Outcome measures of disease activity in rare autoimmune rheumatic diseases

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ABSTRACT

Systemic lupus erythematosis (SLE), scleroderma, myositis and Sjögren's sydrome (SS) are rare, complex, multi-systemic rheumatic diseases associated with significant morbidity and mortality. Thorough assessments of disease activity are required to guide clinical management and assess response to new therapies in clinical trials. In this article, we shall review the commonly used outcome measures to assess this group of diseases and discuss the limitations of their use.

INTRODUCTION

Outcome measures form a crucial component of clinical practice and research. A standardised assessment of disease activity provides an accurate trend of disease activity overtime and prompts changes in patient's management. Over the last decade, there has been burgeoning research into the pathogenesis of SLE, scleroderma, autoimmune myopathies and SS, leading to the development of novel therapeutic targets. Robust measures of disease activity are required to accurately assess the efficacy of these new therapies in clinical trials. The Outcomes Measures in Rheumatologic Trials group (OMERACT) (Tugwell *et al.*, 2007) have established clear constructs for outcome measures; stating that they should be valid, sensitive, reproducible, sensitive to change and feasible. In this article, we shall review the common outcome measures used to assess this group of diseases and the limitations of their use.

Systemic lupus erythematosus (SLE)

SLE is a chronic multisystem autoimmune disease with a heterogeneous pattern of clinical and serological manifestations. Pathogenesis of the disease involves a complex interaction between gene susceptibility, hormonal influences and certain environmental triggers which induce autoantibody production (Rahman and Isenberg, 2008). It has an overall incidence of 4.9-5.5 and prevalence of 72.8-97 in recent UK and US population estimates with a 6-10 fold female predominance (Somers *et al.*, 2014) .

Several tools have been developed to assess disease activity both in clinical practice and as primary endpoints in clinical trials. The primary tools used are the BILAG-2004 developed and validated by the British Isles Lupus Assessment Group (Romero-Diaz, Isenberg and Ramsey-Goldman, 2011), SLEADI-2K (systemic lupus erythematosus disease activity index 2000) (Gladman *et al.*, 2003) and SLICC (systemic lupus international collaborating clinics) (Gladman *et al.*, 1996). Limitations of individual disease activity scores lead to the development of composite indices such as SLE responder index (SRI and SRI-50) (Mikdashi and Nived, 2015) (Castrejon *et al.*, 2014) and the BILAG based composite lupus assessment (BLICA) (Castrejon *et al.*, 2014). The most commonly used patient reported outcome score is the Lupus Quality of Life Questionnaire (Lupus-QoL) (Holloway *et al.*, 2014).

Figure 1: Outcome measures in SLE

Disease activity scores
British Isles Lupus Assessment Group Index (BILAG-2004) (Romero-Diaz, Isenberg and Ramsey-Goldman, 2011) • Nine systems are measured: constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, gastrointestinal, ophthalmic, renal and haematological • Features graded as new, the same, worse or improving. • Incorporates severity and provides assessment scales for individual organs and systems • Accurate scoring requires that the physician only counts activity that is attributable to lupus • Activity in each organ system is scored as: A = most active disease (12 points); B = intermediate activity (8 points); C = mild, stable disease (1 point); D = previous involvement, currently inactive (0 points); E = no previous activity (0 points). Flares can also be assessed with a severe flare = A; new appearance and moderate flare = B; and recurrence as score of D or E
Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEADI-2K) (Gladman *et al.*, 2003) • Global index of disease activity in SLE • Consists of 24 questions • Records descriptors of disease activity as present or absent in the preceding 10 or 30 days along with persistent rash, alopecia, oral ulcers and proteinuria limiting its use in clinical trials • Measures disease activity in 9 organ systems: neurological, musculoskeletal, renal, mucocutaneous, general, cardiac, respiratory, vascular, and hematological with a scoring range of 1-8 • Provides a single summary score for disease activity with a maximum score of 105
SLE responder index (SRI) (Castrejon *et al.*, 2014) • Combination index of SELENA-SLEDAI, BILAG and physician global assessment • A responder is classified as SELENA-SLEDIA improvement of 4 or more points from baseline • No new BILAG A or B scores • No worsening of physician global assessment
SLEDAI-2000 Responder Index 50 (SRI 50) (Mikdashi and Nived, 2015) • Composed of SLEDAI-2K and generates a numerical score that reflects disease activity over the previous 30 days • Each descriptor identifies at least a 50% improvement which generates a score for that descriptor
BILAG-Based Composite Lupus Assessment (BICLA) (Castrejon *et al.*, 2014) • Combination of BILAG, PGA and SLEADI • Responder classified as no new BILAG A or B scores • Improvement of BLAG A score to B, BILAG B/C/D to BILAG C/D • No increase in SLEDAI from baseline • No worsening of PGA
Damage indices
Systemic Lupus International Collaborating Clinics Damage Index (SLICC) (Gladman *et al.*, 1996) • Damage assessment index • Includes 42 items in 12 domains with a maximum score of 46. Items are rated as being either present or absent with recurring events being scored either 2 or 3. • Irreversible damage is defined as change in an organ or system that has occurred since the onset of disease and has been present ≥6 months
Patient reported outcomes
Lupus Quality of Life Questionnaire (LupusQoL) (Holloway *et al.*, 2014) • Patient reported quality of life questionnaire • 34 questions covering the preceding four weeks • Five-point scale ranging from “never” to “all of the time”

Scleroderma

Scleroderma, also known as systemic sclerosis, is a rare autoimmune disease associated with significant morbidity and mortality. It is characterised by vascular injury and abnormal fibrotic processes that can affect multiple organ systems, including the skin, lungs, gastrointestinal (GI) tract and cardiovascular system.

Skin involvement in scleroderma is almost universal. The modified Rodnan skin score (mRSS) (Clements *et al.*, 1995) is a validated measure of skin disease and has become the most commonly used measure of disease activity in patients with systemic sclerosis. The mRSS correlates with patient derived measures of disease, physical function and mortality. However, there is a high inter-observer variation in this score. Disease of the GI system occurs in approximately 90% of patients with scleroderma and has a major impact on their health-related quality of life. However, few instruments have been validated for the assessment of GI tract in scleroderma. Interstitial lung disease and pulmonary arterial hypertension are the leading cause of death in patients with scleroderma. Lung function tests and the 6 minute walk test are surrogate markers for these disease parameters in clinical trials. The 6 minute walk test measures the distance a patient can walk in six minutes and has been successfully incorporated into trials of scleroderma-related PAH (Badesch *et al.*, 2000). Raynaud's phenomenon (RP) occurs in more than 90% of patients with scleroderma and is measured using the RP score (Merkel *et al.*, 2002). Severe Raynaud's can lead to digital ulcers (DU). These are manually counted to provide a DU score. The HAQ I is a widely used patient reported outcome score used in rheumatic diseases (Fries *et al.*, 1980) and has been validated in scleroderma. The scleroderma HAQ is a variation of the HAQ incorporating questions specific to scleroderma disease (Steen and Medsger, 1997).

Figure 2: Outcome measures in scleroderma

Disease activity scores
Modified Rodnan skin score (mRSS) (Clements *et al.*, 1995) Skin thickness across 17 regions of the body. Clinician uses index finger and thumb to roll or gently pinch skin. A scale 0-3 is applied. 0-No thickening, 1-Mild thickening, 2-Moderate thickening, 3-Severe thickening **Pulmonary function tests** Vital capacity (VC), Forced vital capacity and Diffusing capacity for carbon monoxide are important variables in the assessment of lung involvement **6 minute walk test** The 6-minute walk test (6MWT) measures the distance a person can walk in 6 minutes **Raynaud's condition score** (Merkel *et al.*, 2002) The RCS is calculated from a summation of 1- or 2-week daily patient self-assessments of RP activity using a 0 to 10 ordinal scale. The RCS incorporates the cumulative daily frequency, duration, severity, and impact of RP attacks. **Digital ulceration count** Manual count of the number of digital ulcers
Patient reported outcomes
HAQ-DI (Fries *et al.*, 1980) The HAQ-DI assesses eight disability categories over the past 7 days (dressing/grooming, arising, eating, walking, hygiene, reach, grip, common daily activities). Items are rated on a 4-point scale, ranging from 0 (without any difficulty) to 3 (unable to do), with higher scores indicating greater functional disability. The total score is the mean of the highest scores of each of the eight categories, ranging from 0 (no disability) to 3 (severe disability).
The Scleroderma HAQ (SHAQ) (Steen and Medsger, 1997) Includes the disability and pain scales of the HAQ plus five visual analogue scales (VASs) that patients use to rate scleroderma-specific problems in the preceding week including pulmonary disease, digital ulcers, Raynaud's phenomenon, GI disease, and skin disease

Inflammatory myopathies

The idiopathic inflammatory myopathies (IIM) are characterised by auto immune mediated muscle inflammation and weakness. They have a worldwide prevalence of 14 in 100,000 (Meyer *et al.*, 2015). Adult polymyositis (PM), dermatomyositis (DM), and juvenile dermatomyositis (JDM) are among the most frequent of the IIM. During the past decade, collaborations such as the International Myositis Assessment & Clinical Studies Group (IMACS) have undertaken projects to define core measures of disease activity and damage in myositis and dermatomyositis, and to develop and validate tools for these measures (Isenberg *et al.*, 2004).

The most commonly-used tools include the Manual Muscle Test 8 (MMT8) (Miller *et al.*, 2001); Myositis Intention to Treat (MITAX); and Myositis Disease Activity Assessment Tool (MYOACT) (Isenberg *et al.*, 2004). Disease damage measures are used to assess the persistent change in anatomy, physiology, pathology or function resulting from previously active disease or complications of therapy. Usually, changes are post-inflammatory, cumulative and irreversible. Damage should be present for at least six months despite previous immunotherapy, rehabilitation or other therapy. The most commonly-used tool to assess disease damage is Myositis Damage Index (MDI) (Isenberg *et al.*, 2004).

In addition to measuring myositis-specific activity and damage, Rider and colleagues (2011) also recommend the use of the following tools: general tools of global disease activity (e.g. physician and patient visual analogue scales - VAS); functional assessment tools (e.g. Health Activity Questionnaire – HAQ, and childhood myositis assessment score); and patient-reported outcome measures (e.g. health-related quality of life measures such as SF36 for adults or CHQ-PF50 for children).

Figure 3: Outcomes measures in myositis

Assessment of myositis activity
Muscle assessment **Manual Muscle Test 8 (MMT8, a modified, shorter version of MMT)** • Part of the physical examination, requiring no specific equipment, to measure muscle strength. • A summary score assessing eight proximal, distal and axial muscles in the upper and lower extremities, using 0-10 point scale. Each muscle group tested is scored by using either the modified MRC or Kendall grading scale, depending on how much the muscle group can do in terms of moving against gravity or against applied pressure. • Partially validated, it is used internationally and in all subsets of myositis including adult and juvenile PM and DM, as well as for a number of neuromuscular conditions. • Extremely useful for long-term monitoring of myositis patients in both clinical and research settings. However, requires adequate training to perform and does not discriminate between activity and damage. (Rider et al 2011) **Extra-muscular assessment:** **Myositis Intention to Treat (MITAX)** • The MITAX assesses specific manifestations in seven organs or systems (constitutional, cutaneous, skeletal, gastrointestinal, pulmonary, cardiac, and muscle). Each clinical features is recorded using a scale of 0-4 (0 = not present; 1 = improving; 2 = the same; 3 = worse; 4 = new). The score is then converted using a scoring schema to an overall disease activity score for each system, which indicates the level of treatment needed. **Myositis Disease Activity Assessment Tool (MYOACT)** • Assesses severity of activity in each organ system with a 10-cm visual analogue scale (VAS), and a global extra-muscular VAS.
Assessment of myositis damage
Myositis Damage Index (MDI) • A comprehensive tool to assess the extent and severity of damage developing in 11 organs systems. A complete history and physical examination is needed, although minimal training required. • Organ-specific questions ask the presence or absence of a given sign or symptom, and the overall rating of disease damage in each system using 10cm visual analogue scale to measure severity. • The MDI can be used in both adult and juvenile PM and DM patients, although due to its comprehensive nature, may reflect damage caused by co-morbid conditions not just myositis.

Dermatomyositis

Myositis occurring with characteristic skin and nail manifestations is coined dermatomyositis (DM). These manifestations may include Gottron's papules, helitrope rash, photo-distributed erythema, poikiloderma, dilated nail fold capillaries, scalp involvement and calcinosis cutis. The Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), is the most commonly used combined tool in clinical practice and therapeutic studies for DM (Klein *et al.*, 2008). It is a clinician scored instrument that measures skin

activity and damage. Activity is measured in three areas – erythema, scale, and erosion/ulceration. Damage is measured in two areas – poikiloderma and calcinosis. In addition, Gottrons papules, periungual changes and alopecia are also scored.

Figure 4: Dermatomyositis-related rash

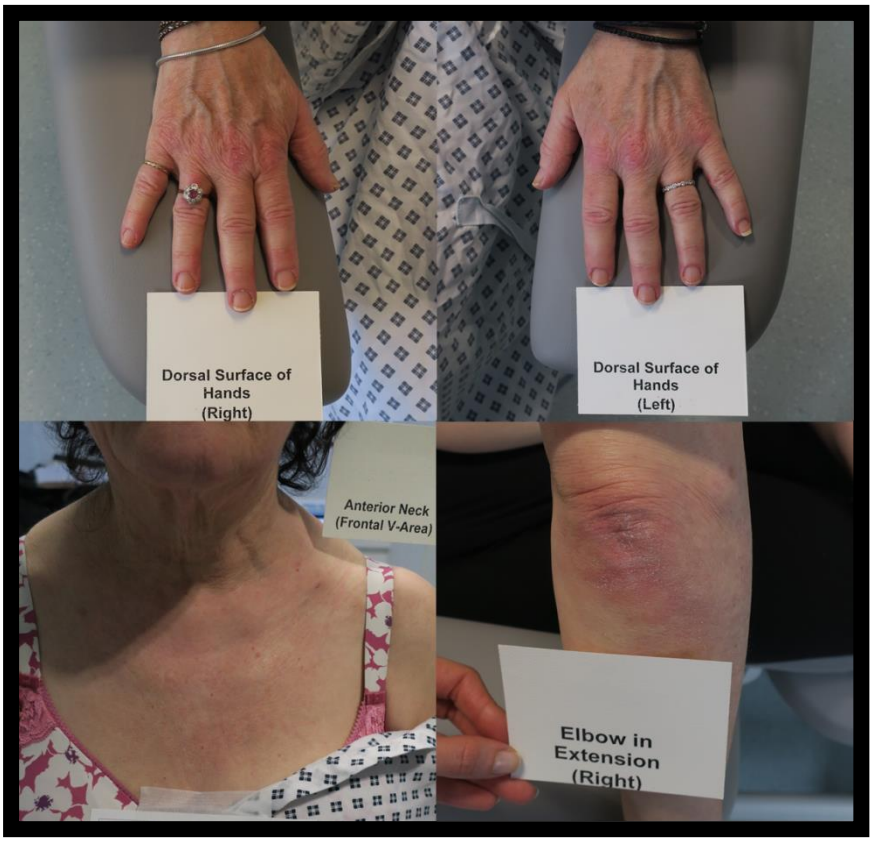
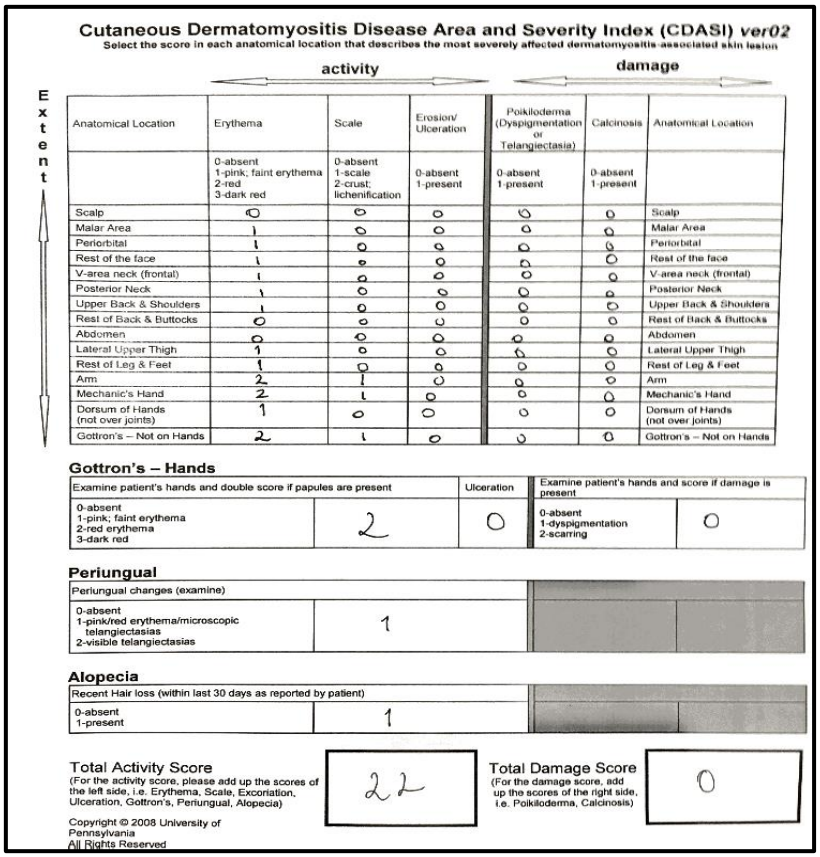


Figure 5: Example of CDASI scoring of dermatomyositis rash



Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) *ver02*

Select the score in each anatomical location that describes the most severely affected dermatomyositis-associated skin lesion

Extent

	activity			damage		
Anatomical Location	Erythema	Scale	Erosion/ Ulceration	Poikiloderma (Dyspigmentation or Telangiectasia)	Calcinosis	Anatomical Location
	0-absent 1-pink; faint erythema 2-red 3-dark red	0-absent 1-scale 2-crust; lichenification	0-absent 1-present	0-absent 1-present	0-absent 1-present	
Scalp	0	0	0	0	0	Scalp
Malar Area	1	0	0	0	0	Malar Area
Periorbital	1	0	0	0	0	Periorbital
Rest of the face	1	0	0	0	0	Rest of the face
V-area neck (frontal)	1	0	0	0	0	V-area neck (frontal)
Posterior Neck	1	0	0	0	0	Posterior Neck
Upper Back & Shoulders	1	0	0	0	0	Upper Back & Shoulders
Rest of Back & Buttocks	0	0	0	0	0	Rest of Back & Buttocks
Abdomen	0	0	0	0	0	Abdomen
Lateral Upper Thigh	1	0	0	0	0	Lateral Upper Thigh
Rest of Leg & Feet	1	0	0	0	0	Rest of Leg & Feet
Arm	2	1	0	0	0	Arm
Mechanic's Hand	2	1	0	0	0	Mechanic's Hand
Dorsum of Hands (not over joints)	1	0	0	0	0	Dorsum of Hands (not over joints)
Gottron's – Not on Hands	2	1	0	0	0	Gottron's – Not on Hands

Gottron's – Hands

Examine patient's hands and double score if papules are present		Ulceration	Examine patient's hands and score if damage is present	
0-absent 1-pink; faint erythema 2-red erythema 3-dark red	2	0	0-absent 1-dyspigmentation 2-scarring	0

Periungual

Periungual changes (examine)			
0-absent 1-pink/red erythema/microscopic telangiectasias 2-visible telangiectasias	1		

Alopecia

Recent Hair loss (within last 30 days as reported by patient)			
0-absent 1-present	1		

Total Activity Score (For the activity score, please add up the scores of the left side, i.e. Erythema, Scale, Excoriation, Ulceration, Gottron's, Periungual, Alopecia): 22

Total Damage Score (For the damage score, add up the scores of the right side, i.e. Poikiloderma, Calcinosis): 0

Sjögren's sydrome

Sjögren's syndrome (SS) is a chronic autoimmune disorder affecting approximately 0.1–0.4% of the general population with a female-to-male ratio of 9:1, usually diagnosed in the fourth and fifth decades of life (Daridon *et al.*, 2007). Clinically, SS is characterised by ocular and oral dryness developed because of the autoimmune infiltrating process affecting the exocrine glands. It may occur either alone, as primary SS, or in association with other autoimmune disease, often rheumatoid arthritis, systemic lupus erythematosus or systemic sclerosis, in which case is called secondary SS. Clinical, laboratory and histological features can be used to classify the systemic manifestations of SS as periepithelial or tissue-specific

(including liver, lung and kidney) and extraepithelial (including vasculitis, peripheral neuropathy, renal involvement and myositis) (Fox *et al.*, 1984).

In the past decades, a core set of domains was defined to facilitate the complex assessment of SS patients' outcomes (Seror *et al.*, 2012). This included sicca symptoms, objective measurements of tear and saliva production, fatigue, quality of life, disease activity and damage indexes.

Significant efforts have been made to develop valid tools for the assessment of various clinical and laboratory manifestation of SS, as the disease can have a heterogeneous presentation. A large international project supported by EULAR, led to the development of two consensus disease activity indexes: the EULAR Sjögren's Syndrome Patients Reported Index (ESSPRI) (Seror *et al.*, 2011), and the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) (Seror *et al.*, 2015), a systemic activity index to assess systemic manifestations, which are the most used outcome measures in SS. In addition, patient questionnaires such as the Profile of Fatigue and Discomfort (PROFAD) and Sicca Symptoms Inventory (SSI) have also been developed. The table below details the most used disease specific outcome measures in SS.

Figure 6: Outcomes measures in Sjögren's sydrome

Disease activity scores

Sjögren's Clinical Activity Index (SCAI) (Bowman *et al.*, 2007)

- Originated from the BILAG
- Consists of 42 questions from 8 domains (constitutional, musculoskeletal, cutaneous/vascular, respiratory, neurological, renal, salivary gland, haematological)
- Scored as new, same, worse, improving or not present

Sjögren's Syndrome Disease Activity Index (SSDAI) (Vitali *et al.*, 2007)

- Assessment of disease activity
- Eight domains: constitutional, salivary gland, articular, haematological, pleuro-pulmonary, vasculitis, renal, peripheral neuropathy

EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) (Seror *et al.*, 2015)

- Assessment tool of disease activity in pSS
- Twelve Domains: constitutional, lymphadenopathy and lymphoma, glandular, articular, cutaneous, pulmonary, renal, muscular, peripheral nervous system, central nervous system, haematological, biological

Damage indexes

Sjögren's Syndrome Disease Damage Index (SSDDI) (Vitali *et al.*, 2007)

- Developed for the Italian cohort
- Assessment of damage
- Six domains: Oral/salivary damage, ocular damage, neurologic damage, pleuropulmonary, renal, lymphoproliferative

Sjögren's Syndrome Damage Index (SSDI) (Barry *et al.*, 2008)

- Developed for the UK cohort
- Assessment of damage
- Ten domains: Ocular, oral, neurological, renal, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, endocrine, malignancy

Patient reported outcomes

EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) (Seror *et al.*, 2011)

- Derived from PROFAD-SSI
- Patient questionnaire to assess symptoms rather than disease activity as the ESSDAI
- Three questions regarding dryness, fatigue, pain
- Scale of 0-10
- Reported to be an independent predictor of health-related quality of life in pSS patients (Cho et al., 2013).

PROFAD-SSI score (profile of fatigue and discomfort sicca symptoms inventory)

- PROFAD-SSI score is a 64-point questionnaire that covers symptoms of somatic fatigue, mental fatigue, arthralgia, vascular symptoms, sicca (ocular and oral) symptoms, cutaneous and vaginal dryness
- The PROFAD-SSI-SF (short form) score is a 19-point questionnaire abbreviated from the above which has been validated as a pSS outcome tool (Bowman et al., 2009)
- Fatigue VAS was found to most closely correlate with somatic fatigue
- The somatic fatigue domain forms the PROF-S whilst the mental fatigue domain forms the PROF-M (derived from patient's descriptions of fatigue)

The ESSDAI and ESSPRI scores are currently used as gold standard in clinical trials. An ESSDAI ≥5 signifies moderately active disease, while a minimal clinically important improvement is defined as a decrease of at least 3 points (Seror *et al.*, 2011). An ESSPRI score above 5 defines significant impact of SS associated symptoms on patients' quality of life (Cho *et al.*, 2013). Both ESSDAI and ESSPRI are found to be sensitive to change (Meiners *et al.*, 2012) ; therefore they are the most used outcome measures in SS.

Conclusions

A number of outcome measures have been validated for the assessment of rare rheumatologic diseases. The multi-systemic nature of these diseases pose a significant challenge to accurately capture the spectrum of disease activity and damage. Furthermore, the rarity of these diseases limits the power of validity and reproducibility assessments for outcome measures. As we advance our understanding of the pathogenesis of these diseases, and develop novel therapeutic targets, refinement of these outcome measures will become necessary.

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