USEFUL I: Musculoskeletal ultrasound to identify patients with lupus arthritis with better response to therapy

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Background: In SLE**,** musculoskeletal manifestations (MSK-SLE) have a major impact on quality of life and disability and are one of the commonest reasons for biologic therapy or inclusion in trials. However, they are hard to assess as patients with MSK-SLE have fewer clinical signs than in RA and PsA. We previously showed that 27% of patients with MSK-SLE pain had synovitis detectable only with ultrasound and that assessment of joint swelling lacks sensitivity, specificity and responsiveness.[1-3] It is unknown whether ultrasound findings should determine immunosuppressive therapy.

Objectives: To determine i) clinical features predicting ultrasound synovitis; ii) whether patients with ultrasound synovitis respond better to therapy (than those with normal ultrasound); and iii) responsiveness of a range of existing and candidate outcome measures in MSK-SLE.

Method: USEFUL was a multicentre longitudinal study. SLE patients were recruited if the referring physician deemed they had inflammatory pain warranting treatment. Stable doses of prednisolone (≤5mg/day), antimalarials or immunosuppressants were allowed. Swollen joints were not required. At baseline, physicians recorded the features that led them to diagnose inflammatory pain (e.g. morning stiffness) as well as features of concurrent fibromyalgia and osteoarthritis. Participants were treated with depomedrone 120mg IM then assessed at 0, 2 and 6 weeks for 66/68 swollen and tender joint counts, BILAG-2004 and SLEDAI-2K, physician global and MSK VAS, inflammatory markers, patient VAS for pain and disease activity, HAQ-DI and LupusQoL, and MSK VAS, ultrasound of hands and wrists (blinded to the patient and clinical assessor).

Blinded analysis of an internal pilot (first 70 patients) determined the primary clinical measure of improvement and statistical power. EMS VAS at week 2 showed the best correlation with patient Likert pain response scale and sample size n = 130. We compared changes in the EMS VAS at 2 weeks (adjusted for the baseline value) between patients with ultrasound synovitis at baseline versus those with normal ultrasound. Sensitivity analyses also adjusted for prednisolone and immunosuppressants.

Results: 133 patients were recruited and 122 completed all visits to protocol. Mean age was 46.1, disease duration 9.3 years, female 126/133 (95%). There was significant disagreement between clinical examination and ultrasound. 78/133 had ultrasound synovitis, but only 68% of these had >=1 swollen joint. Of 66/133 patients with >= 1 swollen joint, 20% had normal ultrasound. Ultrasound-synovitis was more likely if the clinical presentation included joint swelling, a symmetrical small joint distribution and active serology. However, physician's documentation of EMS, other lupus features or prior response to therapy were not associated with ultrasound synovitis. The presence of fibromyalgia or osteoarthritis did not reduce the probability of ultrasound synovitis.

In the full analysis set (n=133) there was no difference in EMS VAS at 2 weeks according to ultrasound synovial status as baseline (difference -8mm, 95% CI -19, 4mm, p=0.178). 32 patients had fibromyalgia. After excluding these patients, we found a better clinical response to depomedrone in patients with ultrasound synovitis at baseline, a difference that was both statistically and clinically significant (baseline-adjusted EMS VAS at 2 weeks -12mm, 95% CI -24, 0mm, p=0.049). The improved response in patients with ultrasound synovitis was greater in the treatment-adjusted sensitivity analysis (-12.8 (95% CI -22, -3mm), p=0.007) and the per-protocol adjusted sensitivity analysis (-14.8mm (95% CI -20.8, -8.8mm), p<0.001). This was supported by higher rates of improvement in MSK components of the BILAG (56% vs. 26%, p=0.09) and SLEDAI (37% vs. 15%, p=0.03).

Conclusion: A substantial proportion of SLE patients with musculoskeletal pain had ultrasound-confirmed synovitis without swollen joints. In others, clinical joint swelling was not confirmed on ultrasound. In MSK-SLE, morning stiffness is not a reliable guide to the presence of ultrasound synovitis, but distribution, symmetry, and serology may help to identify true inflammatory disease. Ultrasound-synovitis was independent of features of fibromyalgia and osteoarthritis. However, fibromyalgia confounded assessment of response. Patients with ultrasound synovitis but without fibromyalgia had a better clinical response to glucocorticoids than if ultrasound was normal.

Ultrasound should be used to select MSK-SLE patients for therapy and clinical trials, especially when there are inflammatory symptoms without swollen joints. Future analysis of this dataset will determine the best clinical criteria to assess disease activity in musculoskeletal SLE, and develop novel trial outcome measures. These will allow design of better clinical trials for new therapies.

References

1. Zayat AS, Md Yusof MY, Wakefield RJ, Conaghan PG, Emery P, Vital EM. The role of ultrasound in assessing musculoskeletal symptoms of systemic lupus erythematosus: a systematic literature review. Rheumatology (Oxford). 2016 Mar; 55(3):485-494.
2. Zayat AS, Mahmoud K, Md Yusof MY, Mukherjee S, D'Agostino MA, Hensor EMA, et al. Defining inflammatory musculoskeletal manifestations in systemic lupus erythematosus. Rheumatology (Oxford). 2019 Feb 1; 58(2):304-312.
3. Mahmoud K, Zayat AS, Yusof Y, Hensor E, Conaghan PG, Emery P, et al. Responsiveness of clinical and ultrasound outcome measures in musculoskeletal systemic lupus erythematosus. Rheumatology (Oxford). 2019 Jan 3.