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Predicting the development of RA in patients with early undifferentiated arthritis

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The rapidity with which bone and cartilage damage occurs in patients with rheumatoid arthritis (RA), and the increasing body of evidence for the effectiveness of early intervention in RA, mean that there is a great need for approaches to accurately predict the development of RA in patients with early undifferentiated arthritis. We will review developments in the prediction of outcome on the basis of clinical and laboratory features, including measures of anti-citrullinated protein/peptide antibody status. Although accurate predictions are possible in the majority of patients using recently developed predictive algorithms which utilize clinical and serological variables, there remains a group of patients for whom it is very difficult to predict the development of RA. The utility of new strategies for prediction will be discussed, including recently discovered genetic associations of RA, an assessment of material from the primary site of pathology (the joint), and assessment using the highly sensitive imaging modalities of ultrasound and magnetic resonance imaging.

Presentation with a new onset of inflammatory arthritis is remarkably common. In at least half of patients with synovitis of less than 6 weeks' duration, the disease resolves spontaneously [1,2]. In the rest, the processes driving the natural resolution of inflammation are disrupted, leading to a switch to chronic persistent disease. Some of these patients will, over a variable length of time, develop a well-defined syndrome such as rheumatoid arthritis (RA), whilst in others the arthritis will remain undifferentiated. An increasing body of evidence suggests that damage to cartilage and bone (which may be

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irreversible) occurs early in patients with RA and is due to synovial inflammation. Furthermore, early treatment of RA is associated with improved outcomes compared with delayed treatments [3–6]. In view of these data, it is important to be able to identify patients with early undifferentiated inflammatory joint disease who are destined to develop established RA to allow early targeted therapy.

Predicting the development of persistent arthritis in patients with early synovitis

A number of studies have addressed predictors of the development of persistent arthritis in patients presenting with early synovitis. In one of the first such studies, Tunn and Bacon identified seropositivity for rheumatoid factor (RF) and an erythrocyte sedimentation rate (ESR) >30 mm/h as the best predictors in a cohort of patient with synovitis of up to 6 months' duration. The specificity of these two variables was 94%, but the sensitivity was only 69% for the prediction of persistence [1]. In a study of patients with symptoms of up to 1 year's duration, Green et al identified a disease duration of >12 weeks as the strongest independent predictor of persistence [7]. Seropositivity for rheumatoid factor and the presence of the shared epitope were also predictors of persistence, and the presence of all three variables had a specificity of 100% for the prediction of persistence, but with an extremely low sensitivity (15%). The introduction of assays to measure antibodies against cyclic citrullinated peptides (CCPs) in 2000, and the demonstration that these were highly specific for RA [8,9], led to an assessment of the utility of this test for the prediction of the development of persistent arthritis. In 2002, the Leiden group reported that, in a cohort of patients with synovitis of <2 years' duration, the development of persistent disease could be predicted accurately, with a receiver operating characteristic (ROC) area under the curve (AUC) of 0.84, using a combination of the following seven factors (the first two of which were weighted most heavily): (1) symptom duration; (2) anti-CCP antibody positivity; (3) RF positivity; (4) presence of erosions; (5) morning stiffness ≥1 hour; (6) arthritis in three or more joint areas; (7) bilateral compression pain in metatarsophalangeal (MTP) joints [10]. Data from the Norfolk Arthritis Register have shown that the following three variables can be used to predict remission (the opposite of persistence): (1) RF negativity; (2) fewer than six tender joints; and (3) the absence of ankle swelling. However, the positive and negative predictive values of this model were only 63% and 80% respectively [11]. One of the difficulties with this area of research is that there is a lack of universally accepted definitions either of remission or persistence, as demonstrated by the fact that all of the studies referred to above used different definitions. More importantly, many patients with a persistent arthritis will have a diagnosis other than RA. Given the clear evidence available regarding approaches to the management of and need for early intervention in RA, in contrast to the lack of evidence to support approaches to the management of some other forms of persistent arthritis (e.g. persistent undifferentiated arthritis), it is important to be able to predict which patients with early synovitis will develop RA.

Predicting the development of RA in patients with early synovitis

Any discussion of approaches to predicting the development of RA must begin with a consideration of what we mean by this diagnosis. In contrast to the difficulty in identifying widely accepted definitions of remission and persistence, the current definition of RA is used almost universally, despite attracting its fair share of controversy [12,13]. Current classification criteria were developed by a committee appointed by the American Rheumatism Association to revise the 1958 diagnostic criteria [14]. These 1987 criteria, in list format, comprise seven items: (1) morning stiffness ≥1 hour (2) arthritis (soft tissue swelling or fluid) of three or more joint areas; (3) arthritis of proximal interphalangeal (PIP), metacarpophalyngeal (MCP) or wrist joints; (4) symmetrical arthritis; (5) rheumatoid nodules; (6) seropositivity for RF; and (7) radiographic change (erosion or peri-articular osteopenia on a radiograph of the hand and wrist). Patients are classified as having RA if at least four of these items are present, with items 1–4 being present for ≥6 weeks. The 1987 ARA criteria were derived from an analysis of 262 RA patients – each diagnosed on the opinion of one of 41 referring rheumatologists, without explicit reference to previous diagnostic criteria – and 262 rheumatological patients with non-RA diagnoses. All patients were from hospital-based populations, and most RA patients had long-standing disease (mean 8 years). When the criteria were applied to the 47 RA patients with a disease