A3 DOES TESTING FOR CIRCULATING AUTOANTIBODIES AGAINST DISEASE-RELEVANT CITRULLINATED ANTIGENS ADD VALUE TO THE CCP2 ASSAY IN DIAGNOSING RA AMONG EARLY UNDIFFERENTIATED ARTHRITIS PATIENTS?

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Background The antigen substrates employed in the widely-used CCP2 assay do not correspond to in vivo-generated citrullinated proteins so far implicated in the potential pathogenesis of rheumatoid arthritis (RA). We assessed the diagnostic utility of circulating autoantibodies to a panel of such peptides among undifferentiated arthritis (UA) patients, and whether permutations thereof might improve upon the diagnostic utility of CCP2 testing alone.

Materials and methods UA patients presenting to the Newcastle Early Arthritis Clinic who were naïve to immunomodulatory treatment were recruited. In addition to routine testing using the CCP2 assay, baseline sera were tested for reactivity to citrullinated forms of fibrinogen (cFbg), vimentin (cVim), cyclic α enolase peptides 1 and 11 (CEP-1 and CEP-11), linear filaggrin (Fil-LC), and a panel of six citrullinated pro-filaggrin-derived peptides. Corresponding native forms of the same peptides were used as negative controls where possible, and testing for IgA and IgM rheumatoid factor (RF) was also undertaken, with assay cut-offs being determined based on healthy control populations. Clinicians were blinded to all but the CCP2 results, and follow-up was for ≥1 year (median 28 months) Individuals for whom definitive outcome diagnosis was not reached within the study

period were excluded from analysis. The 1987 American College of Rheumatology classification criteria were used for the diagnosis of RA.

Results Assays were carried out for 75 newly presenting UA patients, of whom 29 (39%) developed RA.The specificity, sensitivity, positive and negative predictive values (PPV and NPV) of CCP2 with respect to an RA outcome in this cohort (95% CIs) were 0.98 (0.87-1.0), 0.48 (0.30-0.67), 0.93 (0.66-1.0) and 0.75 (0.62-0.85) respectively. No single assay evaluated displayed superior NPV over CCP2 without compromising the PPV afforded by that test. Neither did combinations of assays, considered in permutations with or without CCP2, add value to CCP2-testing alone in predicting RA. Hierarchical clustering of all assay profiles revealed cFbg reactivity to correlate most closely with CCP2 test positivity among these sera (PPV and NPV 0.80 (0.51–0.95) and 0.70 (0.56–0.81)) respectively. In general, IgM RF positivity had a NPV equivalent to that of the CCP2 test, but an inferior PPV (0.65 (0.44–0.82)), and, after the CCP test, the best assay with regards PPV for RA was found to be CEP-1 (0.83 (0.36–0.99)).

Conclusions The CCP2 test remains an invaluable diagnostic tool in the assessment of UA because of its impressive PPV, but the identification of biomarkers for the diagnosis of autoantibody negative RA must remain a priority.