

ABSTRACT: 2013 ELAM Institutional Action Project Poster Symposium

Project Title: External validation and Finalization of Provisional American College of Rheumatology Classification Criteria for Sjögren's Syndrome

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Collaborators: Stephen Shiboski, PhD, Lindsey Criswell, MD, MPH, DSc, Xavier Mariette, MD, John Greenspan, BDS, PhD, Troy Daniels, DDS, MS.

Background, Challenge or Opportunity: Sjögren's syndrome (SS) is a multisystem autoimmune disease characterized by salivary and lacrimal glands hypofunction. Because of its multi-organ involvement and autoimmune etiology, it is overseen by rheumatologists in collaboration with ophthalmologists and oral medicine specialists. While there have been 11 classification or diagnostic criteria published for SS since 1965, until recently none had been endorsed by the American College of Rheumatology (ACR) or European League Against Rheumatism (EULAR). During the past decade, the most commonly used classification criteria have been the American European Consensus Group (AECG) criteria. In April 2012, new classification criteria developed within the UCSF-led Sjögren's International Collaborative Clinical Alliance (SICCA) registry, an NIH-funded contract, were provisionally approved by ACR. While the criteria set has been quantitatively validated using patient data, definitive endorsement by ACR will require a validation in an external data set.

Although the AECG criteria have not been endorsed by ACR or EULAR, they have proven useful in a range of studies and are widely used in practice. The challenge is now to get universal acceptance of the ACR criteria by the SS scientific community. Recent validation analyses revealed a high level of concordance between the ACR and AECG criteria. However, the degree of correspondence was decreased when more flexibility was allowed within the AECG definition. Although both criteria sets involve similar component tests, the AECG criteria allow substitutions for alternatives, and also allow the use of symptoms of dry eyes and mouth in classifying patients. The provisional ACR criteria are based solely on objective tests.

Purpose/Objectives:

- 1) To create an ACR-EULAR international working group of SS investigators/experts
- 2) To perform an external validation of the Provisional ACR classification criteria for SS developed by our group at UCSF in collaboration with the ACR-EULAR working group
- 3) To finalize and obtain definitive approval by ACR and EULAR of a unique set of classification criteria for SS

Methods/Approach: An ACR-EULAR collaborative group of SS scientists and clinician-experts will be created to obtain buy-in from this group for the need for a unique set of criteria that will be endorsed by ACR and EULAR, and universally accepted in the scientific community. The external validation will be performed in a European cohort of patients (cohort identified), and a systematic comparison between ACR and AECG criteria in this cohort will be performed, to better understand the similarities and differences between the 2 criteria sets. Input from the ACR-EULAR working group for the development of an analysis plan will be sought, and a data-driven consensus methodology will be used to develop the final set of criteria.

Outcomes and Evaluation: The final outcome is the development of a final set of classification criteria for SS approved by ACR and EULAR and endorsed by the SS scientific community. Intermediary outcomes include 1) successfully convening an ACR-EULAR working group; 2) performing the external validation; 3) arriving to a consensus within the working group on the analysis plan comparing AECG and ACR criteria. To-date outcomes 1) and 2) have been achieved.



External Validation and Finalization of Provisional American College of Rheumatology Classification Criteria for Sjögren's Syndrome

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Background/Challenge

- **Sjögren's syndrome (SS)** is a **multisystem autoimmune disease** characterized by salivary and lacrimal glands hypofunction overseen by **rheumatologists** in collaboration with **ophthalmologists** and **oral medicine specialists**.
- While there have been 11 classification or diagnostic criteria published for SS since 1965, until recently none had been endorsed by the **American College of Rheumatology (ACR)** or **European League Against Rheumatism (EULAR)**.
- Until recently, since few therapeutic agents were being considered in the systemic management of SS, the development of classification criteria was mainly for the purpose of epidemiologic studies to estimate SS prevalence and investigate underlying disease mechanisms. Also, many criteria sets were primarily used as diagnostic criteria in clinical practice.
- However, the development of new biologic immunomodulating agents now considered in the treatment of SS increases the need and importance of developing stringent classification criteria to be used in the context of clinical trials. The consequence of misclassifying someone without SS as a case would be serious given the potentially toxic side effects of these agents.
- During the past decade, the most commonly used classification criteria have been the American European Consensus Group (AECG) criteria¹.
- In April 2012, **new classification criteria developed within the UCSF-led Sjögren's International Collaborative Clinical Alliance (SICCA)** registry, an **NIH-funded contract** co-directed by Caroline Shiboski and Lindsey Criswell, were **provisionally approved by ACR**.² **Criteria development was required by the contract**. While the criteria set has been quantitatively validated using patient data, definitive endorsement by ACR will require a validation in an external data set.
- Although the **AECG criteria have not been endorsed by ACR or EULAR, they are widely used in practice**. The **challenge** is now to get **universal acceptance of the ACR criteria** by the SS scientific community who has been using AECG for 10 yrs.
- Recent validation analyses revealed a high level of concordance between the ACR and AECG criteria. However, the degree of correspondence was decreased when more flexibility was allowed within the AECG definition. Although both criteria sets involve similar component tests, the AECG criteria allow substitutions for alternatives, and allow use of symptoms of dry eyes/mouth in classifying patients. The **provisional ACR criteria are based solely on objective tests**.

Objectives

1. To create an ACR-EULAR international working group of SS investigators/experts
2. To perform an external validation of the Provisional ACR classification criteria for SS developed by our group at UCSF in collaboration with the ACR-EULAR working group
3. To finalize and obtain definitive approval by ACR and EULAR of a unique set of classification criteria for SS

Collaborators

Key collaborators: Stephen Shiboski, PhD (SICCA Statistician), Lindsey Criswell, MD, MPH (SICCA co-PI), DSc, Xavier Mariette, MD (PI, French SS cohort and former president EULAR), John Greenspan, BDS, PhD (SICCA investigator, former co-PI), Troy Daniels, DDS, MS (SICCA investigator, former co-PI).

ACR-EULAR Working Group (in addition to the key collaborators): investigators from SS scientific community from the US (n=7), Europe (n=18), South America (n=3); Asia (n=3)

Methods/Approach

The **provisional ACR classification criteria for SS**² require at least 2 out of the following 3 items for disease classification:

- Positive serum anti-SSA and/or anti-SSB or [positive rheumatoid factor and ANA $\geq 1:320$];
- Ocular staining score (OSS) ≥ 3 (using lissamine green on the conjunctiva and fluorescein on the cornea);
- Presence of focal lymphocytic sialadenitis (FLS) with focus score (FS) ≥ 1 focus/4mm² in labial salivary gland biopsies.

The provisional ACR classification criteria were developed using a consensus-based data-driven process in a large cohort of 1362 participants recruited from 6 countries in 4 continents. The target population was individuals for whom SS was suspected based on symptoms of dry eyes and/or mouth or other suggestive symptoms or signs.

The **AECG criteria**¹ require 4 out of 6 of the following items, with items IV or VI a mandatory requirement, or any 3 of the 4 objective criteria (items III, IV, V or VI) for classification as SS:

- I. Ocular Symptoms (at least one)
 - Dry eyes >3 months
 - Foreign body sensation in the eyes
 - Use of artificial tears >3x per day
- II. Oral Symptoms (at least one)
 - Dry mouth >3 months
 - Recurrent or persistently swollen salivary glands
 - Need liquids to swallow dry foods
- III. Ocular Signs (at least one)
 - Schirmer's test, (without anesthesia) ≤ 5 mm/5 minutes
 - Positive vital dye staining (van Bijsterveld ≥ 4)
- IV. Histopathology Lip biopsy showing focal lymphocytic sialoadenitis (focus score ≥ 1 per 4 mm²)
- V. Oral Signs (at least one)
 - Unstimulated whole salivary flow (≤ 1.5 mL in 15 minutes)
 - Abnormal parotid sialography
 - Abnormal salivary scintigraphy
- VI. Autoantibodies (at least one)
 - Anti-SSA (Ro) or Anti-SSB (La)

References

1. 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*. Jun 2002;61(6):554-558.
2. Shiboski SC, Shiboski CH, Criswell LA, et al. American College of Rheumatology Classification Criteria for Sjögren's Syndrome: A Data-Driven, Expert Consensus Approach in the SICCA Cohort. *Arthritis Care Res* 2012;64:475-487

Methods/Approach

Population: The Paris-Sud University Cohort is followed by Xavier Mariette at Bicêtre hospital in Paris and includes all patients referred to the Department for possible SS: 350 cases classified using the AECG criteria (based on objective tests), and 350 controls. The availability of ocular staining measures using lissamine green and fluorescein (not available in most cohorts) and the availability of the same objective measures used in development of the provisional ACR criteria, make the Paris-Sud ideal for cohort comparisons and external validation. Data on demographic characteristics, symptoms, and variables measured from clinical examinations (rheumatology, ocular, and oral) are also available from both cohorts.

ACR-EULAR Working Group

A working group of SS experts will be identified to review the definition and application of the two criteria sets. The primary objectives will be to perform external validation of the new provisional ACR criteria, and to conduct a detailed comparison of the provisional ACR and AECG criteria sets. All cases with discordant diagnoses based on application of the provisional ACR and AECG criteria will be summarized as short clinical vignettes to be considered by the expert panel for their expert opinion. A consensus methodology derived from the Nominal Group Technique (NGT) will be used whenever expert opinion is elicited. The majority of experts are rheumatologists affiliated with ACR or EULAR, although the group also includes some ophthalmologists and oral medicine/pathology specialists. Experts will be identified based on their involvement in clinical, epidemiologic or other research in SS and/or based on their involvement in the SICCA registry project or the EULAR disease activity index development efforts. Since the process will be primarily data-driven, it will be led by a statistician (S. Shiboski) and an epidemiologist (C. Shiboski).

Statistical approaches overview

Validation will be conducted using cases and controls from the Paris-Sud cohort, with case and control definitions, using the AECG criteria based on objective tests. Criteria comparison will include evaluation of sensitivity and specificity under a number of pre-determined scenarios defined with respect to key criteria components for the ocular, oral and systemic manifestations of the disease. The definition of "gold standard" classification for these analyses will be varied to allow performance of the different criteria sets to be assessed under a variety of conditions. Analyses and their interpretation will follow published ACR guidelines.

A report detailing the results of the validation and cohort comparison analyses will be circulated to the expert panel members 1 month prior to the proposed meeting. Based on review, and a presentation summarizing the results, panel members will outline final analyses needed to refine criteria definitions. A major part of these analyses will focus on comparisons between classifications based on both the provisional ACR and AECG criteria.

Cases classified differently by application of the two criteria sets will be characterized by "vignettes" describing their key features. These blinded vignettes will then be submitted to a selected team of expert clinicians for assignment of individual disease status. The results of these classifications of discordant cases by the experts will be considered as the gold standard and will allow us to draw conclusions about relative strengths and weaknesses of the provisional ACR and AECG approaches to classification, to improve both of them and to find a new consensus bridging between the 2 criteria sets.

Progress to-date & lessons learned

- 1) **Identified members of ACR-EULAR Working Group** with help from Xavier Mariette, former EULAR president, and collaborator of SICCA co-PI who did her sabbatical in his lab
- 2) **Invited members to join Working Group** as SICCA PI and lead epidemiologist, I took the lead on this process. Identified 32 potential members from Europe, Australia, Asia, North and South America. All but 1 accepted to participate
- 3) **Submitted grant proposal to ACR-EULAR Collaborative Initiative** mainly to obtain travel funds to convene the Working Group at the stage of the NGT consensus methodology
- 4) **Convened an exploratory meeting of a sub-set of the ACR-EULAR Working Group**
 - mainly rheumatologists attending the ACR annual meeting in DC in Nov 2012. The SS Foundation or SSF was hosting an SS related lunch meeting, and the CEO and VP for research who were hosting the lunch, agreed to host our meeting also, following the lunch. The SSF was founded in 1983 by a patient, with the mission to be a voice for patients while educating physicians and increasing awareness of SS worldwide. The ACR-EULAR Working Group exploratory meeting was introduced by the SSF CEO and VP for Research (important politically because the SSF is highly respected by the international SS scientific community)
 - Xavier Mariette and I co-Chaired the meeting representing EULAR and ACR, respectively. We invited the lead author of the AECG classification paper and other members of the European SS community to present their perspective on AECG versus ACR, and the SICCA statistician to introduce a potential analysis plan for external validation and AECG/ACR comparison.
 - Overall, the meeting went well despite strong opposition to the new ACR criteria raised by some European members who would prefer to keep using AECG criteria, although now sub-optimal since they have not been ACR endorsed. I found that using empathy/active listening and focusing on the data-driven aspect of the project were very helpful in leading the discussion and steering it towards a positive outcome.
 - The meeting was concluded with a general consensus that this project was worth pursuing.
- 5) **Wrote a detailed summary report of the meeting**, and circulated it to the larger ACR-EULAR Working Group
- 6) **ACR-EULAR proposal was reviewed, but not funded**. Currently exploring creative solutions to organize virtual meetings of the ACR-EULAR working group and a web-based consensus methodology voting process, although the 12th International Symposium on SS will be held in Kyoto in October 2013, and will be another opportunity for meeting as many Working Group members will attend.
- 7) **Statistician currently performing exploratory analyses to compare AECG and ACR within SICCA data as a first step**

Conclusions

First phase of this project has been accomplished. Next phase is to complete the analyses and consensus methodology to arrive to the final criteria set. Successful outcome would be critical for future clinical trials testing new therapies for SS. It would benefit the UCSF School of Dentistry by raising our profile as a leader in a multidisciplinary project with global health significance.