Disease-specific quality indicators, guidelines and outcome measures in scleroderma

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ABSTRACT

The assessment of the patient with systemic sclerosis remains a challenge for the clinical investigator and the clinician. The measures used to assess the impact of the disease on the quality of life and the outcome measures for both clinical practice and clinical research, including therapeutic trials, are presented and discussed, with emphasis on present limitations.

Introduction

Systemic sclerosis (SSc) is a multi-system disorder of the connective tissue characterized by vascular disease and the deposition of collagen and other matrix constituents in the skin and other target organs, *i.e.*, the gut, lung, heart, kidney, joints and muscles (1). Considerable variability is seen among SSc patients in the extent of skin and internal organ involvement, the pace of disease progression, and the long-term prognosis. These complexities, which are shared by other autoimmune systemic rheumatic diseases, present a challenge to researchers and clinicians. The assessment of SSc patients can take place in three different settings: clinical practice, clinical investigation (*i.e.*, performing cross-sectional or longitudinal studies on specific aspects of the disease), and therapeutic trials (2). In each of these settings evaluation of disease activity and severity, as well as quality of life, are required.

Disease-specific quality of life indicators

SSc is frequently a disabling disease. Moreover, because of changes in the patient's appearance due to skin sclerosis, muscle atrophy and joint contractures, it also has a substantial impact on the patient's emotional and psychological well-being. The assessment of quality of life is carried out using both generic and disease-specific instruments (3).

The HAQ-DI is a self-administered measure that was developed to evaluate the activities of daily living in arthritis (4). It assesses the patient's level of functional ability through questions regarding fine movements of the upper extremities, locomotor activities in the lower extremities, and movements of both the upper and lower limbs. It includes 8 domains, each of which is scored from 0 (no disability) to 3 (severe disability). The standard HAQ-DI represents the average of the worst scores in each of the 8 domains. Having been originally developed for arthritis, the HAQ-DI cannot be considered "specific" for SSc. Nevertheless, the demonstrated correlation between the HAQ-DI score and a number of parameters of SSc (5), the correlation between decreases in the HAQ-DI score and decreases in the skin sclerosis score (6), and its value in predicting survival (6, 7) make the HAQ-DI a useful tool in the management of SSc.

At the Second University of Naples, the HAQ-DI is currently administered to all SSc patients. An analysis carried out on 121 consecutive patients enrolled over the course of one year (8) confirmed that patients with diffuse SSc had higher HAQ-DI scores than patients with limited disease. Moreover, a significant trend toward an increase in the HAQ-DI in SSc patients with higher Medsger's severity scale values (9) was detected, underlining the greater disability in patients with more severe internal organ involvement.

Alongside the HAQ-DI, a scleroderma HAQ has been proposed. This instrument includes 5 visual analogue scales (VAS, from 0 to 100 mm), in which the patient's condition during the previous week is evaluated on the basis of digital ulcers, intestinal involvement, lung involvement, Raynaud's phenomenon, and overall disease (10). The scleroderma HAQ assesses important quality-of-life indicators and may constitute a useful tool for the assessment of SSc patients.

Competing interests: none declared.

Recently, a scleroderma functional score (FS), a self-administered 11-item functional questionnaire [scoring from 0 (normal) to 3 (impossible to achieve), with an overall score between 0 and 33], was reported to be strongly correlated with the HAQ-DI in 135 SSc patients both at baseline and after a mean follow-up of 1.8 years. This could be considered a disease-specific instrument for assessing functional status in SSc and a potentially useful tool for evaluating new treatments (11). Concerns may be raised about any questionnaire or clinical measure specific for SSc since the disease manifestations are so varied. Nevertheless, these preliminary results appear encouraging.

The role of specific organ involvement in the quality of life has been recently addressed.

In 2006 Furst and co-workers (12) began working on the development of a reliable, feasible and valid symptom-based, self-reporting questionnaire for the assessment of gastrointestinal tract (GIT) involvement in SSc and its impact on the quality of life. The SSc-GIT 1.0 was developed (13), a 52-item, self-administered instrument that includes six scales to measure different aspects of gastrointestinal involvement.

A generic instrument designed to measure the quality of life in patients with chronic diseases can also be useful in collecting information on the multifaceted burden of SSc. The SF-36 questionnaire is currently used for this purpose (14), and has been validated as an outcome measure in clinical trials on patients with diffuse SSc (15). Recently the SF-6D, a preference-based measure that assesses the desirability of living with a current health state, has also been tested in SSc (16).

Guidelines

A few years ago, on behalf of the American College of Rheumatology (ACR), White *et al*. (17) developed (using the Delphi technique) general guidelines to be followed in planning clinical trials in SSc. As well as proposing outcome measures and the estimated clinically meaningful changes for each measure, these authors emphasized the need for clinical trials to be sensitive to change. For example, patients with early (< 3 years) diffuse disease should be studied to assess the efficacy of a given drug on the whole disease process. Patients with reversible lesions (*i.e*., active ulcers rather than permanent damage) such as digital ulcers or active alveolitis should be included in studies of drugs that impact on a single organ or system. These guidelines – which also cover the issue of the rationale for using the drug under study, and criteria for the planning of a trial (number of patients to be enrolled, exclusion criteria, and statistical analyses to be performed) – have been defined and constitute a suitable basis to plan clinical trials in patients with SSc (18).

Outcome measures for clinical trials

Whole disease process

The outcome measures to be used when assessing the influence of a drug on the overall disease process must be differentiated from measures useful for investigating the efficacy of treatment on a single disease manifestation. The "gold standard" outcome measure to assess overall disease is survival and/or end-stage organ disease. Such measures, however, require a long time period or high-risk patients.

The need for surrogate measures could be met by the modified Rodnan skin score (mRss) and the HAQ-DI; both have been validated (19) and satisfy the OMERACT filter (20) with regard to feasibility, truth (including face, content, construct, and criterion validity), and discrimination (including responsiveness and reliability). The mRss is a measure of skin thickening, assessing it on a scale from 0 (normal skin) to 3 (severe thickening) in 17 body areas: the fingers, hands, forearms, arms, feet, legs, thighs, face, chest and abdomen (21). The HAQ-DI has been described above.

It is important to establish the minimal clinically relevant treatment effect for clinical trials and clinical practice, as has been addressed in two recent studies. Khanna *et al*. (22) calculated the minimally important differences in mRss and HAQ-DI by reviewing the charts of patients with diffuse SSc enrolled in the D-penicillamine study, and defining as minimally important those differences detected in patients in whom the physician had noted the occurrence of a slight improvement with respect to the previous visit. The difference ranged from 3.2 to 5.3 for mRss and from 0.10 to 0.14 for HAQ-DI. Gazi *et al*. (23) conducted a Delphi consensus exercise by asking members of the Scleroderma Clinical Trial Consortium what they judged to be the minimal clinically relevant treatment effects for a number of outcome measures: these were found to be 3 to 7.5 units for mRss and 0.2 to 0.25 units for HAQ-DI. While the range for HAQ could be considered acceptable, the range for mRss could be confusing. As a relevant treatment effect can depend on the baseline value, a decrease of 30-35% from baseline may represent a more acceptable criterion.

Single organ manifestations

A number of outcome measures have been identified for single organ involvement. In 2002 a group of scleroderma experts came together in Brisbane during the OMERACT meeting and drew up a list of outcome measures that were considered to be fully validated (19). Along with the mRss and HAQ-DI, which are outcome measures for the overall disease process, a few parameters useful in assessing the response of specific disease manifestations to drugs, such as the Raynaud Condition Score (24), were identified (Table I). The number of validated measures is actually quite low. Furthermore, forced vital capacity, which is considered to be a measure of restrictive disease, may also be decreased in obstructive diseases such as emphysema; the standard measure for restrictive disease is total lung capacity, which unfortunately is not generally investigated in SSc.

Since the Brisbane meeting, other measures have been proposed (25, 26), some of which satisfy the OMERACT filter, including the durometer measurement of skin hardness (27), 6-minute walking time for SSc-related pulmonary arterial hypertension, the diffusing lung capacity for carbon monoxide (DLCO), the SSc-GIT 1.0 already discussed above, and creatinine clearance as estimated by the Modification of Diet in Renal Disease formula (28). In their study, Gazi *et al*. (23) calculated the minimal clinically relevant difference for DLCO and reported

Table I. Fully validated measures of outcome in SSc.

System	Measure
Skin	Modified Rodnan skin score (mRss)
Cardiopulmonary	Forced vital capacity Right heart catheterization Congestive heart disease on clinical examination
Vascular	Raynaud's condition score Patient Raynaud's phenomenon activity Physician Raynaud's phenomenon activity Frequency of Raynaud's phenomenon Duration of Raynaud's phenomenon Patient's assessment of digital ulcer activity Physician's digital ulcer count
Renal	Blood pressure, creatinine
Patient/function	HAQ Disability Index

Table II. Core set items selected for 11 domains.

Skin
Modified Rodnan skin score (mRss)
Visual analog scale (VAS) or Likert scale for patient's global assessment of skin activity
VAS or Likert scale for physician's global assessment of skin activity
Durometer
Musculoskeletal
Tender joint count
Tendon friction rubs assessed by the physician
Serum creatinine phosphokinase, aldolase
Cardiac
Cardiac echocardiogram with doppler
Right heart catheterization
6-minute walk test
Borg dyspnea instrument
Pulmonary
Pulmonary function
Validated measure of dyspnea
Breathing VAS, from the Scleroderma Health Assessment Questionnaire (S-HAQ)
High resolution computer tomography (HRCT): quantifiable scale
Renal
Calculated creatinine clearance based on serum creatinine (MDRD formula)
Pre-defined renal crisis (presence or absence)
Gastrointestinal
Body mass index (BMI)
Validated gastrointestinal tract VAS scale (part of the S-HAQ) or other SSc-validated GI questionnaire
Health-related quality of life and function
Health Assessment Questionnaire-Disability Index (HAQ-DI)
VAS-pain scale from the HAQ-DI
SF-36
Global health
VAS/Likert patient's global severity assessment
VAS/Likert physician's global severity assessment
Scleroderma-related health transition according to patient
Scleroderma-related health transition according to physician
Raynaud's phenomenon
Raynaud's condition score
VAS Raynaud's (part of the S-HAQ)
Digital ulcers
Active digital tip ulcer count on the volar surface
VAS digital ulcers (part of the S-HAQ)
Biomarkers
Erythrocyte sedimentation rate and/or C-reactive protein

it to be about 10% of the predicted value, while other parameters were not considered, the scenarios being weighted toward overall disease modification.

Very recently Khanna *et al*. (29) proposed a core set of measures (developed using a Delphi exercise) for the assessment of disease activity and severity in SSc. These measures are divided into 11 domains (Table II) and should provide a suitable basis for future studies.

Predictors of outcome

Diffuse disease and clinically evident internal organ involvement have long been known to be associated with a shorter survival (30). The autoantibody profile (*i.e*., anti-Scl-70, anti- RNA polymerase titers) as well as intermediate cutaneous skin sclerosis (*i.e*., limb but not trunk involvement) predict a poorer prognosis compared to anti-centromere antibody (ACA) positivity and limited disease (*i.e*., involvement limited to the fingers and face) (31, 32). In 1999 Bryan *et al*. (33) developed a 3-item score (proteinuria, low DLCO, high ESR) that accurately predicted 5-year survival. Subsequently, Medsger *et al*. (9) proposed a scale that divided the severity of disease in nine organ systems into 5 subgroups (from 0 = absent, through 4 = end stage disease). Unfortunately, the domains were not weighted, so that the global severity score obtained by summing the single items seems debatable.

Limitations and future trends

At present, five main limitations can be identified in the disease measures for SSc:

1. A number of conclusions are based on Delphi exercises. Studies on real patients are needed.
2. Instruments to assess the evolution of the overall disease process in patients with limited disease are not available. HAQ-DI and the recently developed FS assess change in limited disease, but often at a very slow speed. Studies devoted to this topic should be encouraged.
3. Biological markers reflecting the activation of cell types involved in the pathogenesis of the disease are not considered. Feasible markers should be selected and tested on real patients.
4. A universally accepted disease activity index does not yet exist (34). Studies of the European activity index are

encouraging and its construct validity has been demonstrated (35, 36). A recent analysis of the charts of 77 patients from the original cohort has shown its sensitivity to change (37). Moreover, in the cross-sectional study of Cuomo *et al*. (8), the index was significantly correlated with the HAQ-DI; in uncontrolled trials (38-40) changes in the EScSG score not only paralleled changes in the mRss (which is included in the index), but also the HAQ-DI, which is an independent parameter. However, this does not constitute a formal validation that satisfies the OMERACT filter.

5. A weighted severity scale is warranted in order to improve the ability of the clinician to predict survival.

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