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Disease activity and patient reported outcome measures in Sjogren's – what are the best tools to evaluate?

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Abstract (150 words)

In primary Sjögren's syndrome (pSS), clinical features in SS can be divided into two facets: the patient perceived manifestations such as dryness, pain and fatigue, and the systemic manifestations.

In the past decades, with efforts made by an international collaboration, consensual clinical indexes were developed for assessing both facets: one patient reported outcome, the EULAR Sjögren's Syndrome Patients Reported Index (ESSPRI), and one activity index for systemic manifestations, the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI). In addition, objective measures were developed to quantify the importance and consequence of ocular and oral dryness, few being specific of pSS. Work is ongoing to develop indexes combining all these approaches.

Recent changes in the way to assess pSS patients, and emergence of new targeted therapies, have put a great input in the design of clinical trials in pSS, and led for the first time to a positive randomised clinical trial.

Key messages (15 words each)

- **Clinical features in primary Sjögren's syndrome (pSS), in SS can be divided in patient symptoms (dryness, pain and fatigue) and systemic manifestations.**
- **Clinical evaluation of pSS has evolved through the development of tools for the 2 facets**
- **In the most recent pSS trials, evaluation of systemic manifestations as primary outcome led for the first time to encouraging results**
- **Current work is ongoing to develop a pSS response criteria combining both PROs and systemic measures.**

Introduction

Primary Sjögren's syndrome (pSS) is a systemic disorder primarily characterized by lymphocytic infiltration of exocrine glands, resulting in functional impairment of salivary and lachrymal glands. The inflammatory process, however, extends beyond the exocrine glands and can potentially affect any organ. Therefore, along with dryness features, systemic manifestations such as synovitis, vasculitis, and skin, lung, renal and neurological involvement may occur. Also, chronic B cell activation, which is a hallmark of the disease, is responsible for an increased risk of lymphoma [1].

As a result, clinical features can be divided into two facets: (i) benign but disabling patients' symptoms such as dryness, pain and fatigue that affect almost all patients; and (ii) potentially severe systemic manifestations that affect 20%– 40% of patients. During the past decade, with the arrival of targeted therapies, outcome assessment has largely progressed thanks to the effort of the international collaboration set up by the EULAR Sjögren's task force. Thus, two outcome measures have been developed for evaluation of both disease facets: the EULAR SS Patient Reported Index (ESSPRI) for patients' symptoms [2] and the EULAR SS Disease Activity Index (ESSDAI) for systemic features [3]. As a consequence, evidence-based therapy for Sjögren's syndrome has evolved, from addressing principally sicca features and Patient Reported Outcomes (PROs) [4] [5-7] [8, 9] to the use of systemic disease activity measures, ie ESSDAI as the primary outcome measure for almost all recent and ongoing clinical trials. The purpose of this article is to address the evidence-based evaluations that have emerged in pSS.

1. Systemic Disease Activity Measures, through a consensual scoring: the ESSDAI

For the evaluation of systemic activity, the SS disease activity index (SSDAI) [10] was the first activity index proposed for SS. It had the benefit of simplicity, but lacked exhaustiveness and missed some of the rare but severe manifestations of pSS [11]. By contrast, the Sjögren's Systemic Clinical Activity Index (SCAI)[12] developed at the same time was much more exhaustive, but was complex to rate such that it was challenging to use it in clinical practice. These tools, however, served as the basis for developing the ESSDAI that offers the advantage of being exhaustive but also simple to use.

The ESSDAI is a disease activity index that was generated in 2009. The score was developed by consensus of a large group of worldwide experts from European and North American countries [12, 13] using patients' data. The ESSDAI (table 1) is a systemic disease activity index and includes 12 domains (i.e. organ systems: cutaneous, respiratory, renal, articular, muscular, PNS, CNS, haematological, glandular, constitutional, lymphadenopathy, biological). Before rating each domain, physician is asked to rate only manifestations related to the disease and to avoid rating long lasting clinical features and exclude rating of damage. The final score sums all domain scores and falls between 0 and, theoretically, 123, with 0 indicating no disease activity. Disease activity levels have been determined as follows: low activity (ESSDAI < 5), moderate (ESSDAI: 5 to 13) and high activity (ESSDAI ≥14) [14]. Also, minimal clinically important improvement (MCII) has been defined as an improvement of the ESSDAI score by at least 3 points.

To date, the ESSDAI has been used and evaluated in many studies and has become the consensus tool to evaluate systemic disease activity. The good sensitivity to change of ESSDAI has been confirmed in independent cohorts of patients treated by rituximab in clinical trials [15, 16], even though the randomized controlled trials failed to demonstrate treatment efficacy when ESSDAI was not used a primary outcome [17, 18]. Of note, ESSPRI and ESSDAI have been found to be poorly correlated in different studies [19-21], which suggests that patients' symptoms and systemic complications are two different components, that should both be evaluated, but separately. With the increasing use of ESSDAI, it became clear that a more extensive explanation of the way to use it would be helpful for clinical trials. Thus, a user guide has been published to help and clarify the rating of each domain [22]. These tools are now used to define entry criteria and the primary outcome of most of the recent and ongoing trials and a recent trial using ESSDAI as primary outcome demonstrated efficacy of an anti-CD40 monoclonal antibody [23].

2. Patient Reported Outcome Measures & Glandular Disease Activity Indices

Dryness (Sicca), particularly of eyes and mouth, are the key symptoms of Sjogren's syndrome and are present in 95% of patients with pSS [24]. Fatigue is also a major problem reported by 65-70% of patients and is also linked to reduced health-related quality of life (HRQoL) in pSS

[25]. Arthralgia/myalgia under the broader term of 'limb pain' is the third commonly recognized component of the Sjogren's 'symptom triad' of 'dryness', 'fatigue' and 'pain'.

The distinction between 'fatigue and pain' on the one hand and 'dryness' on the other is that the formers are purely symptomatic, at least in this context, ie there is no objective measure of fatiguability, or pain threshold currently used in the assessment of pain and fatigue in pSS. These are rather measured by visual analogue scales (VAS) or by a discrete numeric Likert scale (eg 0-10), or by questionnaire. Conversely, whilst improvement in symptomatic dryness is also a critical goal of therapy in pSS this is generally linked to a co-assessment of objective measures of glandular function such as tear production, ocular surface staining (reflecting a lack of tear production) and salivary flow. This applies to the assessment of both salivary stimulants such as Pilocarpine and potential disease-modifying therapies to suppress glandular inflammation.

We will therefore consider these separately as well as considering how they integrate together in composite measures and how 'global' or HRQoL measures fit into the overall picture.

2.1. Oral Features

One of the main complaints of SS is dry mouth. The definition of dry mouth includes xerostomia, subjective sensation of dryness, and hyposalivation (ie. quantitative decrease of saliva production due to salivary gland impairment). Also, xerostomia should lead to further explorations, as it could result from other conditions, mainly medication side effects [26]. Interestingly, in general as in pSS, xerostomia does not necessarily correlate with measures of hyposalivation [27]. In pSS, changes in saliva composition have been described, such as increased mucin glycosylation that could explain the dry mouth sensation [28]. Today, no tools are available to assess saliva qualitative changes. The alterations of saliva flow and composition affect the equilibrium of the mouth, leading to a higher rate of oral disabilities, such as dental caries, periodontal disease, candidiasis, taste disturbances and a burning mouth sensation [29], decreased health-related quality of life [30] and anxiety, and stress and depression [31]. Clinical evaluation of dental and periondontal diseases should not be neglected and patients should be referred to oral medicine specialists.

From the patient point of view, xerostomia assessment could be performed using different tools [32] such as the Xerostomia-Related Quality of Life Scale (XeQOLS) [33]) or the Xerostomia Inventory [34]. None of these questionnaires have been designed specifically for the assessment of xerostomia in pSS patients, and few data are available in this population. The XeQOLS was initially designed for patients with hyposalivation complicating salivary gland irradiation in orofacial cancer. It includes 15 items exploring 4 domains (physical functioning, pain/discomfort, personal/psychological functioning and social functioning) [33]. The Xerostomia Inventory has been set up in ageing people (≥ 65 years old). It includes 11 items that cover both experiential and behavioural aspects of dryness and 4 items are dedicated for extra-oral tissue dryness assessment (eyes, nose, face, lips) [34]. Both tools are easy to use in daily practice for physicians and dentists.

For assessment of oral health-related quality of life, the Oral Health Impact Profile OHIP-14 [30] is one of the most widely used questionnaires in dental research studies in various populations (elderly, children…) and conditions (tooth decay, periodontal diseases, prosthesis…). OHIP-14 is a shorter version of the OHIP-49 previously developed [35]. OHIP-14 is patient-centred and aims to assess seven dimensions of impacts of oral conditions on people's oral quality of life, including functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability and handicap on the last past year. In patients with pSS, it has been found that salivary flow rate correlated significantly with OHIP-14 ratings [36, 37].

In daily practice, dry mouth can be easily screened for using the two questions of the 2002 American-European consensus classification criteria for SS: (1) the presence of dry mouth more than 3 months and (2) the need to drink liquids to aid in swallowing dry [38]. Then, the objective assessment of hyposalivation should be performed with a measure of the Unstimulated Whole Salivary Flow (UWSF), considered as abnormal if ≤ 0.1 mL/min [39]. This was also incorporated into the 2016 ACR-EULAR classification criteria [40]. UWSF is physiologically mainly produced by the submandibular glands at a 0.3-0.4 mL/min rate [32]. UWSF appears to be more sensitive for the diagnosis of SS because it is more frequently abnormal than the stimulated WSF in patients with pSS [41]. Recently, the Clinical Oral Dryness Score has been proposed as an alternative to USWF measurement which is very rarely performed in daily practice. This score includes 10 items to assess oral dryness by simple tests

such as placing a mirror onto the oral mucosa and tongue to assess 'stickiness' or observations such as the glassy appearance of the oral mucosa, especially the palate, or the presence of frothy saliva. However, the score of each items was not correlated with the value of hyposalivation (severe, moderate or none hyposalivation) [42]. Once SS is diagnosed, the assessment of dryness symptoms of patients with SS, both of mouth and eyes, are recorded by specific PROs, such as the Sicca Symptom Inventory (SSI) [43] but also the ESSPRI, also integrating the other main patients features, ie pain and fatigue [2] into a single measure.

Some clinical data has suggested that the salivary flow rate and symptoms may transiently improve after rituximab , particularily in patients having a residual salivary flow before treatment and/or recently diagnosed pSS (less than 5 years) [44] [45, 46].

2.2. Ocular Indices

Inflammation of the lacrimal glands with reduced or absent tear production leading to ocular sicca (dryness) symptoms was embedded within the classification criteria for pSS [38]. The presence of dry eyes for more than three months, foreign-body sensation, use of tear substitutes more than three times daily in association with signs of ocular surface staining representing areas of devitalised or absent epithelial cells are symptoms that should encourage physician to perform diagnostic procedures for SS. In 2017, the Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) revised their definition of dry eye to a multifactorial disease of the ocular surface characterised by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play aetiological roles [47]. This differs from the 2007 definition [48] by recognising the significant role of inflammation and hyperosmolarity within the dry eye pathway and the presence of corneal neuropathic pain in the absence of clinical signs of dry eye [49]; a phenomenon previously known as 'pain without stain' [50]. The diagnostic methodology report from TFOS DEWS II undertook a detailed meta-analysis of the methods available for scoring patients perception of dry eye disease and quantifying clinical aspects of disease activity [51], and goes a considerable way to simplifying quantification of disease for diagnosis and monitoring of management strategies (**Figure 1**), but is not widely used in pSS.

Challenged by the fact that the patients' symptoms and clinical signs of dry eye do not represent a linear relationship and vary from patient to patient within a specific diagnostic category such as pSS, recommendation of a validated symptom questionnaire is critical, pivoted against activity and damage scoring of clinical disease [52]. The ocular symptomatology can lead to high levels of anxiety, depression and fatigue [53, 54]. Non-scripted, non-standardised verbal interviews are discouraged and questionnaires validated for discriminative ability, reproducibility and repeatability are recommended. The ocular surface disease index© (OSDI, Allergan Inc) score measuring domains of experience, performance and discomfort related quality of life spread over 12 questions provides a score out of 100 gauging severity of dry eye symptoms. It is the most widely used and accepted. An alternative, if time is limited, is the shorter five item Dry Eye Questionnaire (DEQ-5) covering discomfort, dryness and watery eye domains [55]. Continuous visual analogue scales for daily monitoring such as the Symptoms Analysis in Dry Eye (SANDE), tested against the OSDI, showed a significant correlation and negligible score differences compared with those from the OSDI, [56] making it a short, quick and reliable measure for dry eye symptom. A DEQ-5 ≥ 7 or OSDI ≥ 13, together with a positive response to the TFOS DEWS II triage question "*Do you have any moth dryness and swollen glands?*" should raise the suspicion of Sjögren's Syndrome [51].

Objective homeostatic markers for the measurement of clinical aspects of disease includes a range of tests summarised in **Table 2**. Tear film osmolarity provides an objective, automated means of sampling the tear film just above the lower lid that can easily be carried out in non-specialist clinics. A positive result is considered to be ≥308mOsm/L or an interocular difference of >8mOsm/L. Due to the variability between patients, longitudinal sampling is required to map progression of disease or response to therapy. The test could be useful in a clinical trial setting for measuring the impact of innovative technologies for the treatment of pSS on the ocular aspects of the disease.

In day to day clinical practice, TFOS DEWS II recommends non-invasive break-up time and ocular surface staining for the diagnosis and monitoring of dry eye disease. Non-invasive

break-up time without the use of fluorescein is preferred but invasive (fluorescein) break-up time may be substituted if non-invasive imaging is not available. In this situation, fluorescein is instilled in the outer canthus and slit-lamp viewing should take place 1-3 minutes after instillation with a positive finding recorded as <10 seconds. Quantification of ocular surface staining remains the mainstay for dry eye assessment. The two most commonly used staining patterns for pSS are the van Bijsterveld schema [57] and the Ocular Staining Score (OSS) [58] (figure 2). In the van Bijsterveld schema the intensity of lissamine green (a dye that stains devitalised epithelial cells and has replaced Rose Bengal) is scored in the two exposed conjunctival zones and cornea are scored between 0-3, giving a maximum score of 9. The Ocular Staining Score is more sensitive technique. The use of lissamine green for conjunctival scoring for nasal and temporal regions (grades 0-3) giving a maximum conjunctival score of 6 per eye and fluorescein (a dye that stains de-epithelialised areas) for corneal scoring delivering a score of 0-3 with added weighting for confluent and pupillary area staining and the presence of filaments, giving a maximum corneal score of 6 per eye. The resultant composite conjunctival and corneal score confirms clinical features compatible with dry eye with a score >3, but the threshold of 5 has been retained for the ACR/EULAR diagnosis criteria [40]. Due to the non-linear relationship of the symptoms and signs, the OSDI and OSS used together provide a tailored monitoring ocular tool-set to enable effective counselling of pSS with improvement in either score motivating the patient to continue with self-help interventions such as modification of local environment and diet, together with warm compresses, lid hygiene and the use of regular and frequent lubricants. Schirmer's test uses graduated filter paper strips inserted into the eye for 5 minutes to measure the production of tears. The paper is then removed, and the amount of moisture is measured: the test is considered as positive for pSS diagnosis if moisture is ≤ 5 mm in 5 minutes. Despite a relatively poor sensitivity, the Schirmer's test is still also use in clinical practice and remained in the most recent ACR/EULAR diagnosis criteria [40]. Effectively, easily done by any physician, without requiring an ophthalmologist expertise, it represents a practical screening alternative to more complex test. However, it cannot assess the severity of ocular surface involvement.

Evidence based experience in pSS is extremely limited since clinical trials focusing on dry eye usually recruit patients with various underlying disease that do not allow us to generalise their conclusion to pSS patients. By contrast in pSS dedicated trials, evaluation of dry eye is usually limited and generally there is no record of ocular symptoms and signs as an outcome

measure, or outcome measures with poor sensitivity (such as the Schirmer's test) are used that do not generate robust efficacy data. In addition, the generic evaluation of dryness usually does not clearly differentiate between oral, ocular and eventually other dryness features.

2.3. Fatigue and Pain

The simplest way of measuring fatigue (or pain) is to use a 10 cm VAS or 0-10 Likert rating scale from 'no fatigue (or pain)' to 'worst fatigue (or pain) imaginable'. Using fatigue as an exemplar this approach has been used in a number of Sjogren's trials [8, 46, 59]. To date none of the larger studies have demonstrated a clear-cut effect on improving fatigue, although the TEARS study of Rituximab led to a modest 10-15% improvement in fatigue at 6 weeks. Another approach is to use a questionnaire comprising a series of questions addressing different components of fatigue. Some of these such as the FACIT-F scale [60] and the Fatigue Severity Scale [61] are 'uni-dimensional i.e. they give a total score for fatigue whereas others such as the Multidimensional Fatigue Inventory (MFI) [62] or the Piper Fatigue Scale (PFS) [63] are 'multi-dimensional' i.e. they have a number of domains or subscales that measure different aspects of fatigue such as physical or mental components of fatigue, fatigue severity, the effect of fatigue on daily activities or the emotional consequences of fatigue. In terms of their use in clinical trials in pSS they are typically used as a secondary outcome measure to validate the data from the VAS or Likert scale.

The Profile of Fatigue and Discomfort (PROFAD) questionnaire [64] was specifically developed from interviews with pSS patients and by using the qualitative data from these to create and then refine an initially very broad questionnaire that captured key symptoms in patients with pSS. The key domains identified were, as expected, physical and mental fatigue, limb pain and also vascular features attributed to Raynaud's syndrome. Both a short-form and brief version [65] of this questionnaire were developed. In parallel to the PROFAD, a Sicca Symptoms Inventory (SSI) using the same methodology in the same participant group was also developed as a measure of dryness symptoms [43] and offers an alternative to the OSDI described in the ocular indices section of this chapter. The brief form of the PROFAD-SSI, alongside the empiric measurement of dryness, fatigue, pain, and 'global' health in trials such

as TRIPPS was in turn the progenitor of the EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI) now widely used to measure dryness, fatigue and pain in clinical trials and other studies in pSS [2]. The ESSPRI uses 0 to 10 numerical scales, one for the assessment of each of the 3 domains: dryness, fatigue and musculoskeletal pain (**Figure 3**). The weights of the domains are identical, and the mean of the scores of the 3 domains represents the final score.

The ESSPRI has been shown to have an excellent reliability, but a lower sensitivity to change than ESSDAI [66]. As for ESSDAI, relevant thresholds have been determined with ESSPRI [14]. Thus, the patient satisfactory symptom state (PASS) has been defined as an ESSPRI<5 and MCII as an improvement of ESSPRI at least 1 point or 15%.

2.4. Global and Health-Related Quality of Life Measures

Quality of Life (QoL) is a broad concept generally described as a sense of well-being. It attempts to compare this across very different cultures and societies. The World Health Organization Quality of Life Questionnaire (WHOQOL) [67] has four principal domains namely; physical, psychological, social relationships and environment. Health-Related QoL (HRQoL) is a more limited concept where the focus is on how a disease affects an individual or a group. The Medical Outcomes Short-Form 36 item (SF-36) questionnaire is the most widely used HRQoL questionnaire. Multiple studies have shown impaired HRQoL levels in pSS patients as measured by the SF-36 or another widely used measure the EQ5D [25, 64, 68, 69]. Generally, these measures are insufficiently sensitive to change in short-duration clinical trials, but they have the benefit of facilitating health economic assessment and are therefore valuable secondary outcome measures to calculate quality assisted life years (QALY's) as a marker of the economic benefit of novel therapies.

3. Combination approaches

Over the past 10 years or so various initiatives have clarified a number of outcome components for use in clinical trials in pSS. The ESSPRI is a simple tool to measure fatigue, pain and dryness symptoms. Combining the dryness component with objective measures of

tear and saliva flow, along with histological evaluation of the salivary glands and with the potential inclusion of an imaging modality allows for a comprehensive evaluation of glandular function. The ESSDAI, described elsewhere in this chapter has been developed to measure systemic features of the disease. In the absence of an effective therapy for pSS, it has been challenging to assess sensitivity to change of these tools and to effectively develop a composite measure to facilitate trials evaluating different components of the disease in the same study.

Extensive work has been conducted and major changes have occurred in the past 5 years in the methodology of conducting clinical trials in pSS. Most recent and ongoing trials focused on patients with moderate to severe activity and used the ESSDAI (table 3), a systemic activity measure. With this new design, for the first time a randomised controlled trial reached its primary endpoint showing a significant improvement of the ESSDAI [23]. Nevertheless, we must emphasise that trials focusing on symptoms and those focusing on systemic activity should not be exclusive. In pSS patients, the lower quality of life is mainly driven by the patient-reported outcomes such as sicca scores or ESSPRI than by the ESSDAI [25]. Also, in *post-hoc* analyses of the TEARS study, a combined index, the Sjogren's syndrome Responder Index (SSRI) has been proposed [70]. It combines patient-assessed visual analogue scale scores for fatigue, oral dryness and ocular dryness with unstimulated whole salivary flow rate and ESR. The SSRI is based on responders in the TEARS study, even though the study drug itself was ineffective. An SSRI-30 response was defined as a ≥30% improvement in at least two of five outcome measures. The potential use of this index to evaluate the effect of targeted therapies other than rituximab needs to be further evaluated. Nevertheless, this data suggests that biologics might be effective on patient's symptoms when considering patients with low or moderately active patients. Thus, although the study conclusions (and therefore the SSRI) are limited as a result, conceptually, this approach of analysis of positive clinical trials is needed to validate a composite measure in the future. Work is currently ongoing to develop a composite index that could include PROs, objective measures of dryness and systemic activity measures.

Conclusion

Overall, the evaluation of clinical manifestations in pSS focus on the 2 disease facets: patient symptoms (dryness, pain and fatigue), using specific and generic PROs, and systemic manifestations, principally using the ESSDAI. In the last 10 years, thanks to the huge methodological work and the emergence of new targeted therapies, major changes have occurred in the way of conducting clinical trials in pSS. And, in the most recent trials, systemic activity measures have been used as inclusion criteria and primary outcome, which led for the first time to encouraging results. Nevertheless, work is still ongoing to define response to treatment by combining PROs and measures of systemic activity

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Conflicts of interest

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Table 1. The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI),

Domain	Activity level	Description
Constitutional Exclusion of fever of infectious origin and voluntary weight loss	No=0	Absence of the following symptoms
	Low=3	Mild or intermittent fever (37.5−38.5°C)/night sweats and/or involuntary weight loss of 5–10% of body weight
	Moderate=6	Severe fever (>38.5°C)/ night sweats and/or involuntary weight loss of>10% of body weigh
Lymphadenopathy and lymphoma Exclusion of infection	No=0	Absence of the following features
	Low=4	Lymphadenopathy≥1 cm in any nodal region or ≥2 cm in inguinal region
	Moderate=8	≥2 cm in any nodal region or ≥3 cm in inguinal region and/or splenomegaly (clinically palpable or assessed by imaging)
	High=12	Current malignant B-cell proliferative disorder
Glandular Exclusion of stone or infection	No=0	Absence of glandular swelling
	Low=2	Small glandular swelling with enlarged parotid (≤3 cm), or limited submandibular (≤2 cm) or lachrymal swelling (≤1 cm)
	Moderate=4	Major glandular swelling with enlarged parotid (>3 cm), or important submandibular (>2 cm) or lachrymal swelling (>1 cm)
Articular Exclusion of osteoarthritis	No=0	Absence of currently active articular involvement
	Low=2	Arthralgias in hands, wrists, ankles and feet accompanied by morning stiffness (>30 min)
	Moderate=4	1–5 (of 28 total count) synovitis
	High=6	≥6 (of 28 total count) synovitis
Cutaneous Rate as 'No activity' stable long-lasting features related to damage	No=0	Absence of currently active cutaneous involvement
	Low=3	Erythema multiforma
	Moderate=6	Limited cutaneous Vasculitis (<18% of body surface area), including urticarial vasculitis, or purpura limited to feet and ankle, or subacute cutaneous lupus
	High=9	Diffuse cutaneous Vasculitis (>18% of body surface area) including urticarial vasculitis, or diffuse purpura, or ulcers related to vasculitis
Pulmonary Rate as 'No activity' stable long-lasting features related to damage, or respiratory involvement not related to the disease (tobacco use, etc)	No=0	Absence of currently active pulmonary involvement
	Low=5	Persistent cough due to bronchial involvement with no radiographic abnormalities on radiography Or radiological or high resolution computed tomography evidence of interstitial lung disease with: no breathlessness and normal lung function test
	Moderate=10	Moderately active pulmonary involvement, such as interstitial lung disease shown by high resolution computed tomography with shortness of breath on exercise (New York Heart Association: NHYA II) or abnormal lung function tests restricted to: 70% >DLCO ≥40% or 80% >Forced vital capacity ≥60%

	High=15	Highly active pulmonary involvement, such as interstitial lung disease shown by high resolution computed tomography with shortness of breath at rest (NHYA III, IV) or with abnormal lung function tests: DLCO <40% or Forced vital capacity <60%
Renal Rate as 'No activity' stable long-lasting features related to damage and renal0involvement not0related to the disease. If biopsy has been performed, please rate activity based on histological features first	No=0	Absence of currently active renal involvement with proteinuria <0.5 g/day, no haematuria, no leucocyturia, no acidosis or long-lasting stable proteinuria due to damage
	Low=5	Evidence of mild active renal involvement, limited to tubular acidosis without renal failure or glomerular involvement with proteinuria (between 0.5 and 1 g/day) and without haematuria or renal failure (glomerular filtration rate (GFR) ≥60 mL/min)
	Moderate=10	Moderately active renal involvement, such as tubular acidosis with renal failure (GFR <60 mL/min) or glomerular involvement with proteinuria between 1 and 1.5 g/day and without haematuria or renal failure (GFR ≥60 mL/min) or histological evidence of extra-membranous glomerulonephritis or important interstitial lymphoid infiltrate
	High=15	Highly active renal involvement, such as glomerular involvement with proteinuria >1.5 g/day, or haematuria or renal failure (GFR <60 mL/min), or histological evidence of proliferative glomerulonephritis or cryoglobulinemia related renal involvement
Muscular Exclusion of weakness due to corticosteroids	No=0	Absence of currently active muscular involvement
	Low=6	Mild active myositis shown by abnormal Electromyogram, Magnetic Resonnance Imaging (MRI)* or biopsy with no weakness and creatine kinase (N≤CK≤2N)
	Moderate=12	Moderately active myositis proven by abnormal Electromyogram, MRI* or biopsy with weakness (maximal deficit of 4/5), or elevated creatine kinase (2N<CK≤4N),
	High=18	Highly active myositis shown by abnormal Electromyogram, MRI* or biopsy with weakness (deficit ≤3/5) or elevated creatine kinase (>4N)
Peripheral nervous system (PNS) Rate as 'No activity' stable long-lasting features related to damage or PNS involvement not related to the disease	No=0	Absence of currently active PNS involvement
	Low=5	Mild active PNS involvement, such as pure sensory axonal polyneuropathy shown by NCS or trigeminal (V) neuralgia, or proven small fiber neuropathy
	Moderate=10	Moderately active PNS involvement shown by NCS, such as axonal sensory–motor neuropathy with maximal motor deficit of 4/5, pure sensory neuropathy with presence of cryoglobulinemic vasculitis, ganglionopathy with symptoms restricted to mild/moderate ataxia, inflammatory demyelinating polyneuropathy (CIDP) with mild functional impairment (maximal motor deficit of 4/5 or mild ataxia) Or cranial nerve involvement of peripheral origin (except trigeminal (V) neuralgia
	High=15	Highly active PNS involvement shown by NCS, such as axonal sensory–motor neuropathy with motor deficit ≤3/5, peripheral nerve involvement due to vasculitis (mononeuritis multiplex, etc), severe ataxia due to ganglionopathy, inflammatory demyelinating polyneuropathy (CIDP) with severe functional impairment: motor deficit ≤3/5 or severe ataxia
Central nervous system (CNS)	No=0	Absence of currently active CNS involvement

Rate as 'No activity' stable long-lasting features related to damage or CNS involvement not related to the disease	Moderate=10	Moderately active CNS features, such as cranial nerve involvement of central origin, optic neuritis or multiple sclerosis-like syndrome with symptoms restricted to pure sensory impairment or proven cognitive impairment
	High=15	Highly active CNS features, such as cerebral vasculitis with cerebrovascular accident or transient ischaemic attack, seizures, transverse myelitis, lymphocytic meningitis, multiple sclerosis-like syndrome with motor deficit
Haematological For anaemia, neutropenia, and thrombopenia. Only auto-immune cytopenia must be considered Exclusion of vitamin or iron deficiency, drug-induced cytopenia	No=0	Absence of autoimmune cytopenia
	Low=2	Cytopenia of autoimmune origin with neutropenia (1000<neutrophils<1500/mm3), and/or anaemia (10<haemoglobin<12 g/dL), and/or thrombocytopenia (100 000<platelets<150 000/mm3) Or lymphopenia (500<lymphocytes<1000/mm3)
	Moderate=4	Cytopenia of autoimmune origin with neutropenia (500≤ neutrophils ≤1000/mm3), and/or anaemia (8≤ haemoglobin ≤10 g/dL), and/or thrombocytopenia (50 000 ≤ platelets ≤100 000/mm3) Or lymphopenia (≤500/mm3)
	High=6	Cytopenia of autoimmune origin with neutropenia (neutrophils<500/ mm3), and/or or anaemia (haemoglobin<8 g/dL) and/or thrombocytopenia (platelets<50 000/mm3)
Biological	No=0	Absence of any of the following biological feature
	Low=1	Clonal component and/or hypocomplementemia (low C4 or C3 or CH50) and/or hypergammaglobulinemia or high IgG level between 16 and 20 g/L
	Moderate=2	Presence of cryoglobulinemia and/ or hypergammaglobulinemia or high IgG level >20 g/L, and/or recent onset hypogammaglobulinemia or recent decrease of IgG level (<5 g/L)

Table 2: Tests for grading clinical features of dry eye disease in Sjögren's Syndrome

Parameter	Test
Tear film instability	Invasive and non-invasive tear film break-up time
	Thermography
Tear film volume	Meniscometry
	Phenol-red test
	Schirmer's test
Tear film Composition	Osmolarity
	Ferning
	Proteonomics
	Metabolomics
Ocular Surface Damage	Ocular surface staining
	Conjunctival impression cytology
	Lid parallel conjunctival folds
	In vivo confocal microscopy
	Corneal sensitivity
Ocular Surface Inflammation	Redness
	Tear cytokine levels
	Surface markers using impression cytology
	In vivo confocal microscopy
Meibomian gland dysfunction	Interferometry
	Meibography
	In vivo confocal microscopy through the lids

Table 3. Main results of randomized controlled studies of biologicals in pSS

Reference	Treatment	N	Primary endpoint	Significant difference for primary endpoint
(Sankar et al. 2004)[9]	Etanercept	14	≥20% improvement from baseline for 2 of 3 domains: subjective or objective measures of dry mouth and dry eyes, and IgG level or ESR	No
(Mariette et al. 2004)[8] TRIPPS	Infliximab	103	At week 10 ≥30% improvement in 2 of 3 VASs measuring joint pain, fatigue, and the most disturbing dryness.	No No differences for secondary outcomes
(Dass et al. 2008)[71]	Rituximab	17	At week 24 20% reduction in VAS fatigue score	Yes
(Meijer et al. 2010)[44]	Rituximab	30	At weeks 5, 12, 24, and 48 Improvement in the stimulated whole saliva flow rate	Yes Significant improvement at weeks 5 and 12
(Devauchelle-Pensec et al. 2014)[46] TEARS	Rituximab	122	At week 24 30-mm improvement in 2 of 4 VAS	No but efficacy at week 6 and on secondary endpoints (mainly biological features)
(Bowman et al. 2017)[59] TRACTISS	Rituximab	110	At 48 weeks 30% improvement in VAS fatigue or oral dryness score	No efficacy on primary and secondary enpoints
(Fisher et al. 2017)[23]	Anti-CD40 Monoclonal Antibody CFZ533	29	At 12 weeks Change in ESSDAI	Yes Significant ESSDAI improvement

VAS: visual analogic Scale

Figure 1 Legend: ***Patient-reported outcomes and disease activity in ocular disease.***

Symptoms and signs frequently do not correlate. Quantification of dry eye disease is based upon TFOS DEWS II recommendations include patient markers using OSDI or DEQ-5 patient outcome instruments together with homeostatic markers of disease activity using non-invasive break-up time without fluorescein or with *fluorescein (if non-invasive technology is not available) after osmolarity measurement, followed by ocular surface staining with fluorescein and lissamine green. Symptoms excess of clinical signs may indicate neuropathic pain. (Abbreviations: **TFOS DEWS II**, Tear Film and Ocular Surface Society Dry Eye Workshop; **DEQ-5**, five-item dry eye questionnaire; **OSDI©**, ocular surface disease index)

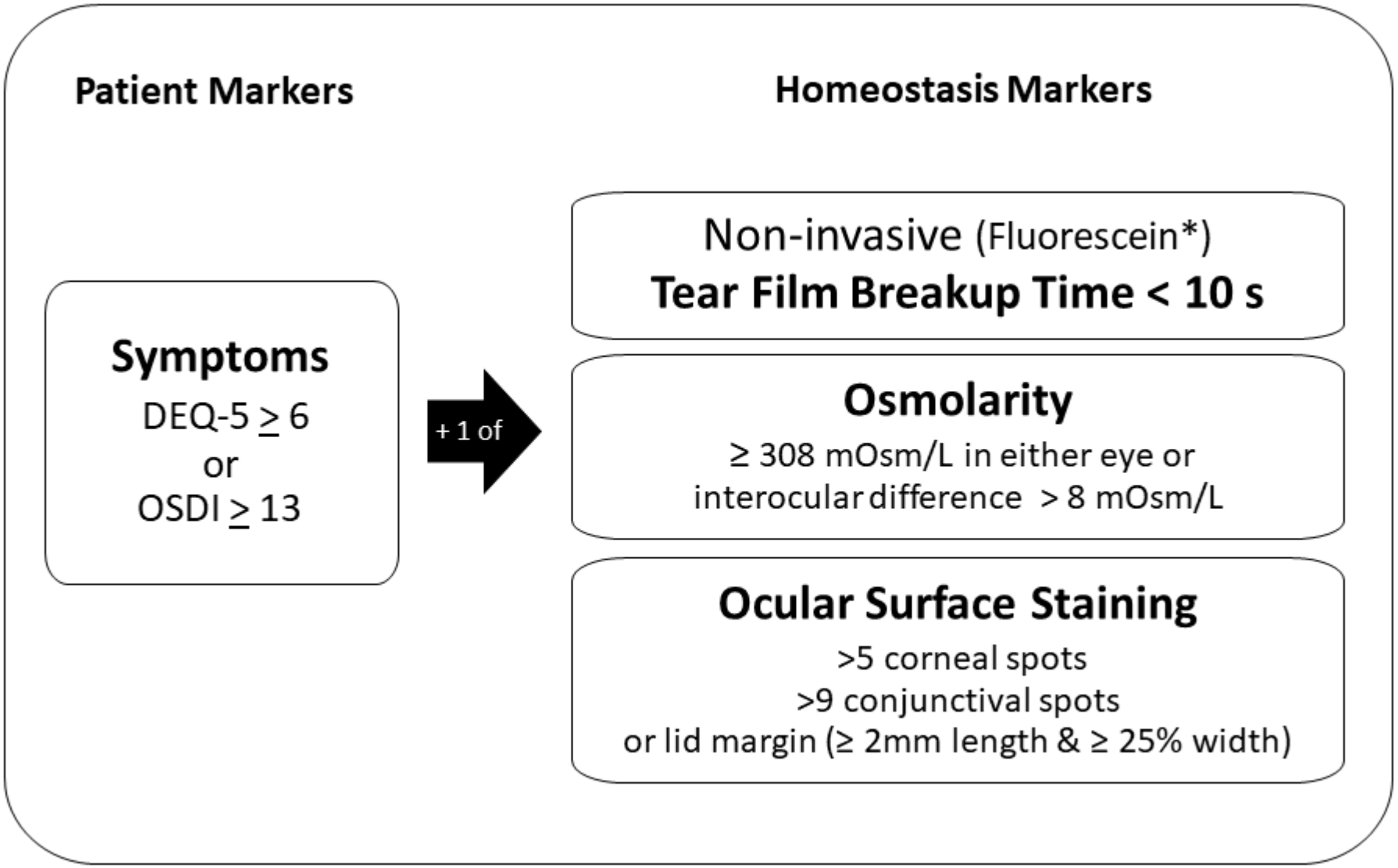
Patient Markers
Homeostasis Markers
Symptoms
DEQ-5 ≥ 6
or
OSDI ≥ 13
+ 1 of
Non-invasive (Fluorescein*)
Tear Film Breakup Time < 10 s
Osmolarity
≥ 308 mOsm/L in either eye or
interocular difference > 8 mOsm/L
Ocular Surface Staining
>5 corneal spots
>9 conjunctival spots
or lid margin (≥ 2mm length & ≥ 25% width)

Figure 2. Comparison of the van Bijsterveld scoring method and the OSS (Ocular Staining Score).

The van Bijsterveld score has a maximum of 9 points per eye and is considered positive if ≥4 in at least one eye. The OSS score has a maximum of 12 points per eye and is considered positive if ≥3 in at least one eye, but the threshold of 5 has been retained in the new ACR/EULAR criteria.

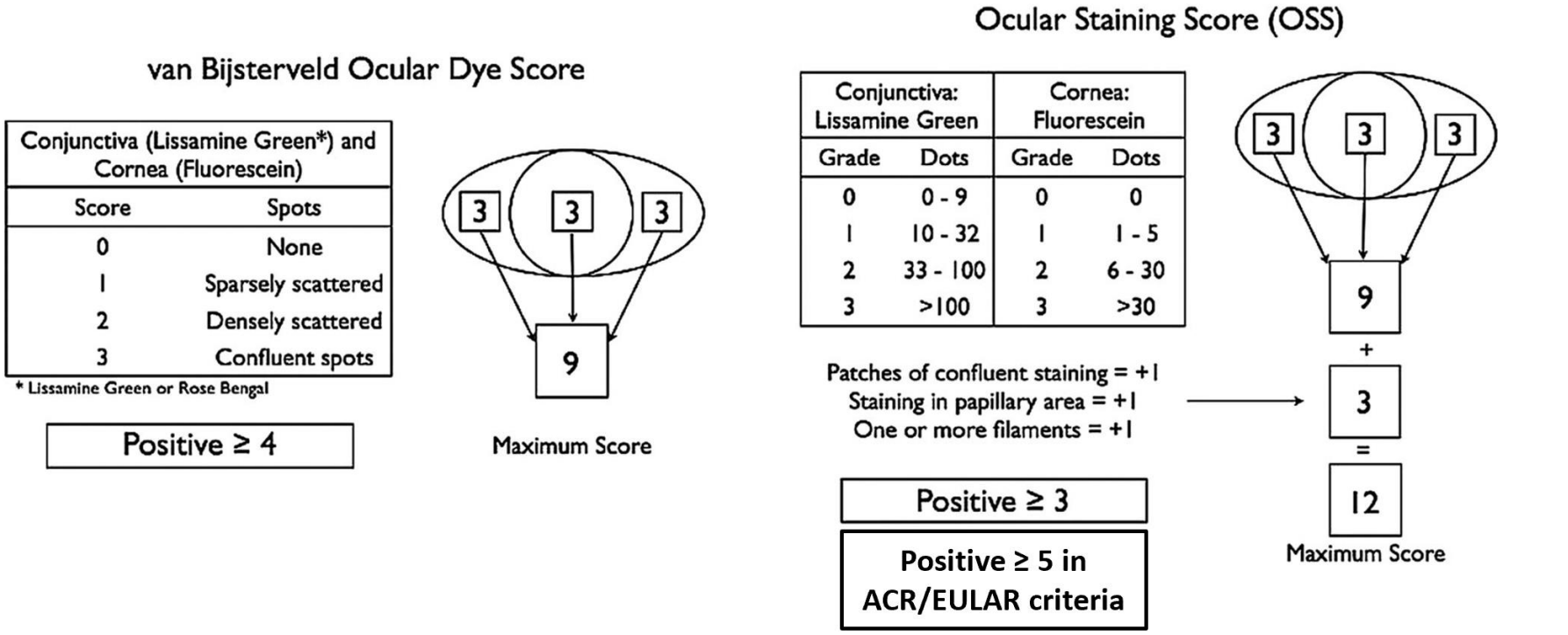

Figure 3 Legend: the the EULAR SS Patient Reported Index (ESSPRI)

The ESSPRI uses 0 to 10 numerical scales, one for the assessment of each of the 3 domains: dryness, fatigue and musculoskeletal pain. The final score is the mean of the scores of the 3 domains represents and range from 0 to 10.