Editorial

Classification criteria in Sjögren's syndrome

Chiara Baldini, Francesco Ferro, Stefano Bombardieri

Rheumatology Unit, University of Pisa, Italy

Correspondence to: Prof. Stefano Bombardieri. Rheumatology Unit, University of Pisa, via Roma, 67 56126 Pisa, Italy. Email: s.bombardieri@int.med.unipi.it.

Provenance: This is a Guest Editorial commissioned by Executive Editor Zhi-De Hu, MD (Department of Laboratory Medicine, General Hospital of Ji'nan Military Region, Ji'nan, China).

Comment on: Shiboski CH, Shiboski SC, Seror R, *et al.* 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. Arthritis Rheumatol 2017;69:35-45.

Submitted Mar 21, 2017. Accepted for publication Mar 27, 2017.
doi: 10.21037/atm.2017.05.07
View this article at: http://dx.doi.org/10.21037/atm.2017.05.07

Sjögren's syndrome (SS) is a heterogeneous disease characterized by a wide spectrum of clinical manifestations ranging from a benign exocrinopathy to a complex systemic disorder (1-3). Over the years several criteria set have been proposed for the classification of the disease. Recently, Shiboski *et al.* (4) have elaborated a novel set of classification criteria for SS. These criteria are intended to replace the pre-existing AECG criteria (5) and the ACR criteria for SS (6), providing a common "language" to the scientific community able to select homogeneous patients to be included in epidemiological, clinical and therapeutic studies. The 2016 ACR/EULAR criteria are based on a weighted scoring system that has been derived taking into account both the opinions of international expert clinicians and a complex statistical analysis methodology, that has allowed to combine items from both the AECG criteria and the ACR criteria. Novel criteria thus, closely resemble the previous classification criteria sets, especially for the relevance given to glandular involvement, to serology and to the minor salivary gland biopsy. This is not surprising, since AECG criteria and ACR criteria have been extensively overlapping, even in their accuracy (7). At a first glance, therefore, the novel classification criteria do not appear so different from the previous ones, also in their performance. This has undoubtedly arisen some issues regarding the opportunity of having developed a novel set of classification criteria based on traditional "items" in the absence of new innovative biomarkers. However, some differences should be recognized whenever novel criteria are carefully examined and compared to previous sets. First of all, similarly to what has recently happened for other systemic autoimmune diseases (8,9), the 2016 ACR/EULAR criteria have provided a weighted score for SS classification with the weights of the variables derived from consensus expert opinion and through the analyses of patient data. This methodology has fostered the development of a more objective classification criteria set shared by expert from all the countries. On the other hand, as a result of the statistical analysis this process has led to the exclusion of some of the previous "traditional" items, such as the questionnaire and the anti-SSB/La positivity, raising some issues on the risk of patient misclassification. The exclusion of patient symptoms from the classification criteria seems in some contrast with the general tendency to rely on self-reported outcomes in the diagnosis and monitoring of the patients (10-13). Actually, the usefulness of the questionnaire for glandular symptoms—a key point in the AECG- has been rescued also in the novel criteria, at least as a tool to pre-select patients with suspicious SS: the 2016 ACR/EULAR criteria are intended to be applied to any patient with at least 1 symptom of ocular or oral dryness (based on AECG questions) or suspicion of SS due to systemic features derived from the ESSDAI score (14). Regarding the exclusion of the anti-SSB/La positivity among the items, we have to consider that the importance of this variable for random forest classification of case/non-case designations in the process of data vignettes development was low. In addition, in a recent study by Baer *et al.* (15) the anti-SSB/La positive/SSA negative serologic profile was not found to be associated with key SS phenotypic features. Danda

et al. (16) moreover, observed that these patients were younger, much less likely to have a lymphocytic infiltrate found on pathological evaluation of minor salivary glands, and presented less frequently extra-glandular manifestations. Finally, the existing literature concordantly reports that anti-SSB/La positive/SSA negative patients are quite uncommon. This point then remains controversial, but the exclusion of the anti-SSB/La item does not seem to affect significantly patients' classification. Finally, the novel criteria have emphasized the importance of an established impairment of the salivary and lachrymal functions, removing from the items those tools that explored the morphology and function of major salivary glands, thus maintaining only the evaluation of unstimulated salivary flow. Consequently, if patients do not have at the same time both a focal sialadenitis at the minor salivary gland biopsy and a positivity for anti-SSA/Ro to be classified as having SS, they must necessary present a severe ocular or oral involvement. This has to be taken into account particularly when using the novel criteria set to recruit patients in clinical trials, as patients are generally required to have a preserved glandular function to be included in RCTs (17). To overcome this limitation, there is an international project ongoing that analyzes whether salivary gland ultrasonography may have an additional place in the algorithm for the classification of the disease, providing information on the morphology, inflammation and damage of the major salivary glands (18,19).

Beyond the specific differences that we can recognize when novel and pre-existing criteria are compared one to each other, the burning question that we should try to answer is whether or not this novel criterion set will allow us to select more effectively homogenous SS patients. These criteria undoubtedly represent a step forward the classification of SS patients, especially since the key elements of the 2016 ACR/EULAR criteria are the minor salivary gland biopsy and the anti-SSA/Ro. However, focusing on the minor salivary gland biopsy, there are some points that we have to consider. First of all, there is a compelling need of standardizing minor salivary gland histopathology for the classification of SS in terms of tissue requirements, identification of the characteristic focal lymphocytic sialadenitis, and evaluation of the focus score and of the germinal centres (20). In fact, there is a relatively low intra-observer and inter-observer reliability in the assessment of minor salivary gland biopsy, as the recent literature has highlighted (21,22). A second point to consider is the heterogeneity of the infiltrate composition in the minor salivary gland biopsy that has been associated to the severity of disease manifestations (23). Independently from the focus score, the complexity of the infiltration and the T or B cells infiltrates seem to identify different phenotypes of the SS, ranging from a mild disease to a systemic disorder at increased risk for lymphoproliferative complications, respectively. Therefore, the simple definition of the focus score as included in the classification criteria may not allow, by itself, to stratify homogeneous subsets of patients with SS, particularly with regards to extra-glandular manifestations. If we consider that different disease phenotypes actually reflect diverse underlying cellular and molecular pathways, it is desirable that basic research foster the identification of novel biomarkers for the disease able to specifically indicate selective subtypes of SS. From this regard, genetic studies and "omics" techniques are continuously generating promising novel biomarkers that, even if far from being transferable to clinical routine, still represent a potential source of novel tools for ameliorating patients' stratification and management (24,25). It would be desirable to be able to assemble together these novel biomarkers as if they were "pieces" of a common puzzle in order to better understand the heterogeneity and the complexity of SS.

In conclusion, the 2016 ACR/EULAR criteria may represent a first attempt forward the identification of homogeneous patients, although these novel criteria need to be verified prospectively on clinical grounds and in real patients. It is likely, however, that novel biomarkers in the next future may ultimately integrate these criteria set, allowing a better selection of patients that will share a common pathogenetic background, a similar disease expression, and will be candidate to respond to specific targeted therapy.

Acknowledgements

None.

Footnote

Conflicts of interest: The authors have no conflicts of interest to declare.

References

1. Baldini C, Pepe P, Quartuccio L, et al. Primary Sjogren's syndrome as a multi-organ disease: impact of the serological profile on the clinical presentation of the disease in a large cohort of Italian patients. Rheumatology (Oxford) 2014;53:839-44.

2. Brito-Zerón P, Baldini C, Bootsma H, et al. Sjogren syndrome. Nat Rev Dis Primers 2016;2:16047.
3. Barone F, Colafrancesco S. Sjogren's syndrome: from pathogenesis to novel therapeutic targets. Clin Exp Rheumatol 2016;34:58-62.
4. Shiboski CH, Shiboski SC, Seror R, et al. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjogren's syndrome A consensus and data-driven methodology involving three international patient cohorts. Ann Rheum Dis 2017;76:9-16.
5. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554-8.
6. Shiboski SC, Shiboski CH, Criswell L, et al. American College of Rheumatology classification criteria for Sjogren's syndrome: a data-driven, expert consensus approach in the Sjogren's International Collaborative Clinical Alliance cohort. Arthritis Care Res (Hoboken) 2012;64:475-87.
7. Rasmussen A, Ice JA, Li H, et al. Comparison of the American-European Consensus Group Sjogren's syndrome classification criteria to newly proposed American College of Rheumatology criteria in a large, carefully characterised sicca cohort. Ann Rheum Dis 2014;73:31-8.
8. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569-81.
9. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum 2013;65:2737-47.
10. Castrejón I, Pincus T. Patient self-report outcomes to guide a treat-to-target strategy in clinical trials and usual clinical care of rheumatoid arthritis. Clin Exp Rheumatol 2012;30:S50-5.
11. Black N. Patient reported outcome measures could help transform healthcare. BMJ 2013;346:f167.
12. Basch E. Patient-Reported Outcomes - Harnessing Patients' Voices to Improve Clinical Care. N Engl J Med 2017;376:105-8.
13. Trenaman L, Boonen A, Guillemin F, et al. OMERACT Quality-adjusted Life-years (QALY) Working Group: Do Current QALY Measures Capture What Matters to Patients? J Rheumatol 2017. [Epub ahead of print].
14. Seror R, Bowman SJ, Brito-Zeron P, et al. EULAR Sjogren's syndrome disease activity index (ESSDAI): a user guide. RMD Open 2015;1:e000022.
15. Baer AN, McAdams DeMarco M, Shiboski SC, et al. The SSB-positive/SSA-negative antibody profile is not associated with key phenotypic features of Sjogren's syndrome. Ann Rheum Dis 2015;74:1557-61.
16. Danda D, Sharma R, Truong D, et al. Anti-La positive, anti-Ro negative subset of primary Sjogren's syndrome: anti-La is a reality but is the disease? Clin Exp Rheumatol 2017.
17. Devauchelle-Pensec V, Gottenberg JE, Jousse-Joulin S, et al. Which and How Many Patients Should Be Included in Randomised Controlled Trials to Demonstrate the Efficacy of Biologics in Primary Sjogren's Syndrome? PLoS One 2015;10:e0133907.
18. Jousse-Joulin S, Milic V, Jonsson MV, et al. Is salivary gland ultrasonography a useful tool in Sjogren's syndrome? A systematic review. Rheumatology (Oxford) 2016;55:789-800.
19. Jonsson MV, Baldini C. Major Salivary Gland Ultrasonography in the Diagnosis of Sjogren's Syndrome: A Place in the Diagnostic Criteria? Rheum Dis Clin North Am 2016;42:501-17.
20. Fisher BA, Jonsson R, Daniels T, et al. Standardisation of labial salivary gland histopathology in clinical trials in primary Sjogren's syndrome. Ann Rheum Dis 2017;76:1161-8.
21. Tavoni AG, Baldini C, Bencivelli W, et al. Minor salivary gland biopsy and Sjogren's syndrome: comparative analysis of biopsies among different Italian rheumatologic centers. Clin Exp Rheumatol 2012;30:929-33.
22. Costa S, Quintin-Roue I, Lesourd A, et al. Reliability of histopathological salivary gland biopsy assessment in Sjogren's syndrome: a multicentre cohort study. Rheumatology (Oxford) 2015;54:1056-64.
23. Christodoulou MI, Kapsogeorgou EK, Moutsopoulos HM. Characteristics of the minor salivary gland infiltrates in Sjogren's syndrome. J Autoimmun 2010;34:400-7.
24. Baldini C, Giusti L, Ciregia F, et al. Proteomic analysis of saliva: a unique tool to distinguish primary Sjogren's syndrome from secondary Sjogren's syndrome and other sicca syndromes. Arthritis Res Ther 2011;13:R194.
25. Goules AV, Tzioufas AG. Primary Sjogren's syndrome: clinical phenotypes, outcome and the development of biomarkers. Immunol Res 2017;65:331-44.

Cite this article as: Baldini C, Ferro F, Bombardieri S. Classification criteria in Sjögren's syndrome. Ann Transl Med 2017;5(15):313. doi: 10.21037/atm.2017.05.07

