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How are rheumatologists managing anti-CCP positive patients without arthritis?

Kulveer Mankia DM, MRCP[1,2], Christopher Briggs MBBS[3], Paul Emery MD, FRCP[1,2]

1. Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, UK
2. NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK
3. Leeds Teaching Hospitals NHS Trust, Leeds, UK

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Corresponding author:

Dr Kulveer Mankia, Academic Clinical Lecturer in Rheumatology, Leeds Institute of Rheumatic and Musculoskeletal Medicine, Chapel Allerton Hospital, Chapeltown Road, Leeds, LS7 4SA

k.s.mankia@leeds.ac.uk

Tel: +44 0113 3924496

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Sir,

Early referral and initiation of disease-modifying anti-rheumatic drugs (DMARDs) is associated with better outcomes for rheumatoid arthritis (RA) patients[1, 2]. In the UK, general practitioners (GPs) are advised to refer patients with suspected RA urgently[3] and rheumatology departments are rewarded for timely management of these patients[4].

Although a positive step, a corollary of this is rheumatologists are now seeing patients earlier in the natural history of RA, e.g. patients with autoantibodies (especially anti-CCP) and symptoms but no clinical synovitis, who are 'at-risk' of developing RA. This presents a clinical problem but also a significant opportunity. There is no evidence for the management of these (often symptomatic) at-risk individuals, but it is possible that the right intervention in this phase may prevent clinical arthritis [5, 6]. This hypothesis is being explored in clinical trials, e.g. rituximab delayed, but did not prevent, arthritis onset in at-risk individuals [7]. We were interested to know, in the absence of guidelines, how such 'at-risk' individuals are managed by UK rheumatologists. We were specifically interested in the use of imaging and hypothesised that rheumatologists use imaging to guide their management.

We conducted a survey by circulating anonymous questionnaires at a national meeting for clinical rheumatologists focused on new developments in rheumatology (Revolutions in Rheumatology 2018, London, UK) and at regional general rheumatology meetings in Yorkshire, UK. Questionnaires were returned from 47 consultant rheumatologists working in 39 different UK hospitals (excluding Leeds) in the UK.

44/47 (94%) rheumatologists reported that they are referred anti-CCP positive (CCP+) patients who have musculoskeletal (MSK) symptoms but no clinical synovitis in their routine

clinical practice. Of these, 32/44 (73%) were referred >5 patients per year. In CCP+ patients with 'inflammatory symptoms' but no clinical synovitis, 36/44 (82%) said they would request an ultrasound (US) scan to help guide management. 2/44 (5%) would request an MRI scan. All respondents said they would follow up these patients regularly and 5/44 (11%) would consider a clinical trial. In CCP+ patients with 'non-inflammatory symptoms' and no clinical synovitis, 12/44 (27%) would discharge back to primary care, whereas 18/44 (41%) would request an US scan and 13/44 (30%) would observe in clinic.

Rheumatologists were then asked 'do you use imaging to help guide your management of anti-CCP positive patients without clinical synovitis?'. The vast majority, 40/44 (91%), reported they used imaging, with most (37/40, 93%) using US. In patients where power Doppler (PD) signal is present on US in at least one joint, the majority of respondents (27/37, 73%) would start treatment, usually a DMARD [corticosteroid alone, 6/27 (22%); methotrexate (MTX), 8/27 (30%); hydroxychloroquine (HCQ), 11/27 (41%); either MTX or HCQ, 2/27 (7%)]. 6/37 (15%) respondents would simply treat according to their standard RA pathway. The remainder would observe without treatment or consider a clinical trial.

In patients with US tenosynovitis but no US synovitis, 27/37 (73%) would treat; the majority with corticosteroids alone (13/27, 48%) compared to DMARDs [MTX, 3/27 (11%); HCQ, 10/27 (37%)]. In patients with no US synovitis or US tenosynovitis, 23/37 (62%) would observe without therapy while 12/37 (32%) would discharge the patient (table 1).

Finally, 35/45 (78%) respondents said formal guidance on how to manage anti-CCP positive individuals without clinical synovitis would be useful.

These data suggest UK rheumatologists see anti-CCP positive patients without clinical arthritis in routine practice and, in the absence of guidelines, use clinical intuition and US

findings to guide management. Interestingly, US was used by 84% of respondents. Furthermore, the pattern of US inflammation appears to influence the choice of treatment; patients with US synovitis (i.e. PD in the joints) receive the most intensive therapy, with 71% either treated as a standard RA patient or given a DMARD. In contrast 94% of patients with no US inflammation are either observed in clinic without therapy or discharged. There is certainly some logic to this approach; US is a readily available, non-invasive test, and the presence of PD has been shown to predict clinical arthritis development in anti-CCP positive patients without clinical synovitis [8].

However, there are many unanswered questions: for example, should US or other serological biomarkers be used to stratify for treatment intensity?, are synthetic DMARDs an appropriate choice in the 'pre - clinical arthritis' phase of RA?, if so what is the optimum treatment regimen?. What are rheumatologists views on RA prevention both in the UK and worldwide? Clearly these and other questions must be addressed through research and it is encouraging that some of the surveyed rheumatologists considered these patients for clinical trials.

In conclusion, our survey suggests rheumatologists are seeing patients in the 'pre – clinical arthritis' phase of RA and often using DMARDs, guided by US findings. Whether this pragmatic approach is an appropriate one should now be tested in optimally-designed clinical trials, with RA prevention the ultimate ambition.

(799 words)

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