Diagnostic and Prognostic Value of Antibodies and Soluble Biomarkers in Undifferentiated Peripheral Inflammatory Arthritis: A Systematic Review

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ABSTRACT. ***Objective.*** When patients present with undifferentiated peripheral inflammatory arthritis (UPIA), early diagnosis and evaluation of prognostic factors are decisive steps for therapeutic success. We reviewed published evidence on the diagnostic and prognostic performance of autoantibodies and soluble biomarkers in UPIA.

Methods. We conducted a systematic literature search covering studies published until January 2009. Additionally, we screened conference abstracts presented at European League Against Rheumatism and American College of Rheumatology meetings in 2007 and 2008.

Results. We included 52 full-text articles and 12 abstracts. The association of anti-cyclic citrullinated peptide antibody (anti-CCP) and rheumatoid factor (RF) with diagnosis of rheumatoid arthritis at followup is compelling, supported by positive likelihood ratios (LR+) ranging between 1.2 and 20.5 for anti-CCP and 1.1 to 13.5 for RF. The same applies to radiographic outcome. For antikeratin antibodies (AKA) and antiperinuclear factor, existing evidence suggests diagnostic usefulness; AKA also showed prognostic value. Diagnostic and prognostic evidence for other autoantibodies and for bone and cartilage biomarkers was scarce, negative, or controversial.

Conclusion. Among serological tests, unanimous evidence of substantial diagnostic value exists only for anti-CCP and RF, but is scarce for other markers. (J Rheumatol 2010;38 Suppl 87:20–25; doi:10.3899/jrheum.101070)

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At first presentation of early inflammatory arthritis, about 35% to 55% of patients are classified as undifferentiated arthritis[1]. Among them, the proportion that will later be diagnosed with rheumatoid arthritis (RA) is reported to be highly variable in different cohorts, ranging from 6% to 55%[2]. Early therapeutic intervention in patients at risk of developing persistent and aggressive disease is required[3,4]. Aside from clinical tests and results of imaging techniques, serologic tests and other biomarkers are important tools for identification of such patients. We systematically reviewed current evidence on the diagnostic and prognostic performance of autoantibodies and soluble biomarkers in early arthritis.

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MATERIALS AND METHODS

The multinational 3e (evidence, expertise, exchange) Initiative elaborated recommendations on the investigation and followup of undifferentiated peripheral inflammatory arthritis (UPIA)[5]. To gather the evidence regarding diagnostic and prognostic value of autoantibodies and soluble biomarkers, we searched the Medline, Embase, and Cochrane databases, as well as conference abstracts presented in 2007 and 2008 at the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) annual meetings. We included applicable studies that were published in the English literature until January 2009, and hand-searched selected articles and pertinent reviews for further publications of relevance. From the retrieved articles, we extracted the reported test sensitivities and specificities of autoantibodies and biomarkers for specific diagnoses at followup. Also, we gathered information on the prognostic value for persistence, function, and radiographic damage in patients with UPIA, and compiled positive (LR+) or negative likelihood ratios (LR–) where available. For details of the search strategy [a PICO approach (Patients, Intervention/index test, Comparison, Outcome), search strings, and flow charts of the search and selection process] see also additional online material at www.3eupia.com.

RESULTS

We retrieved 65 publications[6-70], among them 53 full text articles[6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,22,23,26,29,30,32,34,35,36,37,38,39,41,42,43,45,46,47,48,49,50,51,52,53,54,55,59,60,61,62,63,64,65,66,67,68,69,70] and 12 abstracts[21,24,25,27,28,31,33,40,44,56,57,58]. Followup mostly lasted one year[6,8,9,10,11,12,13,14,15,16,17,18,19,30,31,32,44,69], but some studies reported on observation periods of up to 3 years[20,21,22,23,24,25,26,27,28,36,37,38,48] or longer[29,45,52]. The majority of studies included UPIA patients solely, or presented stratified analyses with regard to fulfilment of ACR criteria at baseline, whereas other studies investigated mixed populations[8,9,10,17,24,25,42,44,48,49,51,52,54,55,59,64,66].

Rheumatoid factor (RF)

RF is the longest-standing autoantibody test to distinguish RA from other forms of arthritis. RF testing is included in the ACR (formerly American Rheumatism Association) criteria for diagnosis of RA[71,72], as well as in the 2010 classification criteria for RA[73] replacing the 1987 criteria. Also, testing for RF is recommended in guidelines for management of early arthritis[3].

There is considerable evidence for the diagnostic value of RF in UPIA, where its presence has been associated with later diagnosis of RA in healthy blood donors[74]. Evidence in UPIA cohorts is not as overwhelming as that in early RA cohorts, but the diagnostic value has been proved in several studies[6,11,13,15,22,36,37,38,39,40,41,68,75]. Reported LR+ have ranged from 1.1 to 13.5. Absence of RF is diagnostically less helpful (LR– ranged from 0.3 to 0.8). An improvement in diagnostic test performance for RA was reported if the cutoff value was increased from 20 U/ml to 50 U/ml[6].

Presence of RF at baseline has significant predictive value for the development of erosions[6,8,26,28,29,36,44,45]. Followup mostly ranged from 1 to 2 years; however, one article reported association with radiographic outcomes after 8 years[45]. Apart from radiographic damage, RF seropositivity also predicted persistence of synovitis[26,30,39,47,48,58], and the necessity of intensive treatment[33,40]. Also, premature death was associated with seropositivity at baseline[34]. Appraisal of the predictive value of RF regarding remission and function[51] has been controversial.

Anti-citrullinated protein antibodies

Anti-cyclic citrullinated peptide antibodies (anti-CCP). The presence of anti-CCP antibodies has been linked to later development of RA even in healthy populations[72,76]. In the EULAR recommendations for management of early arthritis, anti-CCP antibody testing is recommended[3], and testing for anti-CCP antibodies is part of the new RA criteria[73]. In UPIA, several studies describe high diagnostic value of anti-CCP antibody positivity at baseline, mostly for prediction of RA at 1-year followup[6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23], several studies also affirmed evidence for a diagnosis of RA 2–3 years later[20,21,22,23].

Anti-CCP positivity at baseline showed predictive value for subsequent structural damage[6,8]; further, there is a close association with persistence of synovitis[20,26,30,31], the need for intensive treatment[32,33], decline of function in the course of disease[20], and premature death[34]. In direct comparison of test versions, the second generation was superior for prediction of joint damage[16]. While the above studies support anti-CCP IgG antibodies, the use of specific serotypes such as IgA, IgG1, or IgG4 might not be of equal diagnostic value[19]. Some studies evaluated whether testing for anti-CCP antibodies was useful in patients with UPIA seronegative for RF[6,7,8,9,12]. In this situation, a stepwise approach was recommended, with anti-CCP testing considered only when RF is below 50 U/ml[6]. In summary, anti-CCP is consistently associated with diagnosis of RA (LR+ 1.2–20.5 in various studies), but negative test results are diagnostically less helpful (LR– 0.4–0.9).

Antibodies to citrullinated human fibrinogen (ACF). ACF showed a sensitivity of 55.8% and a specificity of 92.6% for diagnosis of RA after 1 year[9]. ACF were found to be as sensitive as anti-CCP antibodies and more sensitive than RF; ACF were also good predictors of radiographic progression[9].

Antifilaggrin antibodies (AFA). AFA comprise both antikeratin antibodies (AKA) and the antiperinuclear factor (APF). The 2 antibodies have been appraised to be identical or at least closely related[77], both being IgG isotype antibodies that correlate with each other[78,79]. They are both specific markers for diagnosis and prognosis of RA[80,81]. APF proved to be specific for RA, but has not found broad use for reasons of feasibility. The value of APF in UPIA has been investigated by a number of studies[35] that found evidence for diagnostic value, with the exception of one small study (n = 44)[37]. Nevertheless, their prognostic value is considered controversial. AKA are highly specific markers for RA[79]. In undifferentiated arthritis, testing for AKA demonstrated diagnostic and prognostic value[10,11,35,36,37,38,43,45].

Antinuclear antibodies

No association with radiographic outcomes[26], persistence[30], or remission[51] at followup has been documented[69].

Soluble biomarkers of bone and cartilage

Assuming that erosive disease would be reflected in markers of bone and cartilage turnover as well as enzymes involved in these processes[82], such biomarkers have been investigated in RA[83,84,85].

Matrix metalloproteinases (MMP). Although proteolytic enzymes MMP-2 and MMP-9 showed some association with erosive disease, overall serum levels did not correlate with tissue expression[53]. In UPIA, MMP-1 but not MMP-3 or tissue inhibitor of metalloproteinases (TIMP1) serum

levels were of diagnostic value[55] and of limited value for the prediction of joint erosions[55]. Prognostic performance of MMP-3 is poor[21,44]. In conclusion, the value of serum levels of MMP is controversial, and very small at best.

Cartilage oligometric matrix protein (COMP). COMP has been found to have no diagnostic value[18], but Type I and II collagen cleavage and markers of collagen synthesis (CPII)[28] have shown prognostic value for radiographic damage. Other investigated biomarkers have shown no relevant association with radiographic outcome[28,55].

DISCUSSION

In our systematic review of the diagnostic and prognostic value of biomarkers in UPIA, the major results were not unexpected: most evidence on serological markers exists for anti-CCP antibodies and RF, for which an association with diagnosis of RA and radiographic outcome is evident. For AKA and APF, the literature suggests some diagnostic value. For AKA there is also prognostic value, but the respective literature is scant, and therefore additional studies are likely needed to establish more routine use of tests for these antibodies in investigation for UPIA. For all other markers, current evidence does not allow clear conclusions on diagnostic or prognostic merits in the UPIA setting, since the number of studies is small, and results are controversial.

In conclusion, our review aimed to address not only the usefulness of different serologic markers, but also, if applicable, to assess whether repetition of these tests in the followup of patients with UPIA is advisable. However, published data do not allow us to draw conclusions on the optimal frequency of serological or biomarker assessments, and therefore no recommendation can be made in this respect.

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