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Original article

Ultrasound to identify systemic lupus erythematosus patients with musculoskeletal symptoms who respond best to therapy: the US Evaluation For mUsculoskeletal Lupus longitudinal multicentre study

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Abstract

Objectives. To determine whether SLE patients with inflammatory joint symptoms and US synovitis/tenosyovitis achieve better clinical responses to glucocorticoids compared with patients with normal scans. Secondary objectives included identification of clinical features predicting US synovitis/tenosynovitis.

Methods. In a longitudinal multicentre study, SLE patients with physician-diagnosed inflammatory joint pain received intramuscular methylprednisolone 120 mg once. Clinical assessments, patient-reported outcomes and bilateral hand/wrist USs were collected at 0, 2 and 6 weeks. The primary outcome (determined via internal pilot) was the early morning stiffness visual analogue scale (EMS-VAS) at 2 weeks, adjusted for baseline, comparing patients with positive (greyscale $\geq$2 and/or power Doppler $\geq$1) and negative US. Post hoc analyses excluded FM.

Results. Of 133 patients, 78 had a positive US. Only 53 (68%) of these had one or more swollen joint. Of 66 patients with one or more swollen joint, 20% had a negative US. A positive US was associated with joint swelling, symmetrical small joint distribution and serology. The primary endpoint was not met: in the full analysis set ($N = 133$) there was no difference in baseline-adjusted EMS-VAS at week 2 [−7.7 mm (95% CI −19.0, 3.5); $P = 0.178$]. After excluding 32 patients with FM, response was significantly better in patients with a positive US at baseline [baseline-adjusted EMS-VAS at 2 weeks −12.1 mm (95% CI −22.2, −0.1); $P = 0.049$]. This difference was greater when adjusted for treatment [−12.8 mm (95% CI −22, −3); $P = 0.007$]. BILAG and SLEDAI responses were higher in US-positive patients.

Conclusion. In SLE patients without FM, those with a positive US had a better clinical response to therapy. Imaging-detected synovitis/tenosynovitis may be considered to decide on therapy and enrich clinical trials.

Key words: systemic lupus erythematosus, ultrasound, outcome measures, clinical trials and methods, biomarkers

CLINICAL SCIENCE

Rheumatology key messages

- There is substantial disagreement between clinical examination and ultrasound in SLE patients with inflammatory joint pain.
- Ultrasound-confirmed synovitis is more likely with symmetrical small joint distribution, higher IgG levels and RNP antibodies.
- Patients with ultrasound synovitis are more likely to respond to glucocorticoid therapy, provided fibromyalgia is excluded.

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Introduction

Inflammatory joint disease affects >90% of patients with SLE and is a major determinant of long-term quality of life and disability [1, 2]. Our previous work suggests that this disproportionate impact on quality of life and disability may be due to undertreatment [1, 3]. SLE patients often have less joint swelling than RA or PsA patients.

In the BILAG-2004 index [4], A and B scores for the musculoskeletal domain (indicating active disease needing additional immunosuppression) can only be achieved if joints are swollen. The SELENA and SLEDAI-2K score 'arthritis' if there are at least three or two inflamed joints, respectively [5, 6]. There is scope for interpretation of which signs qualify for this 'inflamed' criterion, but swelling is often sought before scoring this feature in clinical trials and routine practice. Patients who fail to score on these scales invariably fail to qualify for treatment with biologic therapies [7].

Previous US studies have shown that clinical joint swelling underestimates synovitis severity, although a systematic review found several methodological factors leading to uncertain estimates of the rates of US synovitis [8]. We therefore conducted a large cross-sectional study to address these problems and estimated the rates of clinical and US abnormality in SLE patients presenting with inflammatory joint pain: 38% had clinical joint swelling and 35% had neither swelling on clinical examination nor evidence of US synovitis. However, 27% of patients had synovitis only detectable with US. US-only synovitis appeared more clinically significant, being associated with a worse tender joint count, physician visual analogue scale (VAS) and serum IgG level [9].

We hypothesized that SLE patients presenting with inflammatory joint disease would demonstrate a better clinical response to therapy if synovitis was confirmed by US. To test this hypothesis we conducted a prospective, longitudinal, multicentre study: US Evaluation For mUsculoskeletal Lupus (USEFUL). The primary objective was to determine whether patients with US synovitis had better clinical responses to glucocorticoid therapy compared with patients without US synovitis. Other objectives included a comparison of US with the clinical variables at baseline to understand which are most useful when evaluating SLE patients.

Methods

The study was approved by the North West Greater Manchester Central Research Ethics Committee (reference 16/NW/0060). All participants gave written consent. Full details about the methodology can be found in the supplementary files, available at *Rheumatology* online.

Patients and design

A prospective longitudinal UK multicentre cohort study was conducted in adults with SLE (meeting the revised ACR/SLICC 2012 criteria) [10], deemed by their physicians to have inflammatory joint pain requiring glucocorticoid therapy (swollen joints or specific BILAG-2004/SLEDAI-2K scores were not required). Stable doses of immunosuppressants and prednisolone up to 5 mg were permitted. All patients recruited received one injection of i.m. methylprednisolone acetate 120 mg at week 0 and had clinical and US assessments at weeks 0, 2 and 6 (Fig. 1).

Data and outcomes

Physician assessments included demographics, BILAG-2004, SLEDAI-2K, joint counts and global and musculoskeletal VASs, inflammatory markers and lupus serology and recorded features of inflammation, FM, OA, early morning stiffness (EMS) and prior response to therapy. Patient-reported outcomes (LupusQoL, L-QoL, EMS min, EMS severity VAS, Likert scale for improvement in symptoms and patient-acceptable symptom state) were collected [11]. US was used to assess greyscale (GS), power Doppler (PD) and tenosynovitis according to OMERACT criteria [12, 13] in both hands and wrists. US was deemed 'positive' if there was synovitis GS $\geq$2 and/or PD $\geq$1 or tenosynovitis GS $\geq$1 and/or PD $\geq$1. Physicians, ultrasonographers and patients were all blinded to each other's assessments.

Details of US assessments are given in the supplementary methods, available at *Rheumatology* online. All sonographers attended a training event at baseline. The same four SLE patients were scored by each sonographer and proportions of agreement were calculated. These were GS $\kappa = 0.69$, PD $\kappa = 0.98$ and erosions $\kappa = 0.85$.

Internal pilot

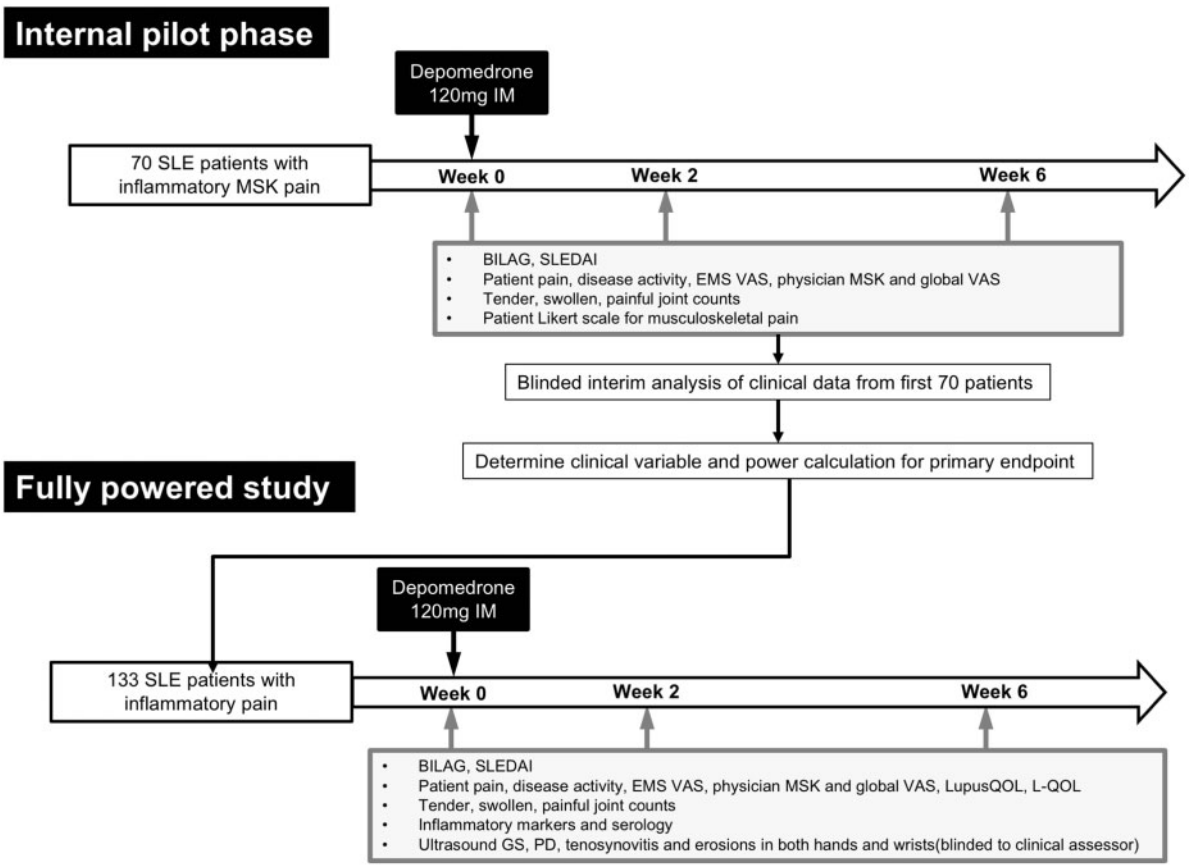
There were limited existing data on the most appropriate clinical measure of improvement [14]. We therefore conducted an internal pilot analysis of the first 70 patients (clinical data only). In this analysis we evaluated various clinical variables with the best association with patient-reported improvement in symptoms based on a Likert scale. This determined power calculations for the full study and how many further patients should be recruited.

Change in the EMS severity based on VAS (EMS-VAS, mm) at week 2 from baseline (week 0) was selected as the primary outcome (see supplementary material, Table S1, available at *Rheumatology* online). In other inflammatory arthritis, this scale is better at discriminating high and low disease activity and more responsive than EMS duration [15, 16]. We considered a difference of 20% compared with US-inactive to be the minimum difference of interest.

Statistical analyses

At baseline, descriptive data were presented on levels of agreement between US activity and joint swelling, BILAG-2004 and SLEDAI-2K musculoskeletal grades. In

Fig. 1 Study schematic



All patients followed the same treatment and assessment protocol. Clinical data shown from the first 70 patients was used to decide the primary clinical response variable and thereby calculate statistical power. Additional patients were then recruited to this target. US data was not unblinded until all patients were recruited.

order to understand which symptoms, signs and routine laboratory tests were associated with US activity at baseline, we compared physician-reported features using Pearson's chi-squared for categorical variables or *t*-tests for continuous variables. These variables were also compared between SLEDAI-2K and BILAG-2004 categories.

The primary outcome was compared between patients with definite synovitis (US-active) and low-level/no synovitis (US-inactive) at week 2 using quantile (median) regression, with cluster-robust standard errors employed to account for clustering of patients within centres. The primary analysis model adjusted for EMS-VAS at baseline; the unadjusted difference is presented for comparison.

In a planned sensitivity analysis, concomitant immunosuppressant and oral glucocorticoid (both recorded yes/no) were also added to the model. In a further planned sensitivity analysis, the above approaches were repeated in the per protocol set. Because there were a substantial number of patients with FM, which may confound symptom responses, additional unplanned sensitivity analyses were performed in patients deemed not to have FM at baseline [17]. The same analytical approach was then used to compare the other clinical variables at 2 and 6 weeks according to baseline US activity, controlling for baseline values of the outcome in each case. Because BILAG-2004, SLEDAI-2K and LupusQoL scores evaluate symptoms over the past month, we analysed these endpoints at week 6 only, using unadjusted changes from baseline between groups. An additional sensitivity analysis compared unadjusted changes from baseline between groups for all other clinical variables. This was added for comparison because baseline-adjusted analyses can potentially be biased when comparing non-randomized groups.

Detailed summary tables have been provided in the supplementary material (available at *Rheumatology* online). Requests for full data can be made via the corresponding author.

Results

A total of 133 SLE patients were recruited and 121 completed all visits (see supplementary data, available at *Rheumatology* online). Baseline characteristics are summarized in Table 1.

Association of clinical features and US synovitis status

Active arthritis on US examination ('active US') was more likely if the clinical presentation included joint swelling, a symmetrical small joint distribution and active serology. Physician report of EMS, a common symptom used to identify inflammatory arthritis in routine practice, was not associated with US findings. There was also no association between active US findings and other SLE features nor with the physician's impression of their prior response to therapy (Table 1).

We found no association between ethnicity and US features, although low numbers of non-white, non-South Asian patients limited this analysis. Although there were only seven men in this study, all of them had US synovitis.

There was substantial disagreement between US and conventional clinical definitions of disease activity (Table 2).

We compared swollen joint counts in all joints with US scans in the hands and wrists (a typical US examination in routine practice, confirmed as clinically relevant in our previous study and systematic review [3, 9]; Table 2A). Thirteen of 66 (20%) patients with clinical joint swelling did not have active US. Twenty-five of 78 (32%) patients with active US findings did not have joint swelling.

Table 1 Clinical characteristics and US findings at baseline

Characteristics	All patients ($N = 133$)	US activity at baseline		P-value
		Inactive ($n = 55$)	Active ($n = 78$)	
Patient disposition				
Completed all study visits per protocol	121/133 (91)	52/55 (95)	69/78 (88)	N/A
Demographics				
Age, years, mean (S.D.)	46.1 (13.5)	47.9 (12.3)	44.8 (14.3)	0.190
Disease duration, years, mean (S.D.)	9.3 (8.9)	10.2 (9.8)	8.7 (8.1)	0.352
Male, *n/N* (%)	7/133 (5)	0/55 0	7/78 (9)	0.022
Therapy, *n/N* (%)				
NSAID or COX-2 inhibitor	27/133 (20)	12/55 (22)	15/78 (19)	0.421
Prednisolone (maximum 5 mg/day)	31/133 (23)	12/55 (22)	19/78 (24)	0.733
Antimalarials	89/133 (67)	38/55 (69)	51/78 (65)	0.456
Immunosuppressant (MMF, MTX, AZA)	40/133 (30)	17/55 (31)	23/78 (29)	0.125
Biologic	0 (0)	0 (0)	0 (0)	NA
Inflammatory features (physician rated), *n/N* (%)				
EMS	115/133 (86)	47/55 (85)	68/78 (87)	0.775
Distribution	113/133 (85)	43/55 (78)	70/78 (90)	0.066
Symmetry	121/133 (91)	46/55 (84)	75/78 (96)	0.013
Swelling	83/132 (63)	28/54 (52)	55/78 (71)	0.029
Serology	87/130 (67)	31/53 (58)	56/77 (73)	0.090
Other lupus features	66/133 (50)	26/55 (47)	40/78 (51)	0.649
Prior therapy response	87/133 (65)	39/55 (71)	48/78 (62)	0.263
Jaccoud arthropathy	6/133 (5)	2/55 (4)	4/78 (5)	0.683
Deformity	6/133 (5)	2/55 (4)	4/78 (5)	0.683
Other lupus inflammatory	3/133 (2)	2/55 (4)	1/78 (1)	0.368
FM features, *n/N* (%)				
Overall opinion of FM	32/133 (24)	14/55 (25)	18/78 (23)	0.752
Fatigue	30/132 (23)	12/55 (22)	18/77 (23)	0.833
Waking unrefreshed	24/132 (18)	9/55 (16)	15/77 (19)	0.647
Cognitive symptoms	20/132 (15)	7/55 (13)	13/77 (17)	0.511
Other somatic symptoms	15/132 (11)	8/55 (15)	7/77 (9)	0.330
Associated disorders (e.g. IBS)	5/133 (4)	4/55 (7)	1/78 (1)	0.074
OA features, *n/N* (%)				
Overall opinion of OA	36/133 (27)	16/55 (29)	20/78 (26)	0.659
Hard tissue enlargement >1 joint	25/133(19)	13/54 (24)	12/77 (16)	0.224
Hard tissue enlargement DIPs	22/133(17)	11/55 (20)	11/77 (14)	0.385
Deformities consistent with OA	14/133(11)	6/55 (11)	8/77 (10)	0.924
Previous radiographic evidence	10/133(8)	3/54 (6)	7/74 (9)	0.416
Other OA features present	5/133(4)	1/54 (2)	4/78 (5)	0.332
Other musculoskeletal disorders, *n/N* (%)				
Any other MSK disorder	9/133 (7)	4/55	5/78	N/A

All data are chi-squared tests except age and disease duration, which are *t*-tests.

Table 2 Agreement between clinical and US assessments at baseline

(A) Clinical joint swelling (any joint) *vs* US synovitis (hands/wrists)				
	≥1 swollen joints, *n* (%)	0 swollen joints, *n* (%)	Total, *N* (%)	
US inactive (<GS2 and <PD1 all joints)	13 (10)	42 (32)	55 (41)	
US active (≥GS2 or ≥PD1 in ≥1 joint)	53 (40)	25 (19)	78 (59)	
Total	66 (50)	67 (50)	133	
(B) Clinical joint swelling (hands/wrists) *vs* US synovitis (hands/wrists)				
	≥1 swollen joints, *n* (%)	0 swollen joints, *n* (%)	Total, *N* (%)	
US inactive (<GS2 and <PD1 all joints)	6 (4)	49 (37)	55 (41)	
US active (≥GS2 or ≥PD1 in ≥1 joint)	54 (41)	24 (18)	78 (59)	
Total	60 (45)	73 (55)	133	
(C) SLEDAI-2K arthritis *vs* US synovitis				
	Arthritis, yes, *n* (%)	Arthritis, no, *n* (%)	Total, *N* (%)	
US inactive (<GS2 and <PD1 all joints)	19 (14)	36 (27)	55 (41)	
US active (≥GS2 or ≥PD1 in ≥1 joint)	59 (44)	19 (14)	78 (59)	
Total	78 (59)	55 (41)	133	
(D) BILAG-2004 musculoskeletal domain *vs* US synovitis				
	BILAG A, *n* (%)	BILAG B, *n* (%)	BILAG C, *n* (%)	Total, *N* (%)
US inactive (<GS2 and <PD1 all joints)	3 (2)	10 (7)	42 (32)	55 (41)
US active (≥GS2 or ≥PD1 in ≥1 joint)	11 (8)	42 (32)	25 (19)	78 (59)
Total	14 (11)	52 (39)	67 (50)	133

To evaluate the same set of joints, we evaluated clinical joint swelling in the 22 joints included in the US scan (Table 2B). This reduced the number of swollen joints not confirmed as having active US, but clinical examination remained insensitive.

Nineteen of 78 (24%) patients scored for arthritis on the SLEDAI-2K did not have active US. Also, 19 of 78 (24%) patients with active US were not scored for arthritis on the SLEDAI-2K.

Thirteen of 66 (20%) patients who scored A or B for the musculoskeletal BILAG-2004 did not have active US. Twenty-five of 78 (32%) patients with active US did not score A or B on the musculoskeletal domain of the BILAG-2004. BILAG-2004 includes a 'C' grade representing inflammatory pain. All patients in the study met this grade since it matched the eligibility criteria. Notably, however, the majority of patients with BILAG-2004 C [42/67 (63%)] did not actually have active US findings. It must be noted that BILAG-2004 and SLEDAI-2K scores could also be influenced by joints that were not included in the US examination. Full details of the BILAG and SLEDAI associations are shown in Supplementary Tables S2 and S3, available at *Rheumatology* online.

Patients with active US had statistically significant worse symptoms and signs of lupus arthritis (Supplementary Table S4, available at *Rheumatology* online) and higher ESR and total IgG levels (Supplementary Table S4, available at *Rheumatology* online). There was a trend towards association between active US and anti-Sm and anti-RNP antibodies (Supplementary Table S5, available at *Rheumatology* online). Twenty of 26 (77%) Sm-positive patients had active US, compared with 58 of 107 (55%) of Sm-negative patients ($P = 0.035$). Similarly, 17 of 22 (77%) RNP-positive patients had active US compared with 61 of 111 (55%) RNP-negative patients ($P = 0.052$).

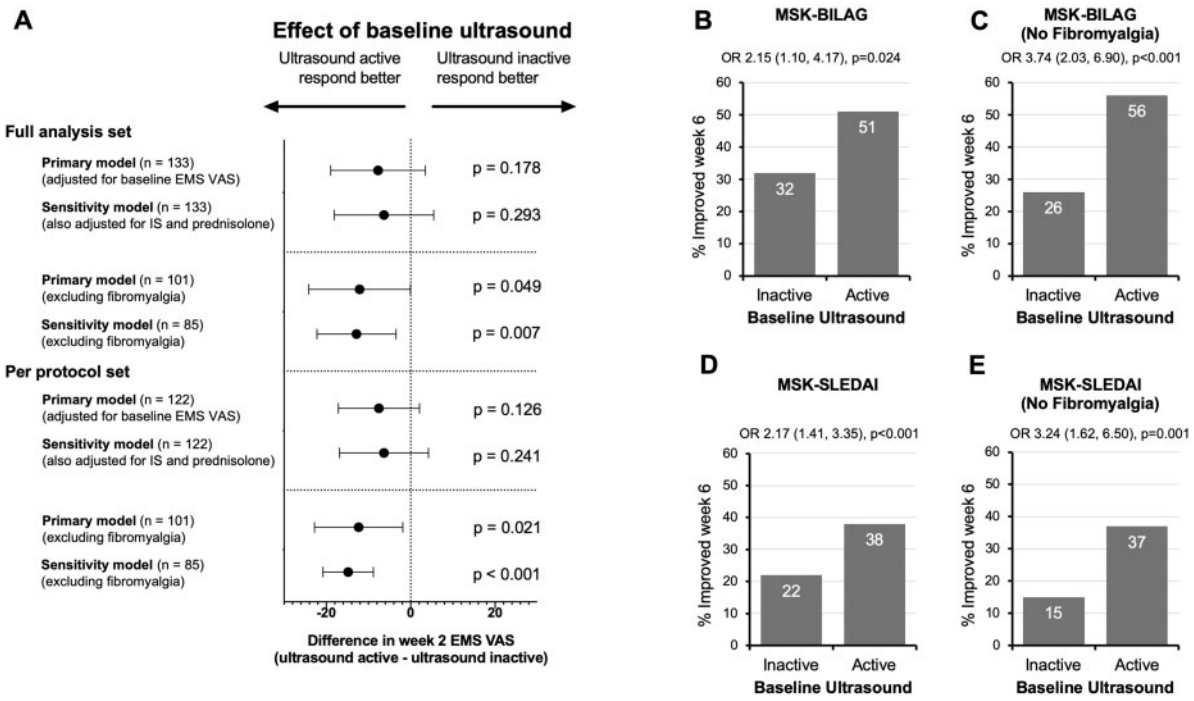
Quality of life scores as measured by the LupusQoL were similar in patients with active and inactive US (Supplementary Table S6, available at *Rheumatology* online). Exclusion of patients with FM did not change this result (data not shown). All patients in this study had active joint symptoms requiring increased therapy at baseline, therefore they would be expected to rate their quality of life as being affected even if this was not due to active inflammation.

Primary outcome

Results from the primary outcome analysis are shown in Fig. 2, with full statistical data in Supplementary Table S7, available at *Rheumatology* online.

In the full analysis set ($N = 133$) the mean baseline EMS-VAS was 57.7 mm (S.D. 4.1) in US-inactive patients and 58.6 mm (S.D. 5.9) in US-active patients. The primary efficacy analysis showed no clinically or statistically significant difference between these groups [baseline-adjusted difference −7.7 mm (95% CI −19.0, 3.5), $P = 0.178$]. The planned sensitivity analysis, which was also adjusted for immunosuppressant and oral glucocorticoid use, did not substantially affect this result

FIG. 2 Primary endpoint: clinical response according to baseline US



(**A**) Primary efficacy variable (EMS-VAS at week 2) according to baseline US status. Vertical dotted line indicates degree of improvement in patients with active US at baseline was the same as patients with inactive US at baseline. Values to the left of this line show patients with active US at baseline had better response to therapy. Primary analysis model was adjusted for the baseline EMS-VAS only. Sensitivity analysis was also adjusted for use of NSAIDs, prednisolone and immunosuppressants. Analyses were also repeated for per-protocol population and exclusion of patients with FM. (**B–E**) Improvement in musculoskeletal components of the BILAG and SLEDAI according to baseline US status. (**B**) Percentage of patients with improvement in the musculoskeletal component of the BILAG. Improvement was defined as a reduction by at least one grade (i.e. A to B, B to C or C to D). (**C**) Same analyses excluding patients with FM. (**D**) Percentage of patients with improvement in the musculoskeletal items on the SLEDAI (arthritis and myositis, although no patient in this study was scored for myositis). Improvement was therefore defined as resolution of arthritis (reduction from 4 points to 0 points). (**E**) Same analysis excluding patients with FM.

[−6.3 mm (95% CI −18.1, 5.5), $P = 0.293$]. Results in the per-protocol set ($n = 122$) were broadly similar.

Post hoc analyses in patients without concurrent FM

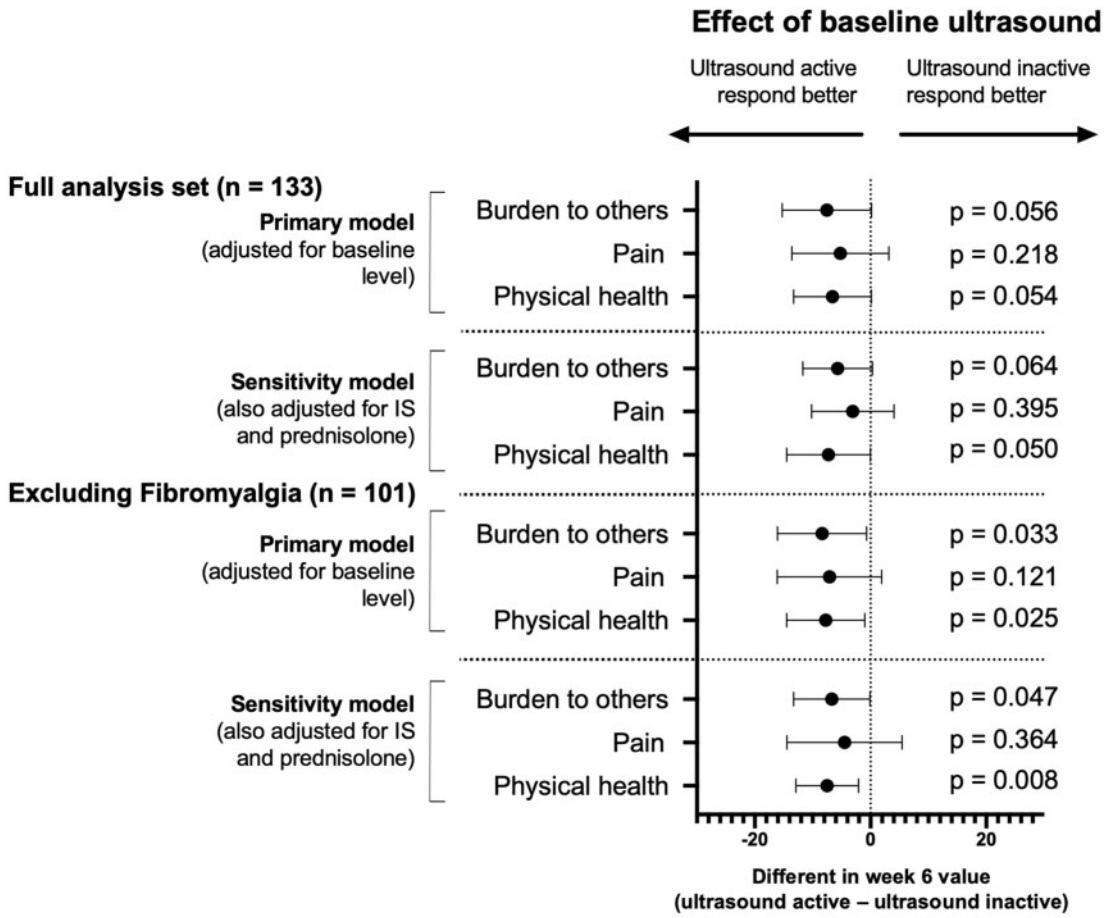
Thirty-two patients had a clinician diagnosis of FM at baseline (which generally does not respond to glucocorticoids [18]). In patients without FM ($n = 101$), the mean baseline EMS-VAS was 56.3 mm (S.D. 4.5) in US-inactive patients and 51.4 mm (S.D. 6.0) in US-active patients. An unplanned sensitivity analysis, repeating the baseline-adjusted primary analysis in this group, showed a significantly lower EMS-VAS at 2 weeks in patients with US synovitis at baseline [US-active − US-inactive −12.1 (95% CI −24.1, −0.1), $P = 0.049$]. This difference was greater in the treatment-adjusted sensitivity analysis [−12.8 (95% CI −22.2, −3.44), $P = 0.007$] and in the per-protocol treatment-adjusted sensitivity analysis [−14.8 (95% CI −20.8, −8.8), $P < 0.001$].

Other clinical endpoints

The BILAG-2004 and SLEDAI scores (which include manifestations from the previous 30 days) at 6 weeks according to baseline US activity are shown in Fig. 3 and Supplementary Tables S8–S9, available at *Rheumatology* online. In the full analysis set ($N = 133$) the musculoskeletal BILAG improved (reduced by at least one grade, i.e. A to B, B to C or C to D) in 32% of US-inactive patients and 51% of US-active patients [odds ratio (OR) 2.15 (95% CI 1.10, 4.17), $P = 0.024$]. The SLEDAI-2K arthritis criterion improved (resolution of arthritis criterion) in 22% of US-inactive patients and 38% of US-active patients [OR 2.17 (95% CI 1.41, 3.35), $P < 0.001$].

The improved responses in US-active patients were again more evident in patients without FM ($n = 101$). The musculoskeletal BILAG-2004 improved in 26% of US-inactive patients and 56% of US-active patients [OR

Fig. 3 Change in the three most relevant domains of LupusQoL according to baseline US status



The vertical dotted line indicates that the degree of improvement in patients with active US at baseline was the same as for patients with inactive US at baseline. Values to the left of this line indicate a better response in patients with active US at baseline. The primary analysis model was adjusted for baseline values. The sensitivity analysis was also adjusted for use of NSAIDs, prednisolone and immunosuppressants. These analyses were repeated excluding patients with FM.

3.74 (95% CI 2.03, 6.90), $P < 0.001$]. The musculoskeletal SLEDAI-2K improved in 15% of US-inactive patients and 37% of US-active patients [OR 3.24 (95% CI 1.62, 6.50), $P = 0.001$].

Data for other clinical outcomes at 2 and 6 weeks are shown in Supplementary Tables S10 and S11, available at *Rheumatology* online.

Quality of life

Three domains of the LupusQoL also showed greater improvement in US-active patients (Table 3). Significantly greater improvement was seen in US-active patients for the physical health, burden to others and body image domains. The size of these effects differed slightly between the 2 and 6 week time points and between the primary and sensitivity analysis. The three domains that appear most relevant to musculoskeletal symptoms are shown in Fig. 3. Although the direction of the numerical differences favoured US-active patients in all cases, improvement in pain was not significantly greater for US-active patients. Patients without FM were significantly more likely to achieve a patient-acceptable symptom state at week 2 if US was active at baseline [38% *vs* 32%; baseline-adjusted primary OR 1.75 (95% CI 1.22, 2.49), $P = 0.002$].

Sensitivity analyses for secondary clinical endpoints

Sensitivity analyses comparing unadjusted changes from baseline between groups (Supplementary Tables S8 and 9 and S12 and 13, available at *Rheumatology* online) generally indicated the same direction of effect for primary and secondary outcomes compared with the main analysis. When patients with FM were excluded, both analysis methods agreed the response was greater in those with baseline US-active for EMS-VAS and the LupusQoL domain 'burden to others' as well as the

Table 3 LupusQoL improvements according to baseline US status

Variable	2 weeks				6 weeks			
	Adjusted primary		Adjusted sensitivity		Adjusted primary		Adjusted sensitivity	
	Difference (95% CI)	*P*-value	Difference (95% CI)	*P*-value	Difference (95% CI)	*P*-value	Difference (95% CI)	*P*-value
All patients ($N = 133$)								
Physical health	−0.45 (−3.93, 3.03)	0.799	−0.57 (−4.10, 2.95)	0.749	−6.57 (−13.27, 0.13)	0.054	−7.25 (−14.48, −0.01)	0.050
Pain	0.65 (−3.84, 5.15)	0.776	1.28 (−3.74, 6.30)	0.616	−5.22 (−13.60, 3.16)	0.218	−3.07 (−10.18, 4.04)	0.395
Planning	−0.17 (−5.35, 5.00)	0.948	−0.14 (−4.58, 4.31)	0.951	−1.75 (−9.93, 6.43)	0.673	−2.22 (−9.63, 5.20)	0.554
Burden to others	−8.33 (−18.45, 1.78)	0.106	−8.33 (−16.68, 0.01)	0.050	−7.54 (−15.27, 0.18)	0.056	−5.67 (−11.68, 0.34)	0.064
Emotional health	0.05 (−3.30, 3.39)	0.978	0.18 (−3.33, 3.68)	0.922	−3.61 (−9.09, 1.88)	0.195	−2.60 (−8.44, 3.24)	0.379
Body image	−0.51 (−6.57, 5.54)	0.867	−0.71 (−7.01, 5.58)	0.823	−8.83 (−16.65, −1.01)	0.027	−7.95 (−15.64, −0.26)	0.043
Fatigue	1.42 (−3.41, 6.26)	0.562	0.86 (−3.04, 4.75)	0.665	−2.56 (−8.15, 3.03)	0.366	−2.78 (−7.95, 2.40)	0.291
No FM ($n = 101$)								
Physical health	−1.37 (−5.58, 2.85)	0.514	−0.93 (−5.33, 3.47)	0.671	−7.74 (−14.47, −1.00)	0.025	−7.49 (−12.90, −2.07)	0.008
Pain	5.24 (−2.32, 12.79)	0.167	3.61 (−2.22, 9.43)	0.221	−7.09 (−16.12, 1.93)	0.121	−4.49 (−14.43, 5.44)	0.364
Planning	−8.33 (−13.57, −3.09)	0.002	−7.85 (−12.96, − 0.75)	0.003	−1.84 (−10.70, 7.02)	0.682	−1.71 (−9.61, 6.19)	0.670
Burden to others	1.19 (−4.33, 6.70)	0.671	1.57 (−3.64, 6.78)	0.551	−8.36 (−16.05, −0.67)	0.033	−6.68 (−13.28, −0.08)	0.047
Emotional health	0.69 (−6.38, 7.75)	0.846	−1.10 (−10.00, 7.81)	0.805	−2.96 (−9.39, 3.47)	0.366	−0.41 (−6.38, 5.56)	0.893
Body image	1.89 (−3.49, 7.27)	0.486	1.25 (−3.61, 6.10)	0.613	−9.02 (−20.08, 2.03)	0.108	−7.72 (−16.46, 1.02)	0.083
Fatigue	−0.70 (−2.28, 0.89)	0.386	−0.50 (−1.72, 0.72)	0.414	−4.29 (−12.27, 3.68)	0.289	−3.96 (−12.57, 4.64)	0.364

Adjusted primary analysis is difference between medians of US-active and US-inactive patients adjusted for baseline value of the outcome variable. Adjusted sensitivity analysis is also adjusted for immunosuppressant and oral glucocorticoid use. Negative values indicate a greater improvement in patients with active US at baseline. Due to failure of the analysis models to converge, possibly due to the large number of patients who said the domain was not applicable, data have not been provided for the LupusQoL domain of Intimate relationship.

musculoskeletal SLEDAI at week 6. However, for physician global and musculoskeletal VAS, the two analysis methods disagreed over the direction of effect.

Discussion

This study reports the most comprehensive clinical and US data to define which SLE patients with inflammatory joint symptoms are most responsive to glucocorticoid therapy. We demonstrated disagreement between US synovitis and features commonly used to guide immunosuppressive therapy: joint swelling or completion of the BILAG-2004 and SLEDAI-2K indices. Although the primary outcome was not met, this may be due to a large proportion of patients having FM. When they were excluded, we found a greater clinical response to glucocorticoids in participants with US synovitis at baseline in several clinical and patient-reported endpoints. These results have importance for the selection of patients for therapy in routine practice, clinical trials in SLE and the utility of US in this disease.

Despite the availability of licensed immunosuppressive therapies, musculoskeletal symptoms continue to have a major negative impact on quality of life in patients with SLE [1]. Our results suggest that patients with no swelling but positive US synovitis may benefit from escalating immunosuppressive therapy. Conversely, a negative US may indicate that it is safe to continue to taper glucocorticoids, which is important given the toxicity of long-term glucocorticoids.

If US is not available, the most useful signs indicating active joint inflammation are distribution, swelling and symmetry. Some other symptoms (EMS, other lupus features, prior therapy response) commonly used in practice may not be helpful. Consistent with our previous work, the level of IgG may be useful in identifying active lupus arthritis [9]. Sm and RNP antibodies are also helpful.

Despite the negative impact of FM on responsiveness, it is important to note that we confirmed US-proven inflammation in patients who also had this condition. There may be longer-term benefits of treatment in these patients. The number of patients diagnosed with FM in our study was high compared with unselected SLE cohorts [19], which is not surprising since the main inclusion criterion was pain.

Accurate scoring of US using OMERACT criteria was an important feature of this study. We previously highlighted the need for standardization of US-reporting in SLE studies in our systematic literature review [3]. We then validated the OMERACT scoring in SLE in two other studies. In a cross-sectional study we showed that OMERACT-scored US had face validity and concurrent validity (association with BILAG-2004 and SLEDAI scores) [8, 20, 21]. In a longitudinal study we showed that OMERACT-scored synovitis was responsive after 120 mg methylprednisolone acetate [14]. The data from the present study fulfil another criterion in the OMERACT filter for validation of US as an outcome measure in SLE [22]. For the first time we demonstrate that it has OMERACT-scored US has predictive validity for therapy response.

Many clinical trials of new therapies in SLE failed to demonstrate any benefit even though there were reasons to believe these therapies should have been effective [23–32]. Our results help to define a target population to enrol or enrich clinical trials with confirmed synovitis and consequent greater response to therapy. Usually eligibility is based on clinical examination for swollen joints. We showed that 20% of such patients do not have active synovitis. Further, we showed that although patients with FM may have confirmed active synovitis, this comorbidity confounds assessment of response. Hence our results suggest that the use of US (or other imaging) synovitis as an inclusion criterion and exclusion of patients with significant FM that would affect disease activity assessment may result in larger effect sizes in clinical trials of new therapies.

The main limitation of our study is the open-label design; this limits understanding of how these patient selection criteria would function in a randomized controlled trial (RCT). Although US is a more sensitive test of inflammation than clinical examination, there could be immune-mediated causes of pain that are not well captured by this tool, such as bone oedema [33]. The FM analysis was post hoc. However, it is logical, in line with clinical practice, since FM is a well-known comorbidity that influences response to therapy [34]. Since our study began, the presence and potential significance of enthesitis has been reported in SLE patients [35]. We did not assess this because we based our US reporting on a systematic review of the published literature at the time. Lastly, a possible explanation for the discrepancy between US and BILAG-2004 and SLEDAI scores was that US was only done on hands while the BILAG and SLEDAI take into account all joints. The data in Table 2 provide an indication of this effect. In our previous study we analysed agreement between US and clinical examination and found this was greatest in the small joints of the hand. It is therefore possible that the BILAG and SLEDAI could be modified in the future to include the clinical features that are best validated by US. For example, the definition of synovitis for BILAG A or B could specify joints in the hands and wrists and the definition of arthralgia for BILAG C could specify a symmetrical small joint distribution. BILAG-2004 and SLEDAI are also dependent on the training of the assessor. Our study was conducted in BILAG member centres. In a less-specialist setting, these instruments may have performed worse compared with US.

Future research should evaluate the use of US in randomized trials to determine whether it can measure and stratify differences between treatment groups. Such an RCT is in progress [Rituximab Objective Outcome Measures Trial in SLE (NCT03054259)]. Future work will define clinical outcome measures for musculoskeletal disease activity that better match the results obtained from US.

In conclusion, our data suggest that US synovitis is clinically important and responsive to therapy in SLE.

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Data availability statement

None declared.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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