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Diagnostic Technology: Autoimmune markers for the diagnosis of Rheumatoid Arthritis in primary care

Clinical Question:
Should General Practitioners use anti-citrullinated peptide antibody (ACPA) testing instead of rheumatoid factor (RF) for diagnosing rheumatoid arthritis?

Background, Current Practice and Advantages over Existing Technology:
Early diagnosis and treatment of rheumatoid arthritis (RA) is important in preventing long-term damage and disability. RA should be suspected in patients largely on the basis of clinical findings, such as persistent joint pain, swelling and stiffness. Further investigations, particularly in primary care, may contribute to the diagnosis. These include the presence of autoimmune antibodies, non-specific markers of inflammation, anaemia and imaging studies. Rheumatoid factor is an autoantibody associated with RA and its presence has traditionally been used to support the diagnosis. Whilst there is some evidence that high titres are useful in diagnosis and estimating prognosis in early arthritis, there are concerns that it is an inappropriate tool in primary care settings.
Anti-citrullinated peptide antibody (ACPA) has emerged as an alternative serological test to RF. It has a greater specificity and may be preferable to RF in the diagnosis of RA[1]. However, is not yet generally available in primary care.

Details of Technology:
Rheumatoid factors were originally described in the late 1930's and have since been widely used in the assessment of patients with inflammatory arthritis.[2] These auto-antibodies are directed against the Fc portion of immunoglobulin IgG. The majority of rheumatoid factors are IgM, but may be IgG or IgA. Rheumatoid factors are measured in the serum using a latex-enhanced immuno-nephelometric method.
Rheumatoid arthritis is associated with the presence of RF in many but not all cases. Raised RF levels are also found in other autoimmune diseases, e.g. Sjogren's syndrome and type 2 cryoglobulinaemia, in infection and in healthy individuals.[3]
Anti-citrullinated peptide antibodies, also called anti-cyclic citrullinated peptide (anti-CCP) antibodies, were first described in 1998.[4] They were found to be reactive to the amino acid citrulline and present in the sera of RA patients.[4] The first serum assay to detect anti-citrullinated peptide antibody, CCP1, was described in 2000 with moderate sensitivity (around 60%).[5] A more sensitive assay, CCP2, became commercially available three years later.[6] The ACPA test is currently available commercially as a lab-based enzyme-linked immunosorbent assay (ELISA) testing kit for antibodies which recognise antigens containing citrulline. There has also been recent evidence for point of care testing (POCT) for both RF and ACPA.[23 24] In one study the sensitivity and specificity of an anti-CCP2 point of care finger prick test when compared with ELISA were 95% (95% CI 90–100) and 95% (95% CI 89–100), respectively.[23] Although early work suggests the accuracy of these tests may be comparable to existing assays, it remains to be seen whether increasing the speed of receiving the result improves patient outcomes.

Patient Group and Use:
- Adult patients with suspected rheumatoid arthritis presenting in primary care

Importance:
Rheumatoid arthritis (RA) is a destructive inflammatory joint disease with an estimated UK prevalence of 1.2% in women and 0.4% in men.[7] Although musculoskeletal symptoms commonly present in primary care, an individual GP is likely to see one new case of RA per year.[8] Nevertheless, early referral of patients with suspected disease is advocated to establish treatment and prevent joint damage and disability[9 10]. A recent study evaluated the delays to starting treatment in 1,674 patients presenting with early arthritis in The Netherlands[11]. . Delays included the time taken for the patient to present, in the GP referring, and in the assessment by a rheumatologist. Those RA patients in whom autoantibodies were found had a longer time to diagnosis than RA patients with no autoantibodies. Assessment by a rheumatologist within 12 weeks was

associated with less joint destruction and a higher chance of achieving disease-modifying antirheumatic drug (DMARD)-free remission as compared with a later assessment. However a study in New Zealand has estimated that the median time from onset of symptoms to starting treatment is 6.1 months.[12]

Prompt presentation and recognition of signs, symptoms and accurate interpretation of early tests in the initial assessment will support earlier referral and treatment. The American College of Rheumatology and European League Against Rheumatism Collaborative Initiative published their revised classification critieria for rheumatoid arthritis[13] in 2010 to focus on early features of the disease. Classification of arthritis as being RA is based on the presence of synovitis in at least one joint, absence of an alternative diagnosis, and a total score of 6 or more out of 10 from a scoring system of 4 domains. These include the number and site of involved joints, serologic abnormality (titres of RF and ACPA), elevated acute-phase response (i.e. CRP or ESR) and symptom duration of more than 6 weeks. This is similar to National Institute for Health and Clinical Excellence (NICE) guidance on the management of RA (CG79) in that both include autoantibody testing in the criteria.[9] However neither recommendation requires a positive RF result to make the diagnosis. The NICE guidance explicitly advises against delaying urgent referral of "any person with suspected persistent synovitis of undetermined cause whose blood tests show a normal acute-phase response or negative rheumatoid factor".

Many GPs undertake investigations including RF to distinguish patients with early RA from a larger number of patients with non-inflammatory joint pain. However most studies on the diagnostic utility of RF are based in secondary care where the pre-test probability of RA is relatively high. In contrast, few studies have investigated the diagnostic utility of RF in primary care where the pre-test probability is low.[3 14] Furthermore, studies suggest that RF results influence referral decisions and that GPs may use a negative RF result to exclude RA, despite the presence of appropriate symptoms.[14] It is unclear whether ACPA instead of RF testing would lead to a higher diagnostic yield in primary care.

Previous Research:

Accuracy of ACPA testing compared with RF

Approximately 60-70% patients with RA have a positive RF which is predictive of disease severity, but not so useful for diagnosis. [15 16] A positive test is present in 4% of the normal population and increases with age up to 25% of those over 85 years. [17 18] Only 11-20% of people with musculoskeletal symptoms and a positive RF actually have RA.[15 18]

Anti-citrullinated peptide antibody (ACPA) has similar sensitivity to RF but better specificity in the diagnosis of RA.[1] A meta-analysis of 50 studies of RF and 37 of ACPA from both primary and secondary care populations reported pooled sensitivity for RF of 69% and specificity 85%.[19] Pooled sensitivity of ACPA was estimated to be 67% and specificity 95%. The positive likelihood ratio was estimated to be 12.5 for ACPA compared to that of 4.9 for RF IgM. A negative likelihood ratio was estimated to be 0.36 compared to 0.38 for RF IgM (Table 1). Studies were based in hospital early arthritis clinics and there are no large studies of RF diagnostic utility based in primary care.

Table 1.

	Rheumatoid factor [95% CI]	ACPA [95% CI]
Sensitivity	69% [65% - 73%]	67% [62% - 72%]
Specificity	85% [82% - 88%]	95% [94% - 97%]
Positive likelihood ratio	4.86 [3.95 – 5.97]	12.46 [9.72-15.98]
Negative likelihood ratio	0.38 [0.33 – 0.44]	0.36 [0.31-0.42]

Impact of testing for ACPA compared with RF

There is currently no evidence to support the use of RF or ACPA as diagnostic tests for RA in primary care. ACPA and RF are not useful in patients with a low pre-test probability of RA (<10%). In patients with a moderate pre-test probability (25-75%) the effect of a positive ACPA test is better than a positive RF. In patients with a high pre-test probability of RA, either test will perform well. Since both tests have poor sensitivities, negative results should not deter the clinician from a diagnosis of RA.[20]

The outcome of a positive RF or ACPA in disease-free patients was reported by Nielen et al where the antibody status of 79 RA patients who had previously donated blood prior to disease onset were compared with samples from healthy individuals.[21] Out of the 79 RA patients, 39 (49.4%) had IgM-RF and/or ACPA on at least one occasion a median of 4.5 years (range 0.1–13.8 years) before symptom onset. They also retrospectively analysed the RF IgM status in sera from a

population of patients with known RA. From this they calculated that the positive predictive value (PPV) of developing RA, 0-5 years before the onset of symptoms was 88.2%. In contrast, the PPV was 96.6% for those RA patients with an initial positive ACPA result. In healthy individuals, a positive RF test resulted in a 1.5% risk of developing RA in the subsequent 5 years, whereas a positive ACPA test had a 5.3% risk of developing RA.
Some studies have investigated whether adding ACPA antibody to RF testing improves diagnostic accuracy. In a recent meta-analysis three cohort studies were identified where early rheumatoid arthritis patients were tested for both RF and ACPA.[22] This showed that the positive likelihood ratio increased from 22.0 (CI, 9.9 to 49.1) for ACPA alone to 27.1 (CI, 10.1 to 72.7) when both ACPA and RF results were positive. However because of these large confidence intervals, the authors were unable to conclude if adding ACPA testing to RF would lead to any significant improvement in aiding diagnosis. In addition they also showed that there was no significant improvement to both sensitivity and specificity.

Relevant Guidelines
NICE clinical guidance: Rheumatoid arthritis: The management of rheumatoid arthritis in adults
http://www.nice.org.uk/nicemedia/pdf/CG79NICEGuideline.pdf
An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative: 2010 Rheumatoid Arthritis Classification Criteria
http://www.rheumatology.org/practice/clinical/classification/ra/2010_revised_criteria_classification_ra.pdf

Cost-effectiveness and economic impact:
The cost-effectiveness of RF and ACPA should consider the economic impact of false negative and positive results. A false negative result may delay diagnosis and treatment resulting in additional subsequent costs to patients and the UK National Health Service (NHS). Similarly, unnecessary referrals to secondary care resulting from a false positive result incur additional health care costs and also creates needless burden to individuals. Accurate estimates of sensitivity and specificity of ACPA and RF in primary care are required to determine the cost-effectiveness of treatment options in RA. The literature on cost-effectiveness evidence of treatments for established rheumatoid arthritis (RA) is comprehensive as recently reported in a large systematic review.[25] However, there is little economic evidence about diagnostic procedures such as RF and ACPA in primary care. The cost-effectiveness of ACPA when compared to the American College of Rheumatology Criteria (ACR) for diagnosis of RA has recently being investigated by Konnopka and colleagues.[26] The authors used a decision analytical model to combine costs and health-related quality of life data associated to each alternative. The researchers reported a baseline cost per QALY gained estimate of €930 (£857) (2008 prices) indicating that ACPA is cost-effective using current thresholds of willingness to pay [27]. The robustness of these results was evaluated using sensitivity analysis.
The cost-effectiveness of RF versus ACPA or any other alternative has not been formally evaluated in the literature.

Recommendations
Despite its widespread use for over sixty years, and established role in early arthritis clinics, the role of RF in diagnosing RA in primary care remains unclear. Furthermore, negative RF results may delay referral to secondary care in patients with clinical features of RA, and raised levels of RF may be present in healthy individuals. Newer tests, such as ACPA, are emerging with higher specificity and positive predictive values to RF, but similar sensitivity. However the true value of these tests is in predicting a poorer prognostic group of patients with arthritis in secondary care. GPs should base diagnostic and referral decisions on clinical features; number and site of involved joints and elevated acute phase response, rather than serological tests. A positive RF or ACPA has value in supporting these decisions, but a negative test does not rule out inflammatory arthritis. Currently there is no more evidence to support the role of ACPA in primary care than there is for RF. Our conclusions support current guidelines on referral of patients with suspected RA on the basis of a combination of factors that predominantly include clinical features irrespective of the RF result.[9]

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Competing interests

The authors have declared no competing interests.

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