-third of the RA patients in clinical remission were also in US remission. In our study population, we could not find a clear association between health status of RA patients and being in US remission. We did find that patients in US remission experienced more pain and anxiety, but this was in the direction opposite to what was expected. This might indicate that health status is not a suitable tool to distinguish patients who do or do not have underlying US synovitis while they are continuing their synthetic and biological DMARDs. We recommend that our results need to be confirmed in other cohorts with RA patients who are in clinical remission.

Acknowledgements

Each author made a substantial contribution to the intellectual content and approved the final version submitted.

Funding: This study was financially funded by an investigator-initiated grant from ZonMw (non-profit organization).

Disclosure statement: The authors have declared no conflicts of interest.

References

1 Smolen JS, Breedveld FC, Burmester GR *et al*. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 2016;75:3–15.

2 Molenaar ET, Voskuyl AE, Dinant HJ *et al*. Progression of radiologic damage in patients with rheumatoid arthritis in clinical remission. Arthritis Rheum 2004;50:36–42.

3 Peluso G, Michelutti A, Bosello S *et al*. Clinical and ultrasonographic remission determines different chances of relapse in early and long standing rheumatoid arthritis. Ann Rheum Dis 2011;70:172–5.

4 Brown AK, Quinn MA, Karim Z *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.

5 Ozgocmen S, Ozdemir H, Kiris A, Bozgeyik Z, Ardicoglu O. Clinical evaluation and power Doppler sonography in rheumatoid arthritis: evidence for ongoing synovial

inflammation in clinical remission. South Med J 2008;101:240–5.

6 Saleem B, Brown AK, Keen H *et al*. Disease remission state in patients treated with the combination of tumor necrosis factor blockade and methotrexate or with disease-modifying antirheumatic drugs: a clinical and imaging comparative study. Arthritis Rheum 2009;60:1915–22.

7 Yoshimi R, Hama M, Takase K *et al*. Ultrasonography is a potent tool for the prediction of progressive joint destruction during clinical remission of rheumatoid arthritis. Mod Rheumatol 2013;23:456–65.

8 Scire CA, Montecucco C, Codullo V *et al*. Ultrasonographic evaluation of joint involvement in early rheumatoid arthritis in clinical remission: power Doppler signal predicts short-term relapse. Rheumatology 2009;48:1092–7.

9 Saleem B, Brown AK, Quinn M *et al*. Can flare be predicted in DMARD treated RA patients in remission, and is it important? A cohort study. Ann Rheum Dis 2012;71:1316–21.

10 Bingham CO, 3rd, Alten R, de Wit MP. The importance of patient participation in measuring rheumatoid arthritis flares. Ann Rheum Dis 2012;71:1107–9.

11 Bingham CO 3rd, Alten R, Bartlett SJ *et al*. Identifying preliminary domains to detect and measure rheumatoid arthritis flares: report of the OMERACT 10 RA Flare Workshop. J Rheumatol 2011;38:1751–8.

12 Bykerk VP, Lie E, Bartlett SJ *et al*. Establishing a core domain set to measure rheumatoid arthritis flares: report of the OMERACT 11 RA Flare Workshop. J Rheumatol 2014;41:799–809.

13 Felson DT, Smolen JS, Wells G *et al*. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis 2011;70:404–13.

14 Backhaus M, Burmester GR, Gerber T *et al*. Guidelines for musculoskeletal ultrasound in rheumatology. Ann Rheum Dis 2001;60:641–9.

15 Naredo E, Möller I, Moragues C *et al*. Interobserver reliability in musculoskeletal ultrasonography: results from a ''Teach the Teachers'' rheumatologist course. Ann Rheum Dis 2006;65:14–9.

16 Torp-Pedersen ST, Terslev L. Settings and artefacts relevant in colour/power Doppler ultrasound in rheumatology. Ann Rheum Dis 2008;67:143–9.

17 Wakefield RJ, Balint PV, Szkudlarek M *et al*. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. J Rheumatol 2005;32:2485–7.

18 Szkudlarek M, Court-Payen M, Jacobsen S *et al*. Interobserver agreement in ultrasonography of the finger and toe joints in rheumatoid arthritis. Arthritis Rheum 2003;48:955–62.

19 Naredo E, Bonilla G, Gamero F *et al*. Assessment of inflammatory activity in rheumatoid arthritis: a comparative study of clinical evaluation with grey scale and power Doppler ultrasonography. Ann Rheum Dis 2005;64:375–81.

20 Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–83.

21 McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993;31:247–63.

22 Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137–45.

23 Michielsen HJ, De Vries J, Van Heck GL. Psychometric qualities of a brief self-rated fatigue measure: the Fatigue Assessment Scale. J Psychosom Res 2003;54:345–52.

24 Nicklin J, Cramp F, Kirwan J *et al*. Measuring fatigue in rheumatoid arthritis: a cross-sectional study to evaluate the Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional questionnaire, visual analog scales, and numerical rating scales. Arthritis Care Res 2010;62:1559–68.

25 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.

26 Naredo E, Valor L, De la Torre I *et al*. Ultrasound joint inflammation in rheumatoid arthritis in clinical remission: how many and which joints should be assessed? Arthritis Care Res 2013;65:512–7.

27 Sakellariou G, Scirè CA, Verstappen SM, Montecucco C, Caporali R. In patients with early rheumatoid arthritis, the new ACR/EULAR definition of remission identifies patients with persistent absence of functional disability and suppression of ultrasonographic synovitis. Ann Rheum Dis 2013;72:245–9.

28 Ten Cate DF, Luime JJ, Swen N *et al*. Role of ultrasonography in diagnosing early rheumatoid arthritis and remission of rheumatoid arthritis - a systematic review of the literature. Arthritis Res Ther 2013;15:R4.

29 Balsa A, de Miguel E, Castillo C, Peiteado D, Martin-Mola E. Superiority of SDAI over DAS-28 in assessment of remission in rheumatoid arthritis patients using power Doppler ultrasonography as a gold standard. Rheumatology 2010;49:683–90.

30 van de Stadt LA, Bos WH, Meursinge Reynders M *et al*. The value of ultrasonography in predicting arthritis in autoantibody positive arthralgia patients: a prospective cohort study. Arthritis Res Ther 2010;12:R98.

31 Lee DM, Weinblatt ME. Rheumatoid arthritis. Lancet 2001;358:903–11.

32 Walter MJ, Mohd Din SH, Hazes JM *et al*. Is tightly controlled disease activity possible with online patient-reported outcomes? J Rheumatol 2014;41:640–7.

33 Blanchais A, Berthelot JM, Fontenoy AM, le Goff B, Maugars Y. Weekly home self-assessment of RAPID-4/3 scores in rheumatoid arthritis: a 6-month study in 26 patients. Joint Bone Spine 2010;77:582–7.