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Review

Outcome measures for primary Sjögren's syndrome

Raphaèle Seror [a,b,c], Hendrika Bootsma [d], Simon J. Bowman [e], Thomas Dörner [f], Jacques-Eric Gottenberg [g], Xavier Mariette [a], Manel Ramos-Casals [h], Philippe Ravaud [b,c], Elke Theander [i], Athanasios Tzioufas [j], Claudio Vitali [k,*]

[a] Assistance Publique–Hopitaux de Paris, Hôpital Bicêtre, Department of Rheumatology, INSERM U802, Le Kremlin Bicêtre, Université Paris-Sud 11, France
[b] Center of Clinical Epidemiology, Hôpital Hôtel Dieu, Paris, France
[c] INSERM U738, Université Paris-René Descartes, Paris, France
[d] University Medical Center Groningen (UMCG), Department of Rheumatology and Clinical Immunology, Groningen, Netherlands
[e] Rheumatology Department, University Hospital Birmingham NHS Foundation Trust, Birmingham, UK
[f] Rheumatology Department, Charité, University Hospital, Berlin, Germany
[g] Department of Rheumatology, Strasbourg University Hospital, Université de Strasbourg, EA 4438, Strasbourg, France
[h] Laboratory of Autoimmune Diseases "Josep Font", Hospital Clinic, Barcelona, Spain
[i] Department of Rheumatology, Malmö University Hospital, Lund University, Sweden
[j] Department of Pathophysiology, School of Medicine, University of Athens, Greece
[k] Department of Internal Medicine and Section of Rheumatology, Villamarina Hospital, Piombino, Italy

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ABSTRACT

Lymphocytic infiltration of different exocrine and non-exocrine epithelia is the pathological hallmark of primary Sjögren's syndrome, whereas involvement of salivary and lachrymal glands with the clinical counterpart of dry eye and dry mouth are the predominant features of the disease, together with fatigue and musculoskeletal pain. In addition, systemic manifestations, like arthritis, skin vasculitis, peripheral neuropathy, glomerulonephritis, may also be present in a consistent number of patients. As result, clinical features in SS can be divided into two facets: the benign subjective but disabling manifestations such as dryness, pain and fatigue, and the systemic manifestations. In the past decades, a core set of domains, which included sicca symptoms, objective measurements of tear and saliva production, fatigue, quality of life, disease activity and damage was indicated as essential for outcome assessment in this disorder. Afterwards, great efforts have been made to develop valid tools for the assessment of different domains. Specific questionnaires such as the Profile of Fatigue and Discomfort (PROFAD) and Sicca Symptoms Inventory (SSI) have been proposed as dedicated tools for the evaluation of patients symptoms, whereas different composite indexes have been suggested for the assessment of disease activity and damage. Some of these preliminary studies served as bases of an international project supported by EULAR, aimed at developing two consensus disease activity indexes: the EULAR Sjögren's Syndrome Patients Reported Index (ESSPRI), and the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), a systemic activity index to assess systemic manifestations. A detailed and critical review of all these indexes is provided in this article. Both EULAR indexes showed, in recent studies, to be feasible, valid, and reliable instruments. After their final validation, which is currently in process, they could be used as consensus outcome criteria in therapeutic trials and in clinical practice.

1. Introduction

Primary Sjögren's syndrome (SS) is a systemic autoimmune disease that mainly affects the exocrine glands. Thus, persistent dryness of the mouth and eyes caused by functional and structural impairment of the salivary and lachrymal glands are the hallmarks of the disease. Furthermore, other epithelial organs, including the liver, lung, and kidney can also be involved. The typical histological aspect of SS is a focal lymphocytic infiltration of the involved tissues (exocrine and non-exocrine epithelia). The infiltrates are mostly constituted of activated T cells in early lesions, whilst B cells appear to be predominant in later phases of the disease. However, chronic B cell activation and proliferation are considered to play a key role in the disease evolution. Finally, the benign B cell proliferation may

* Corresponding author. Tel.: +39 0565 67415; fax: +39 0565 67417.
E-mail address: c.vitali@yahoo.it (C. Vitali).

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sometimes evolve to the development of different forms of B cell lymphoma [1].

The clinical course of SS is slowly progressive in most of patients, in whom sicca symptoms, fatigue, and articular and muscular pain are the most common symptoms. The involvement of other epithelia, e.g., those of the upper airways, renal tubules, and gastrointestinal tract, justifies the term "autoimmune epithelitis" that has been suggested for the disease [2].

In 30–40% of patients the clinical course is marked by extra-epithelial systemic features of variable severity, such as Raynaud's phenomenon, arthritis, palpable purpura, autoimmune cytopenias, peripheral neuropathy, glomerulonephritis, and by higher risk of lymphoma development [3].

Different components of SS progress at different rates. The epithelitis is typically slowly progressive, whereas patients with extra-epithelial disease often have disease courses punctuated by more evident disease flares. As a result, clinical features, and therefore clinical evaluation, can be divided into two facets: (i) benign subjective but disabling symptoms such as dryness, articular and muscular pain, and fatigue, affecting almost all patients, and (ii) potentially severe systemic manifestations such as synovitis, vasculitis, skin and renal involvement, neurological feature, and lymphoma.

Until now, evidence-based therapy for Sjögren's syndrome was largely addressed to the treatment of sicca features [4]. Consequently, for decades, the evaluation of patients with SS in clinical trials has been primarily based on the assessment of glandular features, either with objective or subjective parameter [5–7]. Outcome measures using composite criteria have also been proposed in more recent clinical trials [8,9], but, none of these measures were able to capture the disease activity derived from the systemic features of the disease. The need for valid outcome measures became certainly more stringent [10–12] because of the potential effectiveness of new targeted therapies, such as B-cell-addressed therapies, that have shown promising results in improving both severe systemic [13,14] and glandular features [15–19], and also health related quality of life (HRQoL) [20]. Therefore, in the past decades, a consensus has been reached on the definition of a core set of disease domains for which valid and reliable outcome measures are needed [10,11]. The selected domains included sicca symptoms, objective measurements of tear and saliva production, fatigue, quality of life, disease activity and damage.

Although the concepts of disease activity and damage are easy to formulate in theory, functional definitions have not been established [21]. Generally speaking, activity can be defined as a reversible entity, because the related inflammatory process may have a fluctuating course and may respond to treatment. In contrast, damage, defined as a permanent loss of function, represents a chronic, irreversible component of the disease process.

Different disease-specific indexes have first been developed for evaluation of symptoms (subjective features) in the patients, such as Profile of Fatigue and Discomfort (PROFAD) and Sicca Symptoms Inventory (SSI) [22,23], and, more recently, for systemic features, such as SS disease activity index (SSDAI) [24] and Sjögren's Systemic Clinical Activity Index (SCAI) [25]. At the same time, disease damage indexes had been proposed to measure the chronic consequences of consecutives disease flares [24,26].

Following these first studies, and based on their results, EULAR has promoted an international collaboration between SS experts to develop consensus disease activity indexes. Two indexes have been developed: (i) a patient-administered questionnaire, to evaluate subjective symptoms, i.e., the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), and (ii) a systemic activity index, to assess systemic complications, i.e., the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI).

2. Evaluation of systemic features of primary SS

As mentioned, three disease activity scores are currently available to assess activity in patients with systemic complication of SS (Table 1).

2.1. A. The SSDAI: Sjögren's syndrome disease activity index

The SSDAI [24] is a disease activity index that includes 11 items grouped in 8 domains. Items included in the index were derived using a multivariate model (developed from a cohort of 206 patients), where Physician's Global Assessment (PhGA) was the gold standard (external criterion). The weight of any variable in the scale was extrapolated from the correlation coefficient of the same variable in the model. The correlation between the scores for activity obtained by applying SSDAI and the scores assigned by the observers was used to measure the construct validity of the index. The ability of the SSDAI to detect the over time variation of activity (sensitivity to change) was tested by applying the SSDAI scale at two different observation times characterized by different levels of perceived activity. The final score, obtained from the sum of the scores given to all items, may vary from 0 to 21.

2.2. The SCAI: Sjögren's systemic clinical activity index

The SCAI is an ordinal transition scale, derived from the BILAG scoring system, developed in a cohort of 104 patients [25,27]. It reflects changes in clinical symptoms during the 4-week period prior to evaluation, or compared to the previous visit. SCAI includes 42 items that are clearly defined and grouped into the 8 following domains: constitutional, musculoskeletal, skin/vasculitis, respiratory, neurological, renal, salivary gland, and hematological. Each item is scored as absent, improving, the same, worse or new. This scale is used to score each domain with an "intention to treat" alphabetical scoring system. Category A denotes disease that requires prednisolone $>$20 mg and/or immunosuppressants for treatment. Category B denotes disease requires prednisolone $<$20 mg and/or antimalarials and/or NSAIDs. Category C indicates stable, mild disease. Category D is assigned to a domain that was previously affected, but where disease is currently inactive. Category E indicates an organ system that has never been involved. Categories were derived from the BILAG index for systemic lupus (created by nominal consensus techniques). The nominal scoring system could be converted into a numeric score, according to the author recommendation (A score = 9, B score = 3, C score = 1, and D or E score = 0. Therefore the maximum theoretical SCAI score is 72. This numerical conversion was extrapolated from BILAG.

2.3. The ESSDAI: EULAR Sjögren's syndrome disease activity index

The ESSDAI is a disease activity index that was generated in 2009, by consensus of a large group of worldwide experts from European and North American countries [28]. The ESSDAI is a systemic disease activity index and includes 12 domains (i.e. organ systems). Each domain is divided in 3–4 levels according to their degree of activity. The weights of each domain were obtained with multiple regression modeling, using the PhGA of disease activity as gold standard, in a cohort of 702 clinical vignettes based on 96 real patients. Before rating the score, experts were asked to rate only manifestations related to the disease and to avoid rating long lasting clinical features. The final score, the sum of all weighted scores, falls between 0 and, theoretically, 123, with 0 indicating no disease activity.