Identifying arthralgia suspicious for progression to rheumatoid arthritis

We read with interest the article by van Steenbergen *et al*[1] in which a definition for arthralgia suspicious for progression to rheumatoid arthritis (RA) was proposed. The authors used a three-phase Delphi exercise to crystallise the concept of clinically suspect arthralgia (CSA), which is inherently subjective, into a core set of definable parameters. We agree that this set of characteristics should provide a useful secondary care framework for identifying homogeneous at-risk populations for future clinical studies. Recent data suggest that rheumatologists can use symptoms and signs to identify which patients with arthralgia referred to them will imminently develop RA.[2 3] In the current cohort, up to 20% of individuals identified as CSA by their rheumatologist developed RA during follow-up, the majority doing so within 6 months.[2] Although a useful signpost for the experienced rheumatologist, it is not yet clear whether CSA can be as effectively identified in primary care. This is important as the vast majority of patients with RA will first present to their general practitioner (GP) when they develop symptoms. In general, GPs have less expertise in assessing arthralgia; in the UK it is estimated that patients with RA visit their GP on average four times before being referred to a specialist for diagnosis.[4] Furthermore, patients are usually only referred once synovitis has developed. Thus for many patients with RA, there is no opportunity for the symptomatic pre-RA phase to be captured in secondary care at all. We would, therefore, argue that including primary care in any strategy to identify at-risk individuals would be optimal.

One such approach is to send individuals with any new musculoskeletal (MSK) complaint in primary care for an anti-cyclic citrullinated peptide (anti-CCP) test. Those who test anti-CCP positive are at high risk of imminent RA, with 45% progressing to clinical arthritis, the majority within 1 year.[5] A key advantage of this approach is that it can be performed by healthcare professionals without any specific rheumatology expertise. It also allows at-risk individuals to be identified when they first access healthcare. Interestingly, symptoms in the hands, shoulders and feet were associated with anti-CCP positivity[5] and the European League Against Rheumatism taskforce also agreed that symptoms and signs in the hands were important in identifying arthralgia that precedes RA.[1] One limitation of this primary care approach is that only anti-CCP positive at-risk individuals will be identified. As it is also important to identify seronegative at-risk individuals, a potential algorithm combining the two approaches in a primary care setting will be a strategy worth investigating in the future.

We agree that the next important step is to develop criteria for imminent RA. As suggested by van Steenbergen *et al*,[1] it is likely that this will need to incorporate clinical, laboratory and imaging parameters to achieve superior predictive accuracy compared with clinical parameters alone. Prediction models that combine clinical and laboratory markers in at-risk cohorts have been published.[6–8] Measurement of T-cell subset dysregulation has recently been shown to add predictive accuracy to clinical symptoms in those at risk of RA.[8] The Leeds prediction model also included ultrasound imaging and identified high-risk individuals with a 62% risk of progression to arthritis.[7] MSK ultrasound is now routinely used alongside clinical markers for real-time decision making in early arthritis clinics. Ultrasound examination in at-risk individuals has also recently been included in a diagnostic algorithm for patients with RA.[9]

Identifying individuals at high risk of imminent RA is now achievable. Incorporating clinical, laboratory and imaging biomarkers into an agreed criteria for imminent RA is an important ambition. This will likely accelerate the identification of homogeneous groups of at-risk individuals necessary for larger observational studies and future interventional trials.

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