Outcome measures of disease activity for rare autoimmune rheumatic diseases

ABSTRACT

Systemic lupus erythematosus, scleroderma, myositis and Sjögren's syndrome 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. This article reviews the commonly used outcome measures to assess this group of diseases and discusses the limitations of their use.

Over the last decade, there has been burgeoning research into the pathogenesis of systemic lupus erythematosus, scleroderma, autoimmune myopathies and Sjögren's syndrome. This has lead to changes in clinical management and the development of novel therapeutic targets. Robust measures of disease activity are required to assess patients accurately both in clinical practice and their response to potential therapies in clinical trials.

Systemic lupus erythematosus

Systemic lupus erythematosus 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 UK and American population estimates with a 6–10-fold female predominance (Somers et al, 2014).

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Several tools have been developed to assess disease activity both in clinical practice and as primary endpoints in clinical trials (*Table 1*). The primary tools used are the BILAG-2004 developed and validated by the British Isles Lupus Assessment Group (Romero-Diaz et al, 2011), SLEDAI-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 the systemic lupus erythematosus responder index (SRI and SRI-50) (Castrejón et al, 2014; Mikdashi and Nived, 2015) and the BILAG-based composite lupus assessment (BLICA) (Castrejón et al, 2014). The most commonly used patient-reported outcome score is the Lupus Quality of Life Questionnaire (Lupus-QoL) (Holloway et al, 2014).

Scleroderma

Scleroderma, also known as systemic sclerosis, is a rare autoimmune disease associated with significant morbidity and mortality. It is characterized by vascular injury and abnormal fibrotic processes that can affect multiple organ systems, including the skin, lungs, gastrointestinal tract and cardiovascular system. Outcome measures used in patients with scleroderma are listed in *Table 2*.

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 gastrointestinal 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 the gastrointestinal tract in patients with 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 6 minutes and has been successfully incorporated into trials of scleroderma-related pulmonary arterial hypertension (Badesch et al, 2000). Raynaud's phenomenon occurs in more than 90% of patients with scleroderma and

Table 1. Outcome measures in systemic lupus erythematosus

Disease activity scores	British Isles Lupus Assessment Group Index (BILAG-2004) (Romero-Diaz et al, 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 (SLEDAI-2K) (Gladman et al, 2003)	■ Global index of disease activity in systemic lupus erythematosus ■ 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 nine organ systems: neurological, musculoskeletal, renal, mucocutaneous, general, cardiac, respiratory, vascular and haematological 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) (Castrejón et al, 2014)	■ Combination index of SELENA-SLEDAI, BILAG and physician global assessment ■ A responder is classified as SELENA-SLEDAI 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) (Castrejón et al, 2014)	■ Combination of BILAG, physician global assessment and SLEDAI ■ Responder classified as no new BILAG A or B scores ■ Improvement of BILAG A score to B, BILAG B/C/D to BILAG C/D ■ No increase in SLEDAI from baseline ■ No worsening of physician global assessment
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 4 weeks ■ Five-point scale ranging from 'never' to 'all of the time'

SELENA = Safety of Estrogens in Lupus National Assessment

is measured using the Raynaud's phenomenon score (Merkel et al, 2002). Severe Raynaud's phenomenon can lead to digital ulcers. These are manually counted to provide a digital ulcer score. The Health Assessment Questionnaire index is a widely used patient-reported outcome score used in rheumatic diseases (Fries et al, 1980) and has been validated in scleroderma. The scleroderma Health Assessment Questionnaire is a variation of the Health Assessment Questionnaire incorporating questions specific to scleroderma disease (Steen and Medsger, 1997).

Inflammatory myopathies

The idiopathic inflammatory myopathies are characterized by autoimmune-mediated muscle inflammation and weakness. They have a worldwide prevalence of 14 in 100 000 (Meyer et al, 2015). Adult polymyositis, dermatomyositis and juvenile dermatomyositis are among the most frequent of the idiopathic inflammatory myopathies. During the past decade, collaborations such as the International Myositis Assessment and Clinical Studies Group have undertaken projects to define core measures of disease activity and damage in myositis and

> “Sjögren’s syndrome is characterized by ocular and oral dryness developed because of the autoimmune infiltrating process affecting the exocrine glands.”

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 Activity Index (MITAX), and Myositis Disease Activity Assessment visual analogue scale (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 6 months despite previous immunotherapy, rehabilitation or other therapy. The most commonly used tool to assess disease damage is the 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 general tools of global disease activity, such as physician and patient visual analogue scales, and functional assessment tools, such as the Health Activity Questionnaire and childhood myositis assessment score. They also recommend patient-reported quality of life measures such as the SF36 for adults or CHQ-PF50 for children.

Dermatomyositis

Myositis occurring with characteristic skin and nail manifestations is termed dermatomyositis. 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 dermatomyositis (Klein et al, 2008) (*Table 3*). It is a clinician-scored instrument that measures skin activity and damage (*Figures 1* and *2*). Activity is measured in three areas – erythema, scale and erosion or ulceration. Damage is measured in two areas – poikiloderma and calcinosis. In addition, Gottron’s papules, periungual changes and alopecia are also scored.

Sjögren’s sydrome

Sjögren’s syndrome 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, Sjögren’s syndrome is characterized by ocular and oral dryness developed because of the autoimmune infiltrating process affecting the exocrine glands. It may occur either alone, as primary Sjögren’s syndrome, or in association with other autoimmune disease, often rheumatoid arthritis, systemic lupus erythematosus or systemic sclerosis, in which case it is called secondary Sjögren’s syndrome. Clinical, laboratory and histological features can be used to classify the systemic manifestations of Sjögren’s syndrome as periepithelial or tissue-specific (including liver, lung and kidney) and extraepithelial (including vasculitis, peripheral neuropathy, renal involvement and myositis) (Fox et al, 1984).

Table 2. Outcome measures in scleroderma

Disease activity scores	Modified Rodnan skin score (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 of 0–3 is applied: 0 = no thickening, 1 = mild thickening, 2 = moderate thickening, 3 = severe thickening
	Pulmonary function tests	Vital capacity, forced vital capacity and diffusing capacity for carbon monoxide are important variables in the assessment of lung involvement
	6-minute walk test	Measures the distance a person can walk in 6 minutes
	Raynaud’s condition score (Merkel et al, 2002)	The Raynaud’s condition score is calculated from a summation of 1- or 2-week daily patient self-assessments of Raynaud’s activity using a 0–10 ordinal scale. The Raynaud’s condition score incorporates the cumulative daily frequency, duration, severity, and impact of Raynaud’s attacks
	Digital ulceration score	Manual count of the number of digital ulcers
Patient-reported outcomes	Health Assessment Questionnaire Disability Index (Fries et al, 1980)	The Health Assessment Questionnaire Disability Index 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 Health Assessment Questionnaire (SHAQ) (Steen and Medsger, 1997)	Includes the disability and pain scales of the Health Assessment Questionnaire plus five visual analogue scales that patients use to rate scleroderma-specific problems in the preceding week including pulmonary disease, digital ulcers, Raynaud’s phenomenon, gastrointestinal disease and skin disease

Table 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 Medical Research Council 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 polymyositis and dermatomyositis, 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 visual analogue scale (MYOACT)	Assesses severity of activity in each organ system with a 10-cm visual analogue scale and a global extra-muscular visual analogue scale
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 a 10 cm visual analogue scale to measure severity ■ The MDI can be used in both adult and juvenile polymyositis and dermatomyositis patients, although because of its comprehensive nature, it may reflect damage caused by comorbid conditions not just myositis

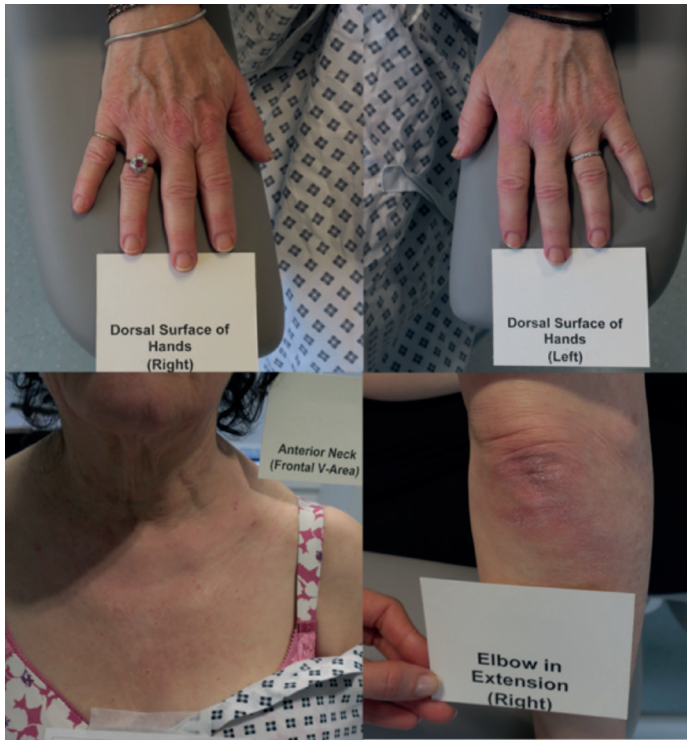

Figure 1. Patient with dermatomyositis.

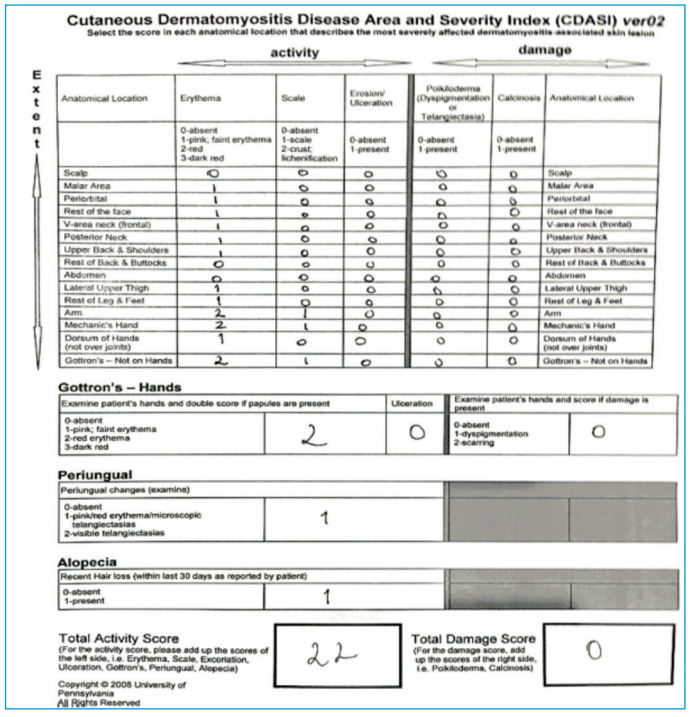

Figure 2. Example of Cutaneous Disease Area and Severity Index (CDASI) scoring of dermatomyositis rash for patient in *Figure 1*.

In the past decades, a core set of domains was defined to facilitate the complex assessment of Sjögren's syndrome 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.

Table 4. Outcome measures in Sjögren's syndrome

Disease activity scores	Sjögren's Clinical Activity Index (SCAI) (Bowman et al, 2007)	■ Originated from the British Isles Lupus Assessment Group Index (BILAG) ■ Consists of 42 questions from eight 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 primary Sjögren's syndrome ■ 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, neurological 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 patients with primary Sjögren's syndrome (Cho et al, 2013)
	PROFAD-SSI score (profile of fatigue and discomfort sicca symptoms inventory) (Bowman et al, 2009)	■ 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 primary Sjögren's syndrome outcome tool (Bowman et al, 2009) ■ Fatigue visual analogue score was found to most closely correlate with somatic fatigue ■ The somatic fatigue domain forms the PROF-S while the mental fatigue domain forms the PROF-M (derived from patient's descriptions of fatigue)

Significant efforts have been made to develop valid tools for the assessment of various clinical and laboratory manifestations of Sjögren's syndrome, 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 Sjögren's syndrome. In addition, patient questionnaires such as the Profile of Fatigue and Discomfort (PROFAD) and Sicca Symptoms Inventory (SSI) have also been developed. *Table 4* details the most used disease-specific outcome measures in Sjögren's syndrome. 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 Sjögren's syndrome-associated symptoms on the patient's quality of life (Cho et al, 2013). Both ESSDAI and ESSPRI are found to be sensitive to change (Meiners et al, 2012), so they are the most used outcome measures in Sjögren's syndrome.

Conclusions

A number of outcome measures have been validated for the assessment of rare rheumatological diseases. The multi-systemic nature of these diseases poses a significant challenge to capturing the full spectrum of disease activity and damage. Furthermore, the rarity of these diseases limits the power of validity and reproducibility assessments for their associated outcome measures. As our understanding of the pathogenesis of these diseases advances, and novel therapeutic targets are developed, refinement of these outcome measures will become necessary. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Outcome measures create a standardized assessment of disease activity, providing an accurate trend of disease activity over time.
- Outcome measures for the rare autoimmune rheumatic diseases are numerous and extensive, reflecting the complexity of these multisystemic diseases.
- As we develop our understanding of these diseases, outcome measures will be crucial in assessing response to novel therapies.