Rheumatoid Factor and Antibodies to Cyclic Citrullinated Peptide Differentiate Rheumatoid Arthritis from Undifferentiated Polyarthritis in Patients with Early Arthritis

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ABSTRACT. ***Objective.*** To study the diagnostic value of IgM rheumatoid factor (RF), IgA-RF, antibodies to cyclic citrullinated peptide (anti-CCP), and combinations of these antibodies, measured at baseline, to discriminate rheumatoid arthritis (RA) from undifferentiated polyarthritis (uPA) in patients with recent onset arthritis.

Methods. Patients with early arthritis with peripheral arthritis of 2 or more joints and symptom duration less than 3 years were clinically diagnosed as having RA or uPA by an experienced rheumatologist during the first year. Patients with bacterial, psoriatic, or crystal induced arthritis or spondyloarthropathy were excluded. Optimal cutoff values for serum IgM RF, IgA RF, and anti-CCP were deduced from receiver operating characteristics curves in order to predict the diagnosis of RA in early arthritis.

Results. A total of 379 patients (69% female, median age 57 yrs, range 17–86 yrs) were studied; 258 patients were clinically diagnosed as RA and 121 as uPA. Both IgM-RF > 40 IU/ml and anti-CCP > 50 AU/ml showed high specificity, but the sensitivity of these tests was low. In many RA patients the occurrence of IgM-RF and anti-CCP antibodies was independent. Thus the optimal criterion proved to be the combination of IgM-RF > 40 or anti-CCP > 50, which yielded sensitivity of 55.4% and specificity of 96.7%.

Conclusion. The criterion IgM-RF > 40 or anti-CCP > 50 is able to predict the diagnosis of RA in early arthritis patients with high specificity and acceptable sensitivity. Anti-CCP testing combined with IgM-RF testing has additional value over IgM-RF testing alone in patients with early undifferentiated oligo and polyarthritis. (J Rheumatol 2002;29:2074–6)

Key Indexing Terms:
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Diagnostic tools that can support the diagnosis of rheumatoid arthritis (RA) include autoantibody tests such as determinations of rheumatoid factor (RF) and antifilaggrin antibodies[1]. Several reports suggest that a combined increase of IgM-RF and IgA-RF is found almost exclusively in patients with RA and therefore has a high specificity for RA[2,3]. Antifilaggrin antibodies are traditionally measured as antiperinuclear factor or as antikeratin antibodies. Recently, a peptide variant of the filaggrin epitope was described[4-6], denoted cyclic citrullinated peptide (CCP). Anti-CCP antibodies are reported to have a remarkably high specificity for RA[7].

We assessed the diagnostic value of IgM-RF, IgA-RF, and anti-CCP antibodies and combinations of these antibodies in discriminating RA from undifferentiated polyarthritis (uPA) in patients with early oligo or polyarthritis at baseline.

The 1987 American College of Rheumatology criteria set for RA[8] has important limitations when used for case recognition in early arthritis. In addition, in a study like this it is not appropriate to classify patients according to a criteria set that includes a criterion under study, i.e., in this case rheumatoid factor. A good alternative is to use the early clinical diagnosis of RA, which is reliable as it will hardly change during the first year[9]. Thus the clinical diagnosis of an experienced rheumatologist was considered the "gold standard" in this study.

MATERIALS AND METHODS

The study population consisted of 379 patients with arthritis of 2 or more

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joints, newly referred to the outpatient Early Arthritis Clinic (EAC) in Amsterdam from 1995 to 1998. The median duration of complaints was 3 months, with a maximum duration of 3 years. Excluded from this EAC group were patients with other rheumatic diseases such as spondyloarthropathy, crystal induced arthropathy, systemic lupus erythematosus, Sjögren's syndrome, and osteoarthritis[10]. The diagnosis of RA was made according to the clinical assessment of an experienced rheumatologist in 258 patients (70% female, median age 57 yrs, range 18–86). The remaining 121 non-RA patients were denoted uPA (65% female, median age 53 yrs, range 17–84); 73 of the patients with uPA had polyarthritis and 48 had oligoarthritis.

At the first visit, IgG anti-CCP antibodies were measured using the Immunoscan RA ELISA kit (Euro-Diagnostika, Arnhem, The Netherlands). IgM-RF and IgA-RF were measured on an ES300 immunochemistry analyser (Roche Diagnostics). Seven hundred microliters of biotinylated rabbit IgG (20 μg/ml phosphate buffered saline, PBS) were pipetted into streptavidin coated tubes together with 20 μl serum diluted 1:50 in PBS containing 0.05% Tween-20 and 2% bovine serum albumin. The tubes were developed with 500 μl diluted $F(ab)_2$ anti-human IgM or IgA, conjugated to horseradish peroxidase (Dako Diagnostics). For IgM-RF the standards were calibrated against the RELARES reference serum containing 200 IU/ml.

RESULTS

Optimal cutoff values to differentiate RA patients from uPA patients were deduced from receiver operating characteristics (ROC) curves. These were 30 IU/ml for IgM-RF, 10 arbitrary units (AU)/ml for IgA-RF, and 50 AU/ml for anti-CCP with specificities of 93.4%, 94.2%, and 97.5%, respectively, and sensitivities of 50.4%, 52.7%, and 42.6% (Table 1).

The next task was to find a combination of tests with the highest possible sensitivity and specificity for detecting RA. Because the specificity of anti-CCP was higher than that of IgM-RF, we first tried to enhance the specificity of the RF determination. This was done in 2 ways. When both IgM-RF > 30 and IgA-RF > 10 were combined into one cutoff criterion, the specificity increased to 96.7%, which is nearly as high as the specificity of anti-CCP (Table 1). However, exactly the same specificity and sensitivity were obtained by increasing the cutoff value for IgM-RF to 40 IU/ml (Table 1). Thus the IgA-RF determination to enhance the specificity of the RF determination has no additional value in this group of patients.

Table 1. Sensitivities and specificities of tests and combinations of tests for diagnosis of RA. Tests were done at baseline in a group of patients with early arthritis comprising 258 early RA patients and 121 undifferentiated polyarthritis (uPA) patients. They are given for several cutoff values denoted IgM-RF > 30 or > 40 IU/ml, IgA-RF > 10 AU/ml, and anti-CCP > 50 AU/ml, respectively.

Criterion	Sensitivity, %	Specificity, %
IgM-RF > 30	50.4	93.4
IgA-RF > 10	52.7	94.2
Anti-CCP > 50	42.6	97.5
IgM-RF > 40	46.5	96.7
IgM-RF > 30 and IgA-RF > 10	46.5	96.7
IgM-RF > 40 or anti-CCP > 50	55.4	96.7
IgM-RF > 40 and anti-CCP > 50	33.3	97.5

Both the IgM-RF > 40 and anti-CCP > 50 criteria had a high specificity, but the sensitivities were low. Therefore, the second step was to enhance the sensitivity by combining these 2 assays. It appeared that in one-quarter of the RA patients, IgM-RF and anti-CCP positivity were independent from each other: 24 RA patients (9%) were negative for the IgM-RF > 40 criterion, but positive for the anti-CCP > 50 criterion, whereas 33 RA patients (13%) were positive for the IgM-RF > 40 criterion but negative for anti-CCP > 50. In the group of uPA patients, none was negative for the IgM-RF > 40 criterion but positive for anti-CCP > 50, and one patient was positive for IgM-RF > 40 but negative for the anti-CCP > 50 criterion. This indicated that the 2 tests measured different entities and might be combined into a logical "or" criterion (either one test positive or the other or both positive). The best test criterion proved to be IgM-RF > 40 or anti-CCP > 50, with a sensitivity of 55.4% and specificity of 96.7% (Table 1). When this was compared with our routine assay for RF (the IgM-RF determination with a cutoff value of 30 IU/ml), the sensitivity increased from 50.4% to 55.4% and the specificity increased from 93.4% to 96.7%. When the combination criterion IgM-RF > 40 or anti-CCP > 50 was applied, 4 of the 121 uPA patients were positive, instead of 8 of the 121 uPA patients with the IgM-RF > 30 criterion.

One hundred fifteen patients were clinically diagnosed as RA without the presence of either IgM-RF > 40 or anti-CCP > 50 antibodies at baseline. In 84 of these patients, serum was available at 1 year followup. Only 2 patients became positive at 1 year, one with IgM-RF of 58 IU/ml and the other with anti-CCP of 101 AU/ml.

DISCUSSION

It is noteworthy that in a similar study[7] a different conclusion was reached as to how IgM-RF and anti-CCP are to be combined into one discrimination criterion. The authors tried to discriminate RA from non-RA patients in the EAC of Leiden, The Netherlands. The sensitivity and specificity of their IgM-RF tests were 54% and 91%, respectively, and for anti-CCP measurements 48% and 96%. The main difference with the present study was the low specificity of their IgM-RF assay of 91%. When either IgM-RF positive or anti-CCP positive were combined into one criterion the sensitivity became high (63%) but the specificity decreased to 88%. Therefore they suggested combining IgM-RF and anti-CCP in such a way that both tests must be positive. In this case their specificity increased to 98% but their sensitivity decreased to 39%. When this criterion IgM-RF > 40 and anti-CCP > 50 was applied to our group of patients, only one-third remained positive (Table 1), too low for practical use.

We conclude that in our group of patients with early arthritis the criterion IgM-RF > 40 or anti-CCP > 50 is able to predict which patients with early arthritis will receive a

clinical diagnosis of RA with a sensitivity of 55.4% and a specificity of 96.7%.

Thus, anti-CCP testing combined with IgM-RF testing has additional value over IgM-RF testing alone in patients with early undifferentiated oligo and polyarthritis.

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