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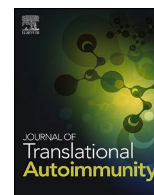

Anti-dsDNA antibodies in the classification criteria of systemic lupus erythematosus

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ABSTRACT

Anti-double stranded DNA (dsDNA) antibodies play an important role in the diagnosis, classification and management of systemic lupus erythematosus (SLE), an autoimmune disease characterized by heterogeneous clinical manifestations and a wide range of autoantibodies, which makes the diagnosis quite challenging. In the absence of diagnostic criteria, classification criteria have been used for many decades. The first classification criteria for SLE were formulated in 1971 by the American College of Rheumatology (ACR), followed by two revisions in 1982 and 1997. In order to improve their clinical performance and to reflect new knowledge on autoantibodies, new classification criteria for SLE were issued in 2012 by the Systemic Lupus International Collaborating Clinics (SLICC). These criteria proposed to classify only patients that have at least one immunologic criterion, overcoming SLE classification based solely on clinical manifestations. In 2019, the European League Against Rheumatism (EULAR)/ACR proposed new criteria that aimed to maintain the high specificity of the ACR criteria with a sensitivity close to the SLICC 2012 criteria. These 2019 criteria reinforced the importance of autoantibodies in SLE diagnosis, assigning the highest score (6 points) to anti-dsDNA antibodies in the fully weighted scoring of the disease. The current criteria require the use of an anti-dsDNA assay with at least 90% specificity, such as the *Crithidia luciliae* immunofluorescence test (CLIFT) or FARR assay. However, the criteria do not comment on all the tests currently widely used in clinical laboratories. Neither do they consider the technological evolutions, nor standardization issues. Since strict adherence to any of the classification criteria, including the serological items, could lead to possible misclassification of SLE and/or delayed diagnosis, test characteristics of the distinct immunoassays should be taken into consideration.

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease with multiorgan involvement, characterized by a wide variety of clinical manifestations and by the production of multiple and heterogeneous autoantibodies. The clinical and serological complexity of the disease makes diagnosis quite challenging, not only in the early stage but also as the disease evolves over time due to overlapping features with other systemic autoimmune rheumatic diseases (SARD).

The importance of autoantibodies in the diagnosis of SLE dates back to 1957, when it was suggested for the first time that antibodies reactive with DNA were responsible for the LE cell phenomenon described previously in SLE patients [1–4]. In the next decades, a remarkable spectrum of autoantibodies targeting other nuclear antigens has been described in SLE (over hundred) [5,6], reflecting the characteristic immunoserological polymorphism of the disease. Anti-nuclear autoantibodies (ANA), including anti-dsDNA, anti-histone, anti-nucleosome and antibodies to extractable nuclear antigens (ENA) [anti-Sm,

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anti-SSA/Ro, anti-SSB/La, anti-small nuclear ribonucleoproteins (anti-snRNP)], are usually responsible for ANA positivity detected in the routine laboratory setting by indirect immunofluorescence assay on HEp-2 cell substrates (HEp-2 IIFA), and as such, became important tools in the diagnosis of SLE. Although highly sensitive for SLE, the specificity of ANA is limited by their occurrence in other autoimmune diseases and in non-autoimmune conditions, including drug use, infection, malignancy and old age. In a recent evaluation of the combined European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) derivation and validation cohorts (1197 SLE patients and 1074 non-SLE population), ANA had high sensitivity, but only 19.4% specificity. The position of ANA as entry criterion as opposed to ANA as separately valued (immunological) criterion in previous classification criteria, and the attribution rule (items count towards SLE only if there is no more likely alternative explanation) proved to be the key element to increase the specificity of the EULAR/ACR criteria [7]. In addition, though the prevalence of individual ANA and their clinical associations [8] is well documented, variation in the frequency of these autoantibodies may be observed among different cross-sectional studies [9–11].

Given this complexity, it is not surprising that development and implementation of diagnostic criteria for SLE is very cumbersome, and as such, still not available. For this reason, classification criteria are often used in the clinical diagnosis of SLE. But unlike diagnostic criteria, which should focus on individual patients in order to reflect all possible features of the disease with both high diagnostic sensitivity and specificity, classification criteria are primarily intended to create a more homogeneous group of patients for clinical research purposes [12], thus privileging specificity even at loss of sensitivity. Diagnostic criteria would also have implications (i.e. potential refusal of necessary therapy in case of not fulfilling the criteria) that may make this concept unsafe. Therefore, neither EULAR nor the ACR will back diagnostic criteria.

2. The 1971 ARA criteria

In 1971, the American Rheumatism Association (ARA) Committee on Diagnostic and Therapeutic Criteria formulated the first classification criteria that became widely used as an aid to diagnose SLE in the routine clinical care [13]. The criteria included one immunological alteration, *i. e.*, a positive LE test, but none of the serologic markers currently used in the diagnosis and management of SLE. Nevertheless, the value of high titer ANA as a possible alternative to the positive LE cell test was used during validation studies [14,15].

3. The 1979/1982 ARA criteria

In 1979, ARA proposed examining new potential serologic criteria in order to update the 1971 criteria. The preparation study proved high sensitivity of the ANA-IIFA test (performed on rodent tissue), although with lower specificity than the LE test. The subsequent inclusion of the more sensitive ANA test performed on HEp-2 cells together with antibodies to native DNA and Sm nuclear antigens, as the most specific immunologic tests, greatly improved the performance of the revised classification criteria published by ARA in 1982 [16]. In the updated criteria, the ANA test was set up as a separate item together with recommendations concerning the testing method, while the highly specific antibodies against native DNA and Sm were weighted as equal in the immunologic item.

Both the 1971 and the revised 1982 criteria, further updated in 1997 by the ACR (formerly ARA) [17], required at least 4 of the 11 criteria for SLE classification to be present serially or simultaneously. Focusing on anti-dsDNA antibodies, the criteria stated a specification of 'an abnormal anti-native DNA titer' but they did not recommend any assay stringency or quality.

4. The 2012 SLICC criteria

The Systemic Lupus International Collaborating Clinics (SLICC) criteria published in 2012 showed that, although highly specific, the sensitivity of the ACR classification criteria for SLE was suboptimal, especially in new-onset SLE. Moreover, the 1982 criteria had been validated, but not the 1997 revised version. In order to improve the performance of classification criteria, the SLICC group took the initiative to assess the clinical and serological concerns that have evolved since the establishment of the ACR criteria and proposed new criteria. The new SLICC classification criteria contain several novelties compared to the ACR criteria [18]. The requirement for at least one positive immunologic criterion emphasizes the importance of autoantibodies in SLE diagnosis. Accordingly, patients without the listed autoantibodies or low complement cannot be classified as having SLE. While the ANA criterion remained unchanged in the new SLICC criteria, the components of the immunologic criteria were separated, and antibodies to dsDNA, Sm and phospholipids (aPL) contributed equally to SLE classification. Furthermore, the combination of antibodies to dsDNA or a positive ANA test with biopsy confirmed nephritis was considered sufficient for SLE classification, underlying the growing weight of anti-dsDNA antibodies. In addition, the SLICC criteria highlighted the low specificity of the Enzyme-Linked Immuno Sorbent Assay (ELISA) for the detection of anti-dsDNA antibodies, especially in the case of low positive values, and recommended to consider as ELISA positive only values twice above the cut-off. However, ELISA methods are increasingly abandoned from use in routine clinical practice and the SLICC criteria did not take into consideration the change of usage of methods towards new technologies [19].

5. The 2019 EULAR/ACR criteria

Although the newly added items improved the sensitivity of the SLICC criteria, this resulted in a decrease of specificity. In order to achieve a maximum combination of sensitivity and specificity, the ACR together with the EULAR aimed to develop new classification criteria for SLE. The evidence-based analysis of possible candidate criteria and the approach of a weighted scoring system resulted in the definition of new ACR/EULAR classification criteria in 2019 [20]. These criteria contain seven clinical and three immunological domains with hierarchical organization within domains.

In the 2019 ACR/EULAR criteria, ANA at a titer of $\geq$1:80 on HEp-2 cells is positioned as an entry criterion (mandatory requirement). This was based on a systematic literature search and meta-regression analysis that showed a 98% sensitivity for an ANA titer of at least 1:80 [21]. However, considering that not all centers have access to ANA HEp-2 IIFA, the criteria allow to use an immunoassay with equivalent performance. Of the three immunological domains, two include autoantibodies that are relevant for the diagnosis of SLE. The more specific antibodies for SLE as anti-dsDNA and anti-Sm are grouped in one domain and weighted equally by 6 points, while aPL antibodies (IgG, IgA and IgM anti-cardiolipin and anti-β2GPI antibodies) are grouped in a second domain accounting for only 2 points. In order to consider the huge variability in the performance of different detection methods for anti-dsDNA, the criteria recognized the need for an immunoassay with high specificity against relevant disease controls. As noted by the European Antibody Standardization Initiative (EASI) recommendations [22], this concept would typically only apply to *Crithidia luciliae* indirect immunofluorescence test (CLIFT) and Farr assays without considering that the former is generally used as a second level confirmatory test, while the latter has almost disappeared in clinical laboratory settings due to the limitations of using radiolabeled dsDNA [23]. To enable alternative solid phase assays for detection of anti-dsDNA antibodies, the criteria defined the specificity to be $\geq$ 90%. It is noteworthy that this is meant on the group level, so that the $\geq$90% value would be the result of essentially all (or at least 95% of) cohort studies validating the

method.

Little information is given on the basis for inclusion of the anti-dsDNA test in the criteria, suggesting that this item is largely based on expert opinion [24,25]. In fact, positive anti-dsDNA antibodies received the highest Delphi score (8.94) which determined the highest score (6 points) in the weighted scoring of the disease. Definitions for many potential criteria are provided but not for anti-dsDNA antibodies [26]. More recently, however, sensitivity (75.6%) and specificity (93.7%) characteristics of anti-dsDNA antibodies were published for the disease cohort used for establishing the new ACR/EULAR criteria, and compared with the ACR 1982 (67% and 92%, respectively) and SLICC 2012 (57.1% and 95.9%, respectively) cohorts [7,20]. The increased sensitivity and decreased specificity in the ACR/EULAR cohort, as compared to the SLICC 2012 cohort, may be the outcome of novel assays that have entered the market in the last decade, but information on the assays used for establishing these criteria is not available.

6. General considerations and open questions

Changes in SLE classification criteria over the years from the perspective of autoantibodies are summarized in Table 1. Although all new revisions try to reflect some improvements in autoimmune serology, they usually do not consider the impact of different methods on autoantibody testing. Neither do they consider standardization issues. Indeed, despite the availability of an international reference standard serum the WHO Wo/80, different methods and/or tests from different manufacturers may give different results for the same sample, each test only detecting a certain anti-dsDNA subpopulation [19,27–29]. Anti-dsDNA are not a well-defined and unique entity. They are induced by different nucleic acids and non-DNA structures, which also define the immune response to be transient or sustained. This is clearly demonstrated by the great heterogeneity in test results among different analytical methods by several comparative studies, which can be related to the type of assay, to the antigen used or to the difference in the avidity of anti-dsDNA antibodies [30,31].

All these differences emphasize that strict adherence to any of the classification criteria could lead to possible misclassification of SLE and, as a consequence, delayed diagnosis [32]. Altogether, it is obvious that classification criteria for a disease should be rather robust in order to enable widespread usage, but as far as autoantibodies are concerned, it should be realized that detection of autoantibodies is not standardized and only poorly harmonized [33]. For detection of anti-dsDNA antibodies only limited requirements for test characteristics were defined, varying from 'increased titer' [16,17], 'above laboratory reference range (except for ELISA)' [18], to '>90% specificity' [**19**]. Given the high impact of a positive result, *i.e.*, 6 out of 10 points required for classification, more attention for test characteristics of the distinct immunoassays is highly necessary. First, it can be speculated that since specificity of 90% could be considered too low for a rare disease, new criteria should increase the level of specificity or ask for confirmation with a high specificity assay. Second, it is crucial to take into account that the test is often added if ANA is positive according to the testing algorithms commonly used in routine labs [23]. This implies that the test is done outside the clinical context of SLE which increases the possibility of false positive results. It could be better to only perform anti-dsDNA testing upon request by the clinician (i.e. when a higher pre-test probability for SLE is present) excluding it from the ANA/ENA testing algorithm to reach a high specificity. Finally, while the original WHO standard for anti-dsDNA could not be reproduced and, eventually, was replaced by a WHO reference reagent coded 15/174 [34], alternative approaches for harmonization, as proposed for anti-neutrophil cytoplasmic antibodies (ANCA) in small vessel vasculitis [35], might offer better solutions to the problem.

Table 1
Anti-dsDNA antibodies included in the different classification criteria of SLE over the years.

Classification Criteria	1982 ARA	1997 ACR	2012 SLICC	2019 EULAR/ACR
Anti-dsDNA	antibody to native DNA at abnormal titer	antibody to native DNA at abnormal titer	anti-dsDNA above laboratory reference range *(except ELISA: twice above laboratory reference range)*	anti-dsDNA antibodies detected by an immunoassay with demonstrated ≥90% specificity for SLE against relevant disease controls
Weight assigned to anti-dsDNA	1	1	1	6
Minimum weighted score to classify as SLE	4 (max 11)	4 (max 11)	4 (max 17)	10 (max 51)

Credit author statement

Maria Infantino: Conceptualization, Methodology, Reviewing and Editing; Eszter Nagy: Investigation, Resources, Editing and Reviewing; Katarzyna Fischer: Visualization, Editing and Reviewing; Xavier Bossuyt: Visualization, Reviewing and Supervision; Nicola Bizzaro: Visualization, Reviewing and Supervision; Jan Damoiseaux: Visualization, Reviewing and Supervision.

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.

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