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Should ACR/EULAR criteria be revised changing the RF and ACPA scores?

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ABSTRACT

Current classification criteria for rheumatoid arthritis (RA) encompass clinical and immunological items and are capable of correctly identifying the majority of symptomatic RA patients. The presence of positive rheumatoid factor (RF) and/or and anti-cyclic citrullinated protein/peptide antibodies (ACPA) gaining increasing importance according to their serological titer eases the recognition of RA, yet the debate is open on whether this scoring system ought to be optimized by hierarchizing ACPA or the combination of ACPA and RF over single positivity, prioritizing specificity over sensitivity. The risk of misdiagnosis and misclassification are often entangled, yet they are not the same. In fact, while ideal diagnosis requires 100% sensitivity and specificity, classification criteria are conceived to gather a homogeneous patient population, favoring specificity over sensitivity. Nevertheless, as they are frequently summoned to support the diagnostic process in clinical practice, issues arise on how comprehensive those should be and on how frequently they should be updated in light of novel acquisitions regarding measurable RA-related abnormalities.

In this viewpoint two different views on the topic are confronted, discussing the performance of available criteria and the potentiality and pitfalls of their refinement according to novel data on ACPA and RF contribution and emergence of newly discovered specificities.

1. Introduction

Rheumatoid arthritis (RA) is classified according to American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR)2010 criteria [1], which encompass clinical and immunological items, requiring a score of at least 6 points for a patients to be classifiable as affected with RA. Current classification criteria include both the hallmark autoantibodies in RA, namely rheumatoid factor (RF) and anti-cyclic citrullinated protein/peptide antibodies (ACPA). Low or high (>3 upper limit of normal) autoantibody titers are differently weighted within the criteria set, resulting in enhanced specificity for RA conferred by higher titers of any. Importantly, classification criteria are most likely to favor specificity over sensitivity, as they are primarily used to gather a homogeneous patient population under a same diagnostic label for research purposes; nonetheless, recent classification criteria sets across different rheumatic diseases aimed at improving both specificity and sensitivity, so that a more comprehensive patient inclusion can occur [2,3]. So far, several autoantibody specificities subjected to different post-translational modifications have emerged in RA [4,5]; moreover, recent data have highlighted the heterogeneity within the ACPA pool [6], ultimately submitting the existence of inherent protective autoantibodies [7], which contribute to the complexity of the overall picture and raise the issue of the current criteria as being capable of comprehensively identify affected patients.

Here, we report the views of prominent experts in the field addressing pros and cons of revising the current EULAR/ACR 2010 classification criteria by modifying the RF and ACPA scores to improve RA recognition in clinical practice.

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2. ACR/EULAR criteria should be revised changing the RF and ACPA scores

RF and ACPA are included in the ACR/EULAR 2010 classification criteria for RA(1). Several studies [8–12] demonstrated an increased diagnostic sensitivity (73.5% to 84%), but decreased diagnostic specificity (60% to 71%) of the ACR/EULAR 2010 criteria to the former ACR 1987 RA criteria [13]. The drawback of decreased specificity of the ACR/EULAR 2010 classification criteria is the risk of misclassification and over-diagnosis at baseline. The lower specificity partially relates to RF and ACPA positivity as documented in a study in which the criteria were applied in a cohort of patients with very early inflammatory arthritis [12].

2.1. Drawbacks in the serological category of the 2010 ACR/EULAR classification criteria for RA

In the ACR/EULAR 2010 classification criteria for RA, a low positive RF or a low positive ACPA contributes two points while a high positive (>3-times the upper limit of normal) RF or ACPA contributes 3 points; a score of ≥6 points allows classification of RA and is therefore indicative of definite RA(1). Several reports in literature agree that the higher the concentration of RF or ACPA, the higher the likelihood ratio (LR) for RA [14,15]. The ACR/EULAR 2010 classification criteria provide the same scoring weight to positive RF and ACPA results. However, it is well known that ACPA has a significantly higher specificity and LR for RA than RF [15–19] as RF can be detected in other rheumatic disorders, infections and in apparently healthy individuals with an incidence that increases with age [20,21]. Moreover, the classification criteria do not consider a difference in scoring weight for combined positivity of RF and ACPA compared to single positivity [22–25]. There is some data that indicated that by changing the weight factors of the serological grades based on the inherent diagnostic performance of RF and ACPA, the specificity of RA classification can be enhanced without affecting sensitivity [26] and Van Hoovels et al., unpublished data). By attributing a higher importance to high antibody levels than to low antibody levels, a higher importance to ACPA than to RF and a higher importance to combined RF and ACPA positivity than to single positivity, a gain in specificity of the 2010 classification is expected.

2.2. Exploratory RA cohort: increasing diagnostic specificity without affecting sensitivity

Taking the different specificities of ACPA and RF into account we aimed to improve diagnostic specificity of the ACR/EULAR 2010 criteria. To address this issue we used the cohort of the SAVE (Stop Arthritis Very Early) trial [27], including 325 patients with early arthritis, derived from 25 clinical centers, of which after a one year follow-up period 131 were diagnosed as having RA while 194 patients had other rheumatic diseases (rheumatic disease control group, RDCG). The SAVE cohort had previously been used for validation of the ACR/EULAR 2010 criteria [12].

Table 1
Serology results of the rheumatoid arthritis cohort (RA, $n = 132$) and inflammatory rheumatic disease control group ($n = 193$) of the SAVE trial (6).

ACPA	RF-IgM	RA (pos) (%)	RDCG (pos) (%)	LR
Total		51.5	3.6	**14.3**
	Total	50.0	8.3	**6.0**
Pos	Pos	45.4	2.1	**21.6**
Neg	Low	2.3	4.1	**0.6**
Neg	High	2.3	2.1	**1.1**
Low	Neg	1.5	0.0	**n.a.**
High	Neg	4.5	1.6	**2.8**
Low	Pos	2.3	0.0	**n.a.**
High	Pos	43.1	2.1	**20.5**

The serology results are summarized in Table 1: positive RF results were obtained for 50.0% of the RA population and 8.3% for the RDCG (LR 6.0); positive ACPA results were obtained for 51.5% of the RA population and 3.6% for the RDCG group (LR 14.3); positive serology for both ACPA and RF was obtained in 45.4% of the RA cohort, but only in 2.1% of the RDCG cohort (LR 21.6). Further analysis of the data revealed that high RF in the absence of ACPA was only weakly specific (LR 1.1) and low RF was even more prevalent in RDCG patients (LR 0.6). In contrast, high ACPA in the absence of RF was moderately specific for RA (LR 2.8); however, specificity was considerably augmented by the presence of both low or high RF (LR 20.5). Low ACPA was rarely observed in RA patients and not at all in the RDCG and therefore its specificity could not be properly evaluated.

2.3. Suggested modification of the 2010 ACR/EULAR classification criteria for RA

Considerable differences in diagnostic performance were not only seen between RF and ACPA but especially also between single and double positivity. Particularly, RF in the absence of ACPA showed little specificity for RA while even high ACPA in the absence of RF was only moderately specific. However, RF/ACPA double positivity was highly specific for RA, being detectable in almost half of the RA patients but rarely in disease controls.

Therefore, we propose that different weights should be given based on the antibody type (RF versus ACPA), the antibody level and the combined positivity. Based on unpublished data (Van Hoovels et al., manuscript in preparation) and on the data presented above, a suggestion for refined weights of serological scores for RA classification is presented in Table 2: “0” for both RF and ACPA negative patients as well as for isolated low positivity for RF; “1” for isolated high positivity for RF; “2” for isolated and low ACPA positivity; “3” for low ACPA combined with RF positivity and for isolated high ACPA positivity; “4” for high ACPA combined with RF positivity.

Applying the refined score in RA classification reduced RA misclassification of seropositive RDCG patients from 79.0% (ACR/EULAR classification) to 47.4% (refined scoring) without affecting diagnostic sensitivity (87.1% for both classification scores).

2.4. YES: modification of the 2010 ACR/EULAR classification criteria is warranted

In conclusion, our results reveal and confirm that:

(i) a positive RF result in absence of ACPA is not specific for RA (with low RF being even more prevalent in disease controls);
(ii) a positive ACPA result in absence of RF is moderately specific for RA;
(iii) the co-occurrence of ACPA and RF is highly specific for RA and considerably more specific than ACPA by itself.

Since a refined serological scoring system significantly reduced misclassification of (seropositive) RDCG patients without affecting sensitivity we strongly suggest to modify the ACR/EULAR 2010 criteria accordingly. The modified criteria are easy to apply and take into account the well-known fact that ACPA is much more specific than RF.

Table 2
Suggestion for refined weights of serological scores for RA classification, with high positivity as defined in the 2010 ACR/EULAR RA classification criteria, i.e. >3-times the upper limit of normal.

Antibody	negative	RF low	RF high	ACPA low	ACPA high	ACPA low/RF	ACPA high/RF
Score	0	0	1	2	3	3	4

Giving the same weight to both antibodies is therefore no longer justified, especially because of the low specificity of RF, and may lead not only to misclassification but also to a false diagnosis with potentially unfavorable consequences for the patient. Moreover, this scoring system would even allow to classify patients with a zero joint score (i.e. no swollen joints) but at high risk for developing RA (i.e. seropositive patients with arthralgia) for inclusion in arthritis prevention trials which are of high interest and might indeed be considered a novel treatment strategy in the not too distant future [28,29].

3. ACR/EULAR criteria should not be revised changing the RF and ACPA scores

The development of RA consists of several step. It starts with initiation by genetic and environmental factors. This would lead to autoimmunity along with the production of RF and ACPA. ACPA might appear in the blood up to 10 years prior to the clinical onset of RA. All this would trigger arthralgia (clinically suspect arthralgia, CSA), then undifferentiated arthritis (UA) and finally the classification criteria for RA would be met [30,31].

There have been several classification criteria systems for RA. In 2010, the ACR/EULR collaborative initiative developed the latest criteria. Within this scoring system, negative, low-positive or high-positive RF or ACPA are scored 0, 2 or 3 points, respectively [31,32].

Recently, the group of Günter Steiner published some studies that at least this part of the ACR/EULAR classification criteria could be refined [14,32].

3.1. The current classification criteria are fine

We think that the above discussed autoantibody part of the classification criteria are fine and sufficient to classify RA [31].

Negative, low- or high-positive RF/ACPA can nicely differentiate between RA and UA. In the SAVE cohort study of Biliavska et al. [12], 144 RA and 98 UA patients, as well as 26 patients with other diagnosis after 12 weeks were compared with respect to the above RF or ACPA criteria. In RA, 42% had high-, only 8% had low-positive RF or ACPA, while 50% had normal RF/ACPA. In contrast, 91% of UA patients and 81% of patients with other diagnosis were RF/ACPA negative. Thus, the current ACR/EULAR criteria were sufficient to differentiate between RA, UA and other diseases [12].

In a Swedish twin study published by Hensvold et al. [33], high-positive ACPA was sufficient for the diagnosis of RA. In the study on 12,590 individuals, ACPA levels were the highest in prevalent RA, lower in future incident RA and the lowest in subjects without RA. The best discriminator was high-positive ACPA. The relative risk (RR) for RA was 64 versus 94 in ACPA positive and ACPA high-positive individuals, respectively [33].

When denominators of CSA progression to definite RA were investigated, Burgers et al. [19] found that ACPA positivity itself was a good prognostic factor. When comparing 30 ACPA positive and 37 ACPA negative patients with CSA, ACPA positive patients had a significantly higher chance to develop RA [19].

ACPA positivity is also sufficient to predict structural damage. Grosse et al. [34] used conventional radiography and ultrasonography to investigate baseline factors predictive for joint erosions. Among several possible denominators (age, gender, disease, duration, disease activity index (DAS)28, ACPA and RF positivity and erythrocyte sedimentation rate [ESR]), in the multivariate regression analysis, only ACPA positivity predicted structural damage as determined by either radiography (OR 4.4) or ultrasonography (OR 3.7). Disease duration only had a very slight impact (OR 1.1–1.2) on radiographic damage. RF positivity was not associated with structural damage in this cohort [34].

Humphreys et al. [35,36] reported mortality data from the British NOAR and the Dutch Leiden EAC cohorts. When antibody negativity, single and double antibody (RF and ACPA) positivity were compared with respect to survival, patients with RF and ACPA double positivity had the poorest survival, followed by single antibody (RF or ACPA) positivity. The most favourable survival was observed in seronegative patients. Thus, RF and/or ACPA positivity are sufficient for assessing prognosis in early RA [35,36].

We have also suggested that in addition to ACPA positivity, ACPA absolute levels might also be important. In our study associating genetic (HLA-DR) background of RA with ACPA levels, we found that RA patients carrying HLA-DR1, -DR4 and, interestingly, HLA-DR13 and -DR15 alleles have much higher ACPA levels (100–500 U/ml) compared with those carrying other HLA-DR alleles (HLA-DR3, -DR7, -DR8, -DR11, -DR14 or -DR16) [37]. Laki et al. [38] also reported very high ACPA levels in patients carrying the non-shared epitope HLA-DR15. Thus, low versus high ACPA positivity might indeed be important and might be associated with genetic susceptibility to RA [37,38].

Finally, the RA classification criteria, as well as studies above mostly put ACPA and RF on the same level. Some studies suggest that ACPA itself, even without RF, could be sufficient for the classification of RA. The studies of Hensvold et al. [33], Grosse et al. [34] and Burgers et al. [19] suggesting that ACPA itself might be sufficient were already discussed above. In addition, van der Linden et al. [8] assessed whether the determination of RF could even be omitted. In this study, early arthritis cohorts were evaluated for clinical remission and radiographic damage in association with ACPA positivity/negativity and low versus high RF levels. ACPA positivity was far the best denominator for cumulative remission and ACPA negativity for radiographic damage. RF levels had much poorer performance [8].

All these studies suggest that autoantibody, especially ACPA positivity versus negativity or low- and high-positivity might be sufficient for RA classification and outcome prediction. Therefore, we do not recommend to modify the current ACR/EULAR classification criteria.

3.2. If modifying, what to change?

So, we suggest that the laboratory part of the ACR/EULAR classification criteria needs no modification. However, some other aspects might be considered.

One could extend the number of anti-modified protein antibody (AMPA) specificities and maybe add anti-carbamylated and anti-acetylated AMPAs. Figueiredo et al. [39] reported that the number of AMPA reactivities were associated with relapse of RA. It is possible that other AMPAs in addition to ACPA could also increase the performance of RA classification [4,39,40].

The group of Günter Steiner in collaboration with van Hoovels et al. [41] also suggested that the standardization of ACPA tests are definitely needed. We highly agree with this. Both ACPA and RF results highly vary among different manufacturers. This needs to be corrected and applied to the RA classification procedure [41].

In summary, we do not recommend the modifications suggested by Günter Steiner and his group. However, on the long-term, ACPA might be preferred over RF and some other modifications (e.g. use of more AMPAs) could be introduced.

4. Conclusions

Classification criteria always deal with the critical trade-off between entailing sufficient sensitivity and adequate specificity, in order to capture a wide yet homogenous patient population. As knowledge on pathogenesis grows leading to identification of distinguishing disease features, the attempt of incorporating novel biomarkers resulting in more precise patient profiling may challenge established settings. Regular reassessment of sets of classification criteria is scheduled to keep track of amenable changes. Currently, data are emerging which suggest that modifications in the composition of the autoantibody panel included in RA classification might improve the performance of present criteria, yet testing in appropriately powered validation cohorts is

needed. While results from ongoing and recently concluded studies gather, careful clinical interpretation, prompt referral to specialized centers and integration of sensitive imaging techniques when deemed appropriate are required to maximize early identification of RA even before criteria are fulfilled, including recognition and tight follow-up of high-risk individuals.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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