2012 ACR Classification Criteria and Preliminary Guidelines for Sjögren's Syndrome

Written by Rita Buckley

Several facts underpin the impetus to develop classification criteria for Sjögren's syndrome (SS). These include the association of serious adverse events and comorbidities associated with the emergence of biologic therapies as potential treatments for SS, the need for further research to investigate the etiology and genetics of SS, and improved, specific classification criteria that can be effectively used for clinical therapeutic trials. Serious adverse events and associated comorbidities associated with the emergence of biologic agents as potential treatments for SS are one factor driving the development of internationally accepted classification criteria to define the autoimmune disorder. Other factors include a need to better support etiologic and genetic research and therapeutic trials, and to support enrollment into clinical trials with clear, easily applied, and highly specific classification criteria [Shiboski SC et al. *Arthritis Care Res (Hoboken)* 2012].

The objectives of the Sjögren's International Collaborative Clinical Alliance (SICCA), which has been funded since 2003 by the National Institute of Dental and Craniofacial Research, were to develop new classification criteria for SS; to better characterize the SS phenotype and genotype; and to establish an SS data and specimen repository to support future research, including genetic studies by investigators worldwide.

Using a consensus methodology derived from the nominal group technique among 20 experts and analyses involving 1362 participants with complete data on 10 individual tests, the SICCA scientists first developed preliminary classification criteria for SS. Then a series of validation analyses was performed, including a comparison with American-European Consensus Group criteria [Shiboski SC et al. *Arthritis Care Res (Hoboken)* 2012].

Stephen Shiboski, PhD, University of California, San Francisco, San Francisco, California, USA, explained that the diagnostic and classification criteria rely on well-established objective tests that are clearly associated with the systemic, oral, and ocular characteristics of the disease and include alternate tests only when diagnostically equivalent. To increase their credibility and maximize standardization when enrolling participants into clinical trials, he cited the need for endorsement by professional rheumatology organizations across the world [Shiboski SC et al. *Arthritis Care Res (Hoboken)* 2012].

Next Step: Guideline Development

According to Steven E. Carsons, MD, Stony Brook University School of Medicine, Stony Brook, New York, USA, multiple challenges have yet to be met to develop guidelines for the treatment of SS.

The first challenge is the comparability of study populations. The diagnosis of SS may be made according to several clinical or classification criteria.

The second challenge is that many methodologies reported in the literature regarding SS are used to assess a particular outcome. Outcome measures used by reviewers to select studies for inclusion were determined by each Topic Review Group (TRG) according to common use in clinical trials and availability in clinical practice. Table 1 shows outcomes selected by the TRGs for study inclusion.

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Table 1. Outcomes Selected by Topic Review Groups for Study Inclusion.

Guideline	Outcomes
DMARDs for inflammatory joint pain	• VAS – Joint pain • Joint counts • AM stiffness • Biomarkers
Management of fatigue	• VAS – Fatigue score • MFI • FSS
Biologics for SICCA manifestations	• VAS – Oral dryness • Salivary flow • Ocular staining • TBUT

DMARDs=disease-modifying antirheumatic drugs; FSS=Fatigue Severity Scale; MFI=Multidimensional Fatigue Inventory; TBUT=tear breakup time; VAS=visual analog scale.

The third challenge is that individual trials involving SS report multiple subspecialty-specific outcomes, requiring subspecialty content experts for the particular endpoint measures.

The fourth challenge is the small body of SS literature that was available to inform the committee. Of the 1300 abstracts initially reviewed, only 31 manuscripts met the criteria for data extraction, which included subjects aged ≥18 years from both genders and all ethnicities, at least 6 subjects/study, a minimum follow-up of 12 weeks, a diagnosis of primary SS, and a study designed for selected intervention.

Dr. Carsons noted that the next steps in the development process for clinical practice guidelines include drafting of preliminary recommendations and use of a Delphi-type process with voting by a consensus panel to finalize recommendations and guideline development; no involvement of TRG members engaged in systematic review and data extraction in the rating of guideline statements; and, in the future, the assessment of an additional 6 topics using identical methodology.

The ACR/EULAR Classification Criteria for SSc

Written by Wayne Kuznar

Proposed new classification criteria developed for systemic sclerosis (scleroderma; SSc) have improved sensitivity and specificity compared with the 1980 American College of Rheumatology (ACR) SSc criteria and should allow for more patients to be classified as having SSc. The proposed classification criteria are preliminary and need to be reviewed by the ACR and the European League Against Rheumatism (EULAR), but the authors do not anticipate they will be altered from the findings presented here.

As reported by Janet E. Pope, MD, St. Joseph's Health Care and University of Western Ontario, London, Ontario, Canada, the 1980 Preliminary Criteria for the Classification of Systemic Sclerosis failed to classify a significant proportion of patients with early SSc and patients with the limited subtype of the disease, who experienced clinicians believed should be classified as having SSc [Pope JE et al. ACR 2012 Poster L3].

A committee to develop new criteria was established jointly by ACR and EULAR. The committee used an 8-step process that included first using an Internet survey of more than 100 potential criteria for SSc sent to multiple experts and narrowing the number down significantly, using a Delphi technique to further reduce the number of criteria, and testing the validity of 23 items selected in existing databases of SSc cases and controls from North America and Europe (further decreasing the number of items to 17). Twenty cases that represented the spectrum of SSc (low probability to high probability) were then used. The cases were ranked by experts, using conjoint analysis to assign weights of importance to 17 preliminary items.

According to Prof. Pope, it was agreed that the 1980 major criteria still worked well in classifying sclerodactyly that was continuous and proximal to the metacarpophalangeal joints (ie, the former major criterion for SSc that is still in the new proposed classification). A provisional threshold was established to classify definite SSc based on the sum of the weights of the 17 items. Experts collected serial cases of new SSc and prevalent SSc, and controls from multiple sites where the sensitivity and specificity of the final criteria were tested and validated. To test the provisional algorithm, data on the 17 items were collected from 605 cases and controls (possible mimickers) in North America and Europe.

From the collected data, the threshold was refined in a subset of 25 cases within the range of borderline probability of SSc. Experts were then asked to determine whether each case had "definite SSc" or not, which led to a new threshold.

The final items with the proposed weights of the classification system are presented in Table 1. A cutoff