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Original article

Validation of the 2010-ACR/EULAR – classification criteria using newly EULAR-defined erosion for rheumatoid arthritis on the very early arthritis community-based (VErA) cohort

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ABSTRACT

Objective: To validate the 2010-ACR/EULAR criteria for rheumatoid arthritis (RA), taking into account the recent EULAR definition of “erosive disease”, on the 310 patients comprising the very early arthritis cohort (VErA).

Methods: 2010-criteria performances were tested by first strictly applying its three items successively: ≥ 1 clinical synovitis/another disease(s)/score $\geq 6/10$, then the typical erosion grid without obtaining a score of ≥ 6 to diagnose RA. We tested successively: no erosion (S1), ≥ 1 erosion(s) (S2), EULAR-defined erosive disease (S3). Two gold standards were used: expert diagnosis at six years and EULAR erosive disease at two years.

Results: At inclusion, median age was 52 years; median RA duration 4.2 months. 2010-ACR/EULAR criteria, including EULAR-defined erosive disease applied at baseline, classified comparable numbers of patients as the 1987 criteria ($P=0.27$). Using expert diagnosis at six years, more patients were classified as RA with S2 than 1987-ACR criteria ($P<0.04$). In contrast, sensitivity and specificity indicated that 2010-ACR/EULAR-S3 criteria performed slightly but not significantly better than 1987-ACR criteria. On ROC curves, a score ≥ 6 correctly classified RA. When EULAR-defined erosion at two years was the gold standard, the 1987-ACR, the 2010-S1, -S2 and -S3 criteria performed comparably.

Conclusions: Using the very early community-based, conservatively treated VErA cohort, the strict application of 2010-ACR/EULAR criteria using the new EULAR definition of erosive disease or not performed slightly but not significantly better than the 1987-ACR criteria.

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1. Introduction

Very early diagnosis and appropriate treatment of rheumatoid arthritis (RA) is now a major goal [1]. The 1987 criteria and their modified versions inadequately classified early stage RA [2–4]. Consequently, algorithms were constructed to predict high risk of persistent and/or erosive disease [5,6]. An American College of Rheumatology/European League against Rheumatism (ACR/EULAR) task force published new 2010 classification criteria for early RA [1]. In those criteria, the definition of “erosive

disease typical of RA” was not clear. Very recently, a EULAR task force proposed a clear definition of erosion status [7]. 2010-ACR/EULAR-classification criteria were based on nine early arthritis cohorts. The objective was to identify, among undifferentiated arthritis, those at high risk for persistent and/or erosive disease, as this paradigm underlies what we commonly call “RA”. The gold standard was starting methotrexate within the first 12 months [1]. Before these new criteria and the new definition of “erosive disease” can be used in practice, their performances must be evaluated on independent cohorts. To assure their robustness, these criteria must be tested on cohorts with different disease probabilities. This study was undertaken to validate the 2010-ACR/EULAR criteria, taking into account the new EULAR definition of erosive disease, on

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the independent, community-based, very early arthritis (VErA) cohort.

2. Methods

The VErA cohort was described previously [8]. Briefly, this community-based, inception cohort was recruited between 1998 and 2002 in two French regions. It comprised 310 patients: male or female, age ≥ 18 years; ≥ 2 swollen joints, swelling persisting for > 4 weeks, symptoms lasting < 6 months; no previous glucocorticoid prescription [only one intra-articular injection > 1 month before or oral prednisone (< 10 mg/day) for 1 week > 2 weeks before enrollment were tolerated] or disease-modifying antirheumatic drugs (DMARDs); no inflammatory back pain; no foreseen move during the 10 next years. The protocol recommended conservative treatment within the first two years [8]. This study was approved by the Upper Normandy Ethics Committee (file 95/138/HP). All patients gave their informed consent. Patients with definitive diagnoses of another classified arthritis (ACA), satisfying international criteria at inclusion, were immediately withdrawn from the cohort. The other patients, including those with self-limiting disease, were followed every six months for at least six years [8]. Every year, a three-expert panel (XLL, AD and PF) classified the patients as having RA, ACA or unclassified arthritis (UA). For patients previously diagnosed as having RA but lost-to-follow-up, this diagnosis was carried forward. This cohort was not used to develop 2010-ACR/EULAR criteria [1].

Performances of the 2010-ACR/EULAR criteria taking into account the new EULAR definition of erosive disease, and 1987-ACR-classification criteria, were compared: numbers of patients classified as having RA, sensitivities, specificities, positive- and negative-predictive values, and likelihood ratios for RA diagnosis using previously proposed thresholds [1,2]. 2010-ACR/EULAR criteria were tested by strictly applying the three items successively (≥ 1 clinical synovitis/another disease(s)/score $\geq 6/10$), and then the typical erosion grid without obtaining a score of at least 6 to diagnose RA. For erosion status, we tested successively the three following situations: S1: ACR/EULAR score ≥ 6 and no erosion; S2: score ≥ 6 or [score < 6 and ≥ 1 erosion(s)], and S3: score ≥ 6 or [score < 6 and EULAR-defined erosive disease]. The EULAR definition applied was: ≥ 3 joints at any of the following sites: proximal interphalangeal, metacarpophalangeal, wrist (counted as one joint) and metatarsophalangeal joints [7]. We tested the one-erosion condition (S2), because it was the lowest number possible not excluded in the initial 2010-ACR/EULAR criteria, and the absence of erosion (S1) to evaluate the relevance of the new EULAR definition of erosion status (S3).

For the diagnosis of RA versus non-RA, we used two gold standards: expert diagnosis at six years of follow-up and EULAR-defined erosive disease at two years [erosion Sharp-van der Heijde score]. Hand and foot X-rays were obtained and analyzed according to a rigorous procedure previously reported [8]; briefly, each antero-posterior, frontal, hand, wrist and foot radiograph was obtained separately. The procedure relied on precise positioning of the patient, centering of the X-ray beam, and exposure of appropriate films. The constants were the same for each series of images of a given patient. Quality was systematically controlled. Films were centralized and read independently by two experienced readers (PF and OM), blinded to the patient's identity and diagnosis. In the case of disagreement, consensus was reached immediately. Inter-reader reproducibility for the presence of erosion(s), defined as an unequivocal cortical break, was estimated with Cohen's kappa (0.94, 95% confidence interval [95% CI] 0.86–1.00), and for the Sharp-van der Heijde erosion score was estimated with the intra-class correlation coefficient (0.92, 95% CI 0.89–0.94) and the

mean \pm SD (0.04 ± 0.9) of the difference between the two readers' measurements. For the expert diagnosis, each patient's 6-year medical file was anonymously reported, including clinical symptoms and signs but not treatment(s). The 1987-ACR-classification components were not explicitly given to the three highly experienced senior experts in RA. For classification as ACA, RA or UA, they first diagnosed ACA (yes/no); second, if not ACA, they used a Likert scale to classify the entity as RA or UA. In the case of disagreement, consensus was reached immediately, i.e., all experts agreed or indicated they accepted the majority decision [8]. Starting methotrexate within the first year was not considered because, as defined in the protocol, the patients were conservatively treated [8]. For baseline characteristics, values are medians [range] or numbers.

Non-parametric receiver operating characteristics (ROC) curves were used to assess the sensitivities and specificities of the 1987-ACR, and 2010-ACR/EULAR-S1, -S2 and -S3 criteria. A patient was classified as having RA versus non-RA at different score-cutoff values: 1987-ACR $\geq x1$ (range 0–7); 2010-ACR/EULAR $\geq x2$ (range 0–10 for all three situations): -S1: $\geq x2$ and no erosion; -S2: $\geq x2$ or [score $< x2$ and ≥ 1 erosion(s)]; -S3: $\geq x2$ or [score $< x2$ and EULAR-defined erosion]. Areas under the curves (AUC) and their 95% CI were calculated and compared. The sensitivities and specificities at thresholds of 4 for 1987-ACR and 6 for 2010-ACR/EULAR criteria were compared with the exact McNemar test. Statistical analyses were run using NCSS v.2007 (Kaysville, UT) and StatXact v.8 software (Cytel Software Corporation, Cambridge, MA). All tests were two-tailed and $P \leq 0.05$ defined significance.

3. Results

At inclusion ($n=310$), median [range] patient age was 52 [19–84] years, with a median of 4.2 [0.9–6] months since symptom onset; 68.1% were female. All patients had ≥ 2 synovitis; 52 (16.8%) were erosive. Median values of relevant parameters were as follows: numbers of painful joints 6/68 [0–58], with 7/66 [2–37] swollen joints; Disease Activity Score-28 (DAS) was 2.95 [0.45–7.53]; erythrocyte sedimentation rate 18 [1–110] mm 1st hour; and C-reactive protein 7 [5–206] mg/L. No patient with a 2010-ACR/EULAR score < 6 had EULAR-defined erosive disease. Forty-one (13.2%) patients were classified as ACA (for details see [8]). The 269 (86.8%) remaining patients had clinical and biological characteristics comparable to those of the whole population (data not shown). The 2010-ACR/EULAR-classification score was applied to these 269 patients: 170/269 (63.2%) scored ≥ 6 were classified as RA: among them, 28/170 (16.5%) had ≥ 1 erosion(s) and 6/170 (3.5%) had EULAR-defined erosive disease; 99/269 (36.8%) had a score < 6 : among them, 12/99 (12.1%) had ≥ 1 erosion(s) and 0/99 had EULAR-defined erosive disease. Classification as RA was not significantly better than that obtained with 1987-ACR criteria, respectively: 63.2% versus 59.5% ($P=0.27$).

3.1. 1st gold standard: expert diagnosis of RA at six years

After six years of follow-up, 227/269 patients were available for analysis; 42 UA had been lost-to-follow-up. The 47 patients previously diagnosed as RA, who had prematurely left the cohort, were included in the analysis (cf. Methods). Compared to the expert panel's diagnoses, the sensitivity of ACR/EULAR-S2 criteria was significantly higher than that of the 1987-ACR criteria: 85.9% versus 77.9% ($P < 0.04$) (Table 1). The 83.9% sensitivity of 2010-ACR/EULAR-S1 or -S3 criteria was slightly but not significantly better ($P=0.15$) than the 77.9% of the 1987-ACR criteria; similarly, the 70.5% specificity of 2010-ACR/EULAR-S1 or -S3 criteria was slightly but not significantly better ($P=0.38$) than the 64.1% of the 1987-ACR criteria. The specificities of the 2010-ACR/EULAR-S1 criteria and -S3

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