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The 2010 ACR/EULAR criteria are not sufficiently accurate in the early identification of autoantibody-negative rheumatoid arthritis: Results from the Leiden-EAC and ESPOIR cohorts



Debbie M. Boeters, MD^{a,*}, Cécile Gaujoux-Viala, MD, PhD^b, Arnaud Constantin, MD, PhD^c, Annette H.M van der Helm-van Mil, MD, PhD^a

^a Department of Rheumatology, C1-R, Leiden University Medical Center, PO Box 9600, Leiden 2300RC, The Netherlands

^b Department of Rheumatology, Nîmes University Hospital, EA2415, Montpellier University, Nîmes, France

^c Department of Rheumatology, Centre Hospitalier Universitaire de Toulouse, Hôpital Purpan, Toulouse, France

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ABSTRACT

Objectives: The 2010 ACR/EULAR criteria were derived to classify rheumatoid arthritis (RA) earlier in time. Previous studies indeed observed that the 2010 criteria were fulfilled earlier than the 1987 criteria. This study determined whether the 2010 criteria perform equally in early classification of autoantibody-positive and autoantibody-negative RA.

Methods: From the total Leiden-EAC ($n = 3448$) and ESPOIR ($n = 813$) RA patients who fulfilled the 1987 RA criteria at 1 year but not at presentation were selected ($n = 463$ and $n = 53$, respectively), as these patients were classified with delay with the 1987 criteria. These RA patients were studied on fulfilling the 2010 criteria at baseline (as 2010 positivity indicated that these RA patients were earlier identified) and these analyses were stratified for patients with and without anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF). Analyses were repeated for DMARD start within the first year as reference for RA (instead of fulfilling the 1987 criteria).

Results: In the EAC, 75% of the selected RA patients did already fulfill the 2010 criteria at baseline. In ESPOIR this was 57%, indeed demonstrating early classification with the 2010 criteria. Among the selected autoantibody-positive RA patients of the EAC, 93% was already identified at baseline with the 2010 criteria. Within autoantibody-negative RA this was 51% ($p < 0.001$), indicating that 49% of autoantibody-negative RA patients were not early classified with the 2010 criteria. Similarly, within autoantibody-positive RA patients in ESPOIR 92% were 2010 positive at baseline, whereas this was only 25% within autoantibody-negative RA ($p < 0.001$), indicating that 75% of autoantibody-negative RA patients were not early classified with the 2010 criteria. Similar results were obtained when DMARD start was the reference for RA.

Conclusions: The 2010 criteria perform well in the early identification of autoantibody-positive RA, but autoantibody-negative RA patients are still frequently missed with these criteria. This implies that other diagnostics are required for ACPA-negative patients.

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Introduction

Previously, the 1987 ACR criteria were used to classify patients as rheumatoid arthritis (RA) [1]. Because these criteria had a low

sensitivity to classify RA in an early stage, the 2010 ACR/EULAR criteria have been developed [2]. Several studies have indeed shown that the 2010 criteria are fulfilled earlier in time than the 1987 criteria [3–5]. Cader et al. nicely demonstrated that the 2010 criteria allowed earlier identification of RA than the 1987 criteria. Van der Linden et al. studied 2258 patients that did fulfil the 1987 criteria during the first year but not at baseline. A total of 68% of these patients did fulfil the 2010 criteria at baseline, thus these data also indicated that the 2010 criteria identified RA patients in an earlier phase of the disease.

Early identification of RA is relevant as it allows early treatment. Anti-citrullinated protein antibody (ACPA)-positive and ACPA-negative RA have different genetic and environmental risk

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* Corresponding author.

E-mail address: D.M.Boeters@lumc.nl (D.M. Boeters).

factors and are considered as separate disease subsets. However, early treatment is associated with a higher chance on achieving DMARD-free sustained remission in both subsets [6,7]. Thus both ACPA-positive and ACPA-negative RA patients should be identified early. As described above several studies have been published on the performance of the 2010 criteria in the earlier identification of RA [3–5,8,9]. However, it is undetermined if the 2010 criteria perform equally well in the earlier identification of ACPA-positive RA and ACPA-negative RA, with the 1987 criteria as reference. The recent findings that ACPA-negative patients with RA according to the 2010 criteria have more inflammation than ACPA-positive patients with 2010 RA suggests that the 2010 criteria may perform differently in the early identification of ACPA-positive and ACPA-negative RA [10,11]. To investigate this, this study compared the earlier identification of RA by the 2010 criteria, in autoantibody-positive patients with that in autoantibody-negative patients using data of two early arthritis cohorts.

Materials and methods

Patients

Patients from two different cohorts were studied [12,13]. The Leiden Early Arthritis Clinic (EAC) is an inception cohort that started in 1993 and includes patients with clinically confirmed arthritis and symptom duration < 2 years at presentation at the rheumatologist. The patients studied were included between 1993 and 2015. The total EAC comprised 3448 patients with early arthritis; of these patients, 1645 were not classified as having RA (according to the 1987 criteria) or with other diagnoses at baseline (thus these patients had undifferentiated arthritis, UA) (Fig.). The remaining 1803 patients had RA according to the 1987 criteria ($n = 751$) or other diagnoses ($n = 1052$) and were excluded from further analyses. The Evaluation et Suivi de Polyarthrites Indifférenciées Récentes (ESPOIR) is a cohort in which patients from 14 regional centers were recruited; it was started in 2002. Included were patients with a symptom duration ≤ 6 months and a high clinical suspicion on RA according to the rheumatologist. Patients were aged between 18 and 70 years and had ≥ 2 swollen joints for at least 6 weeks. The ESPOIR cohort comprised 813 patients with

early RA or UA, included between 2002 and 2005. Of these patients 234 were classified as having UA and were included in the present study. The remaining 579 patients had RA according to the 1987 criteria and were excluded from further analyses. Both studies were approved by the local ethical committees; all patients signed informed consent.

Analyses

The 1987 ACR criteria and 2010 ACR/EULAR criteria were applied as described [1,2]. Because up to 2010, the 1987 criteria were the reference for RA, fulfilling these criteria < 1 year was used as reference for RA. In line with van der Linden et al. [5], we selected RA patients that fulfilled the 1987 criteria within 1 year but not at baseline. These RA patients were identified with delay with the 1987 criteria. Of these patients it was determined whether they already fulfilled the 2010 criteria at baseline and thus were earlier recognized as having RA with the 2010 criteria. These earlier recognized RA patients were studied on the presence of ACPA and rheumatoid factor (RF). In subanalyses, DMARD initiation during the first year was used as reference for RA. The presence of ACPA and RF was determined with ELISA (EAC: RF, in-house ELISA [14] and anti-CCP2, eurodiagnostica, the Netherlands, cut-off value ≥ 25 U/ml and anti-CCP2, EliA CCP, Phadia, Nieuwegein, the Netherlands, cut-off 7 U/ml; ESPOIR: RF, Ménarini, France, cut-off value ≥ 9 U/ml and anti-CCP2, Diasorin, France, cut-off value ≥ 50 U/ml). Differences were tested with chi-square test or Fisher's exact test as appropriate. p -Values < 0.05 were considered significant. Analyses were performed using SPSS version 23.0 (IBM).

Results

Of the total Leiden-EAC, 1645 patients were diagnosed with UA at baseline according to the 1987 criteria (Fig.). Of these RA patients, 483 did fulfil the 1987 criteria at 1 year. In total, 20 of these 483 patients were excluded from further analyses because of missing ACPA or RF, leaving 463 patients to study. Thus during the follow-up, 463 patients were diagnosed with RA; however, these patients were missed when applying the 1987 criteria at baseline.

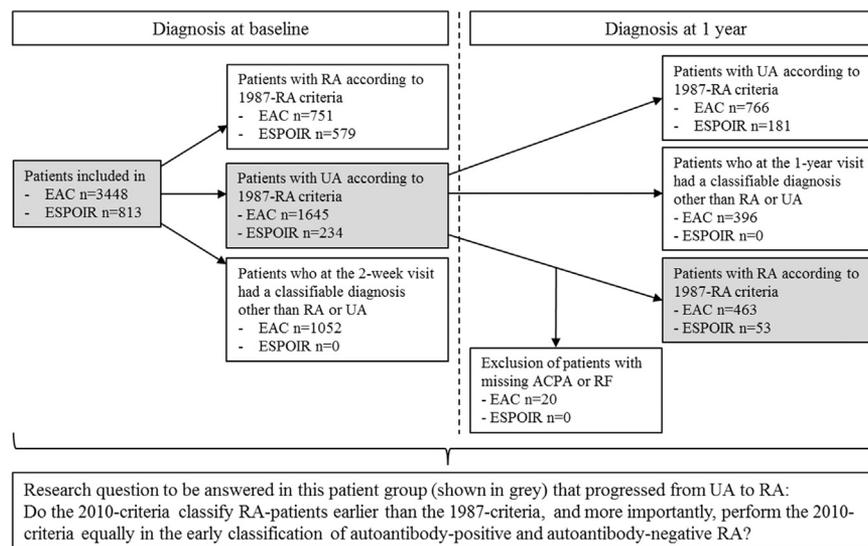


Fig. Flowchart of patient selection (patient group indicated in grey was studied) and research question. Patients that at the 2-week visit (when results of laboratory tests and radiographs were known) had clear diagnoses other than RA were excluded. Also RA patients who fulfilled the 1987 criteria at baseline were excluded. Patients that were classified as having UA according to the 1987 criteria were selected. Of these patients we selected patients who fulfilled the 1987 criteria after 1 year of follow-up; patients with other diagnoses were excluded from further analyses. The selected RA patients were identified with delay with the 1987 criteria. Of these patients it was determined whether they already fulfilled the 2010 criteria at baseline.

Table 1
Baseline characteristics of patients fulfilling the 1987 RA criteria at 1 year but not at baseline

	Leiden EAC (n = 463)				ESPOIR (n = 53)			
	ACPA+ and/or RF+ (n = 258)		ACPA-RF- (n = 205)		ACPA+ and/or RF+ (n = 25)		ACPA-RF- (n = 28)	
Age, mean (SD)	53	(15)	59	(16)	46	(10)	47	(14)
Female, n (%)	181	(70)	128	(62)	20	(80)	23	(82)
Symptom duration, median (IQR), weeks	20	(28)	17	(22)	26	(33)	20	(23)
TJC, median (IQR)	7	(11)	9	(13)	3	(3)	6	(7)
SJC, median (IQR)	5	(6)	7	(11)	3	(1)	4	(3)
ESR (mg/l), median (IQR)	25	(32)	29	(34)	16	(20)	15	(23)
CRP (mg/l), median (IQR)	10	(18)	15	(38)	6	(12)	2	(12)

Leiden EAC, Leiden Early Arthritis Clinic; ESPOIR, Evaluation et Suivi de Polyarthrites Indifférenciées Récentes; N, number of patients; SD, standard deviation; IQR, interquartile range; symptom duration: time between symptom onset and inclusion in cohort; TJC, tender joint count; SJC, swollen joint count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ACPA, anti-citrullinated protein antibodies; RF, rheumatoid factor.

Within the ESPOIR cohort, 234 patients out of 813 RA and UA patients in total were diagnosed with UA at baseline according to the 1987 criteria. Out of these 234 patients 53 did fulfil the 1987 criteria at 1 year and thus were initially missed. Baseline characteristics of the patients studied are shown in Table 1.

Leiden EAC

When applying the 2010 criteria on the 463 RA patients at baseline, 75% (345/463) was identified as RA already at baseline according to the 2010 criteria (Table 2). In total, 200 patients (43%) were ACPA positive and 263 patients (57%) were ACPA negative. Of all 200 ACPA-positive RA patients missed at baseline with the 1987 criteria, 94% (188/200) was 2010 criteria positive at baseline. In contrast, only 60% (157/263) of the ACPA-negative RA patients was 2010 criteria positive at baseline ($p < 0.001$). Similar analyses were performed when considering RF in addition to ACPA (Table 2). Of the 463 patients missed when applying the 1987 criteria at baseline, 258 patients (56%) were autoantibody positive and 205 patients (44%) were autoantibody negative. Of the 258 autoantibody-positive RA patients, who were missed at baseline with the 1987 criteria, 93% (240/258) did fulfil the 2010 criteria at baseline. In contrast, only 51% (105/205) of the autoantibody-negative RA patients was identified at baseline when applying the 2010 criteria ($p < 0.001$).

Finally, to evaluate the frequency with which RA patients were not classified early in time with the current sets of criteria, the proportion of RA patients (fulfilling the 1987 criteria at 1 year) that was missed by both the 1987 and 2010 criteria at baseline was studied. Of the total Leiden-EAC, 1142 patients out of 2396 RA and UA patients in total were diagnosed with RA at 1 year according to the 1987 criteria. In all, 18 autoantibody-positive RA patients were

missed at baseline by both the 1987 and 2010 criteria, which is 1.6% (18/1142) of the total number of RA patients. This is in contrast to 100 autoantibody-negative RA patients that were missed by both criteria at baseline; this comprised 8.8% (100/1142) of the total RA patients.

ESPOIR

Of the 53 RA patients, 57% (30/53) was recognized earlier with the 2010 criteria (Table 2). In total, 15 patients (28%) were ACPA positive and 38 patients (73%) were ACPA negative. Of all ACPA-positive RA patients missed at baseline, 100% (15/15) was 2010 criteria positive at baseline, but only 39% (15/38) of the ACPA-negative RA patients was 2010 criteria positive at baseline ($p < 0.001$). When also considering RF, 92% (23/25) of the autoantibody-positive RA patients was 2010 criteria positive at baseline, in contrast to 25% (7/28) of the autoantibody-negative RA patients ($p < 0.001$).

Subanalyses

To ascertain the validity of our results, the use of DMARDs was also used as outcome measure instead of fulfilment of the 1987 RA criteria at 1 year; this revealed similar results (Table 3).

Discussion

Studying patients from two early arthritis cohorts revealed that the 2010 criteria identify RA patients earlier than the 1987 criteria, which is in line with previous studies [3–5]. The present data now adds the information that autoantibody-positive RA in particular is

Table 2
Proportion of antibody-positive and -negative patients earlier classified with the 2010 RA criteria (2010-RA baseline positive)

	Leiden EAC			p-Value	ESPOIR			p-Value
	ACPA+	ACPA-	Total		ACPA+	ACPA-	Total	
2010 RA baseline negative	12/200 (6%)	106/263 (40%)	118	< 0.001	0/15 (0%)	23/38 (61%)	23	< 0.001
2010 RA baseline positive	188/200 (94%)	157/263 (60%)	345		15/15 (100%)	15/38 (39%)	30	
	200 (100%)	263 (100%)	463		15 (100%)	38 (100%)	53	
	ACPA+ and/or RF+	ACPA-RF-	Total		ACPA+ and/or RF+	ACPA-RF-	Total	
2010 RA baseline negative	18/282 (7%)	100/233 (49%)	170	< 0.001	2/25 ((8%)	21/28 (75%)	23	< 0.001
2010 RA baseline positive	240/282 (93%)	105/233 (51%)	345		23/25 (92%)	7/28 (25%)	30	
	258 (100%)	205 (100%)	463		25 (100%)	28 (100%)	53	

Presented are the patients that fulfilled the 1987 RA criteria within 1-year but not at baseline. Of these patients the number of patients fulfilling the 2010 RA criteria at baseline is presented, divided into ACPA-positive and ACPA-negative patients and into autoantibody-positive and autoantibody-negative patients, respectively. ACPA: anti-citrullinated protein antibodies; RF: rheumatoid factor. Differences were tested with chi-square test or Fisher's exact test as appropriate.

Table 3
Proportion of autoantibody-positive and -negative patients earlier classified with the 2010 RA criteria (outcome DMARD-use)

	Leiden EAC			p-Value	ESPOIR			p-Value
	ACPA+	ACPA–	Total		ACPA+	ACPA–	Total	
2010 RA baseline negative	22/215 (10%)	224/421 (53%)	246	< 0.001	0/34 (0%)	48/101 (48%)	48	< 0.001
2010 RA baseline positive	193/215 (90%)	197/421 (47%)	390		34/34 (100%)	53/101 (52%)	87	
	215	421	636		34	101	135	
	ACPA+ and/or RF+	ACPA-RF-	Total		ACPA+ and/or RF+	ACPA-RF-	Total	
2010 RA baseline negative	36/300 (12%)	217/360 (60%)	253	< 0.001	3/52 (6%)	45/83 (54%)	48	< 0.001
2010 RA baseline positive	264/300 (88%)	143/360 (40%)	407		49/52 (94%)	38/83 (46%)	87	
	300	360	660		52	83	135	

Instead of fulfilling the 1987 criteria at 1 year as outcome, DMARD initiation was used as outcome measure. Total numbers are patients not fulfilling the 1987 criteria at baseline but who are treated with DMARDs at 1-year follow-up. Of these patients the number of patients fulfilling the 2010 RA criteria at baseline is shown, divided into ACPA-positive and ACPA-negative patients and into autoantibody-positive and autoantibody-negative patients, respectively. ACPA, anti-citrullinated protein antibodies; RF, rheumatoid factor; DMARDs, disease modifying antirheumatic drugs. Differences were tested with chi-square test or Fisher's exact test as appropriate.

earlier identified with the 2010 criteria, in contrast to autoantibody-negative RA.

This finding is not surprising since the autoantibodies ACPA and RF are heavily weighted in the 2010 criteria. Autoantibody-negative patients should have more than 10 tender or swollen joints together with abnormal acute phase reactants and ≥ 6 weeks symptom duration to be classified with RA. In contrast, autoantibody-positive patients can already fulfil the 2010 criteria when they only have two involved joints if they fulfil the acute phase reactants and symptom duration criteria [2]. Nordberg recently demonstrated that ACPA-negative patients fulfilling the 2010 criteria for RA indeed had more severe inflammation than ACPA-positive patients fulfilling these criteria [10]. The current data show a consequence of this recent finding for the early identification of RA. This finding is a consequence of the circularity of the different components of the criteria, and awarding a stronger weight on autoantibodies automatically implies that patients without autoantibodies require more of the other components to fulfil the criteria. A recent meta-analysis on the 2010 criteria revealed that the 2010 criteria have a moderate specificity, especially when the expert opinion was used as reference [15]. Additionally, it has been observed that the long-term outcome of patients fulfilling the 2010 criteria is different from that of patients fulfilling the 1987 criteria, suggesting that the criteria identify a slightly different set of patients [16]. Despite the existing literature on the 2010 criteria, the consequence for the early classification of ACPA-negative RA in particular has not yet been clearly described.

Although the findings done here are a logic consequence of the composition of the 2010 criteria, the difference between the “old” versus the “new” classification criteria for RA can have consequences, for instance when the criteria are used to select patients for trials that are performed in very early phases of RA. When conducting clinical trials in early disease stages and fulfilment of the 2010 classification criteria is used in the inclusion criteria, autoantibody-positive patients in particular can be included in an early phase, in contrast to autoantibody-negative patients, who are less often classified as RA in an early phase [8,17]. Then future trials will reveal less evidence on the effect of treatments in early autoantibody-negative RA.

The 2010 criteria were developed for classification and not for diagnosis, but in practice may sometimes be used in the diagnostic process or influence the diagnostic process in daily practice. When this happens, ACPA-negative patients are possibly more often identified later in time than ACPA-positive patients. This is unfortunate as early treatment is observed to be relevant for both subsets of RA [6,7,18]. Thus additional tools are required to also recognize these ACPA-negative RA patients early. In total, 10% of all

RA patients are not early identified of which almost 9% are autoantibody negative.

The pathogenesis of ACPA-negative RA is less well understood and presumably ACPA-negative RA consists of a variety of subgroups with differences in etiopathology. This latter view is supported by the finding that part of the ACPA-negative patients have no joint destruction, whereas others do have a severely destructive disease [19]. Despite the difficulties with the conception of ACPA-negative RA, it is nowadays questionable if ACPA-negative RA patients suffer less than ACPA-positive RA patients. Clinically relevant joint damage has become infrequent and several studies evaluated other disease outcomes and observed that ACPA-negative RA patients have at least as much functional disability and similar disease activity scores as ACPA-positive patients [10,11,20]. In addition, most ACPA-negative RA patients do have a chronic disease course [11]. Moreover, it has been shown that early DMARD initiation is beneficial in ACPA-negative RA [21]. Finally, the recent findings that the majority of autoantibody-negative RA patients who do not fulfil the 2010 criteria do require DMARD therapy over time and have a persistent disease course underline the importance to also classify these RA patients early in time [3,22]. Based on the combination of these findings, we feel that early classification or early identification of ACPA-negative RA is relevant.

In this study, fulfilment of the 1987 RA criteria after 1 year follow-up was chosen as reference because these criteria perform well in advanced disease. Additionally, the 1987 criteria reflect the situation before the introduction of the new 2010 criteria which makes it a specific reference of RA. In sub-analyses, DMARD use during the first year was used as reference for RA and this showed similar findings for the performance of the 2010 criteria in the early classification of RA, showing robustness of the data.

A potential limitation is that the inclusion criteria of both cohorts were slightly different. The EAC is an inception cohort and the only referral center in a region. ESPOIR is a nationwide observational cohort of patients with suspected RA that not necessarily included all patients with RA in the participating regions. Furthermore, in contrast to ESPOIR, the EAC included patients with ≥ 1 swollen joint (and the RA criteria were applied in retrospect). These differences may explain the difference in proportion of RA patients who initially presented with UA. Despite these differences the trend in the data was similar.

Conclusions

In conclusion, this study showed that autoantibody-positive RA is more often early identified with the 2010 criteria than

autoantibody-negative RA. This implies that other diagnostic methods or other diagnostic tests are required for the early identification and early classification of autoantibody-negative RA.

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