

GUIDELINES FOR THE USE OF ANTI-CYCLIC CITRULLINATED PEPTIDE ANTIBODIES

Aim

To provide useful, evidence based recommendations for the requesting of anti cyclic citrullinated (CCP) antibody tests in the investigation of patients with suspected and confirmed rheumatoid arthritis.

Introduction to anti cyclic citrullinated peptide antibodies and rheumatoid factor.

Citrulline is a non-standard amino acid, created by de-amination of arginine residues by the action of peptidylarginine deiminase (PAD) enzymes. De-amination is a calcium dependent post translational modification with no known role. The PAD enzymes (particularly PAD 2 and 4) are found in the inflammatory synovium in rheumatoid arthritis (RA) and cause the local citrullination of synovial proteins. Theoretically, any protein can be citrullinated, but the enzymes show preference for certain amino acid sequences and protein structures. Citrullination is regulated by intracellular calcium concentration, with lower specificity with increased calcium concentrations. Protein citrullination affects how proteins fold together, leading to loss of protein structure and shape and altered antigenicity. Small amounts of citrullination (approx 10%) can be enough to destroy the quaternary structure of a protein.

Citrullinated extracellular fibrin in the RA synovium may be one of the major autoantigens driving the local immune response in RA. Anti cyclic citrullinated peptides (CCP) and anti citrullinated filaggrin antibodies are associated with RA. Anti CCP antibodies are seen in approximately 60% of patients with early RA and can precede the onset of overt arthritis symptoms and positive rheumatoid factor.

Rheumatoid factor (RhF) is the group name given to autoantibodies against the Fc portion of immunoglobulin molecules. RhF is usually considered to be IgM antibodies against the Fc portion of the IgG molecule has been part of the laboratory diagnosis of rheumatoid arthritis for many years. Unfortunately RhF lacks specificity, with positive RhF seen in many conditions including infections, malignancies and with increasing prevalence in the elderly. RhF is readily available test that is often requested indiscriminately, particularly in the investigation of patients who are non-specifically unwell and before any clear differential diagnoses have emerged.

Clinical use of anti CCP antibodies and rheumatoid factor

Measurement of anti CCP is undoubtedly a valuable test in confirming the diagnosis of RA in patients with atypical presentations and excluding a diagnosis of RA in patients where the RhF is positive, but with equivocal findings. Anti CCP antibodies should only be requested when the result will influence the management of the patient. There is currently no indication for either anti CCP antibody or rheumatoid factor to be used to monitor RA patients.

NICE guidelines CG100 rheumatoid arthritis in adults: management makes the following recommendations:

- Offer to carry out a blood test for rheumatoid factor in adults with suspected RA who are found to have synovitis on clinical examination.
- Consider measuring anti-CCP antibodies in adults with suspected RA if they are negative for rheumatoid factor.
- Measure CCP antibodies as soon as possible after a diagnosis of RA
- If CCP antibodies are present or there are erosions on the X-ray, advise the person that they have increased risk of radiological progression.
- In adults with active RA, measure C-reactive protein and disease activity score monthly in specialist care until the target of remission or low disease activity is achieved.

Recommendations

- CCP antibodies should be available to Consultant Rheumatologists in Kent.
- Rheumatoid factor measurements should remain available to primary care requestors.
- Anti CCP antibodies should be restricted to Rheumatology requestors for situations **where the result will influence the patients' management**, including patients with symptoms of RA but with negative RhF.

- Anti CCP antibodies or rheumatoid factor should not be used to monitor patients.
- Under normal circumstances, **there is no reason** to repeat either anti CCP antibodies or rheumatoid factor. If there has been a change in the clinical picture or if there is doubt about the validity of previous results, then rechecking may be indicated.

References

NICE guidelines CG100, Rheumatoid arthritis in adults: management – updated October 2020

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