Scleroderma — Developing Measures of Response

DANIEL E. FURST, DINESH KHANNA, MARCO MATTUCCI-CERINIC, ALAN J. SILMAN, PETER A. MERKEL, and IVAN FOELDVARI

ABSTRACT. The scleroderma research community continued its focus on the development and proper validation of the outcome measures for clinical trials in scleroderma during the special interest group meeting at OMERACT 7. Deliberations focused on progress in the assessment of gastrointestinal disease, renal physiology, vascular damage, and the unique challenges inherent in studying pediatric patients with scleroderma. (J Rheumatol 2005;32:2477–80)

Key Indexing Terms:
SCLERODERMA RESPONSE MEASURES SKIN
RENAL PULMONARY PEDIATRIC SCLERODERMA

Introduction

The scleroderma research community continued its focus on the development and proper validation of the outcome measures for clinical trials in scleroderma during the special interest group meeting at OMERACT 7.

This is an exciting and productive time for the field of outcome measures in scleroderma: there is widespread support and cooperation among members of the international scleroderma research community and heightened interest in scleroderma research secondary to developing medications to treat this illness. This community has forged relationships to provide for collaborative work and consensus approval of new measures. In 2003, an international meeting of scleroderma researchers in Ancona, Italy, studied the area of outcome tools for clinical care and developed ideas in conjunction with the OMERACT agenda[1,2]. The Scleroderma Clinical Trials Consortium, an international umbrella group of scleroderma trial centers, has both endorsed the OMERACT agenda and supported its work with research grants on outcome measure development. A project to build a clinical trial data repository is being considered. Both traditional pharmaceutical companies and biotechnology firms have evinced interest in several aspects of scleroderma and are investing resources into clinical trials in this disease. Industry has an immediate need and interest in well validated assessment measures in scleroderma. Both industry and the research community are eager to ensure that regulatory agencies accept any new outcome measures, or modifications of older approaches, as valid tools for seeking approval for new therapeutic agents to treat systemic sclerosis (SSc).

The special interest group on scleroderma at OMERACT 7 was focused not on areas that already had high levels of research activity such as adult skin assessment, pulmonary disease, or Raynaud's phenomenon, but on bringing attention to some areas of outcome measure development for which new data and initiatives have emerged in the last 2 years or are now emerging. Specifically, OMERACT 7 deliberations focused on progress in the assessment of gastrointestinal (GI) disease, renal physiology, vascular damage, and the unique challenges inherent in studying pediatric patients with scleroderma.

Development of a Health-related Quality of Life Instrument in Scleroderma Patients with Gastrointestinal Involvement

Involvement of the GI tract and SSc is extremely frequent: GI involvement is the leading cause of morbidity and the third most common cause of mortality in SSc[4,5]. Progression of GI involvement is likely to be associated with worsening of GI symptoms and a decrement in other aspects of health-related quality of life (HRQOL). However, there is no GI tract-targeted HRQOL instrument to capture the symptoms

From the University of California at Los Angeles, Los Angeles, CA; University of Cincinnati, Cincinnati, OH, USA; University of Florence, Florence, Italy; University of Manchester, Manchester, UK; Boston University School of Medicine, Boston, MA, USA; and the Pediatric Rheumatology Clinic at AK Eilbek, Hamburg, Germany.

Dr. Khanna is supported by a Physician Scientist Development Award (Arthritis and Scleroderma Foundations). Dr. Merkel is supported by a Mid-Career Development Award in Clinical Investigation (NIH-NIAMS: K24 AR02224).

D.E. Furst, MD, Professor of Rheumatology, University of California at Los Angeles; D. Khanna, MD, MSc, Assistant Professor of Medicine, University of California at Los Angeles, and University of Cincinnati; M. Mattucci-Cerinic, MD, PhD, Professor of Rheumatology and Medicine, University of Florence; A.J. Silman, MD, MSc, Professor of Rheumatic Disease Epidemiology, University of Manchester; P.A. Merkel, MD, MPH, Associate Professor of Medicine, Boston University School of Medicine; I. Foeldvari, MD, Senior Consultant, Pediatric Rheumatology Clinic at Ielbek.

Address reprint requests to Dr. D.E. Furst, UCLA School of Medicine, 1000 Veteran Ave, Rm 32-59, Los Angeles, CA 90025.
E-mail: defurst@mednet.ucla.edu

in SSc, although there are GI tract-related instruments of this sort developed for other diseases[6-8].

A reliable, feasible, and valid symptom-based, self-reported questionnaire is needed to assess activity and severity of GI tract symptoms in SSc and to document the effects of GI tract involvement on HRQOL. After an extensive literature search, an expert panel of rheumatologists, gastroenterologists, and psychometricians were asked to give their opinion on the domains or the areas of interest from the patient's and physician's perspectives. A 74-item, self-reported measure was designed to determine 3 main areas: (1) bowel involvement; (2) emotional function; and (3) social function. Thereafter, 2 focus groups of subjects with SSc were conducted at the University of California at Los Angeles. The goals of the focus groups were to refine the questionnaire, to explore other domains that participants felt might have been missed, and to reduce item redundancy. The 16 patients with SSc were all women and 69% had equal to or less than a high school degree. Their ages ranged between 35 and 74 years, and 69% were Caucasian. Face and content validity have been shown, but the questionnaire needs to be field tested to assess feasibility, criterion validity, and response to change as per the OMERACT filter[1]. Between 100 and 200 SSc patients will complete the GI-SSc questionnaire, the scleroderma health assessment questionnaire, the Medical Outcome Study Short Form-36 Survey, and patient global assessment. In addition, demographic variables and laboratory data will be collected. The test/retest reliability of the questionnaire will be assessed by administering the questionnaire to a subset of patients twice, with one week intervening. It is anticipated that this questionnaire will be fully validated prior to OMERACT 8.

Tools to Measure Renal Involvement in Scleroderma

In SSc, scleroderma renal crisis is the most important renal complication and is well characterized. Chronic renal involvement in SSc is much less well characterized, however, and its existence is sometimes doubted. In a longterm study, glomerular filtration rate (GFR) was reduced significantly after 5 years among 23 SSc patients with no intervening scleroderma renal crisis and whose renal function at diagnosis was normal; however, it is not clear if confounding medications or illnesses were present. Work is under way in the area of chronic renal disease.

Glomerular Filtration Rate

While accurate and reliable, inulin, iothalamate, EDTA (ethylenediamino tetraacetate), and DTPA (diethylenetriamino pentaacetate) clearances are expensive and often not feasible. Serum creatinine is an endogenous substance that is easily measured but that may underestimate a functional defect, so measures of creatinine clearance are often preferred. However, as urine collections are frequently inaccurate, calculations of creatinine clearance based on the serum creatinine and a combination of other factors such as age, weight, sex, ethnicity, serum albumin, etc., have been developed[9].

The Cockcroft Gault equation [creatinine clearance = 1.2 × (140 – age) × weight in kg (× 0.85 if female)/serum creatinine] or the GFR according to the Modification of Diet in Renal Disease[10] has frequently been used to measure GFR [GFR = 170 × serum creatinine – 0.999 × age – 0.176 × urea × albumin × 0.318 (× 0.76 if female; × 1.18 if African-American]. Both formulae correlate well with the GFR as measured by other methods, although both may overestimate the GFR.

Blood Pressure Measurements

Hypertension, per se, is a nonspecific sign associated with renal disease but may be considered as a potential outcome measure. It has significant variability and multiple measurements are needed to define a given blood pressure level[11].

Proteinuria

Proteinuria is a predictor of mortality and is related to renal function damage as well as lung involvement in SSc patients. Proteinuria was found in up to 33% of SSc patients in one study, of whom 13% had hypertension[12]. Like hypertension, proteinuria may be confounded by coexisting illnesses and/or medications and is therefore not specific. Its relevance as a measure of SSc-specific renal disease needs further examination.

The State-of-the-art Regarding Scoring of Digital Ulcers

Digital ulcers are an important vascular outcome in scleroderma clinical trials, and interventions are frequently aimed at reducing the incidence of new ulcers and/or promoting healing of existing lesions. There are several etiological factors linked to ulcer development in scleroderma, including occlusive arterial disease, severity of Raynaud's phenomenon, trauma to already diseased skin, infection, and calcinosis.

There are a number of issues that remain to be resolved in assessing ulcer severity in scleroderma.

1. Determining the presence or absence of an ulcer is subjective, and the reliability of their ascertainment both within and between observers has yet to be tested.
2. Although ulcers typically occur in the pulp of the finger, the occurrence of ulcers in other peripheral sites in the hand (e.g., the dorsum of the fingers) may be important to assess.
3. The severity of ulcers in terms of depth and stage of healing are normally documented based on subjective opinion, which is subject to considerable variability and error. Finally, the relative contribution of the different pathological processes listed above cannot be easily distinguished in a given patient. Such distinctions may be important since they may influence response to therapy.

Several options are being studied with the goal of developing a digital ulcer scoring system that satisfies the

OMERACT filter. One option under discussion from a UK group is the development, based on expert clinical opinion, of an atlas providing pictures of definite scleroderma ulcers as well as lesions, which should not be scored as ulcers. If such an atlas displayed a wide enough range of digital ulcers, it could satisfy both face validity and content criterion of the OMERACT filter. It would also be developed to provide a severity grading system, thus potentially allowing testing of sensitivity to change. The reliability of this atlas would need to be tested both within and between observers using either real patients or photographs. Barriers to the feasibility and practicality of this atlas include the difficulty of obtaining sufficient high-quality photographs and judging ulcer size and depth using such an atlas. An alternative approach might be to grade ulcers clinically and photograph them so that the stored digital images could be scored subsequently in a standardized manner by one or more trained observers. These and other alternatives were discussed and will be considered for further testing.

Skin Scoring Among Pediatric Patients with SSc

The Modified Rodnan Skin Score (mRSS) for skin thickness has been a primary outcome measure in many of the therapeutic trials in adult SSc and is a core assessment technique for most international descriptive investigations in SSc[13]. This skin score is validated in the adult population with face, content, criterion, discrimination, construct validity, and feasibility[2].

The mRSS has never been evaluated prospectively in the pediatric population. Because children are not "small adults" and childhood skin changes occur with growth, the mRSS (17 skin sites, each scored by integers 0–3) was evaluated in 217 healthy children, including 100 girls. The children's ages ranged from 2.9 to 16 years. The mean mRSS was 13.9, with a range between 4 and 25; no single area score was > 2. There was a linear correlation between mean body mass index (BMI) and mRSS through the age of 12, and the mRSS showed a correlation with Tanner stages (ratings for signs of sexual maturation). The mRSS scores in healthy children extended well into the "abnormal" range for adult patients with SSc, as the mean mRSS in healthy adults is 0. For example, in the cohort of Sato, *et al*[14] the mean mRSS score was 6.4 (standard deviation 8.3) among patients with limited SSc and 19.1 (standard deviation 8.1) among those with diffuse SSc[14]. Thus, even the face validity of the mRSS in children requires further consideration. If a modification of the mRSS is to be used in the pediatric population, the whole range of validation criteria will need to be considered, as will compensation for body mass index and stages of growth.

Further Considerations and the Way Forward

In an informal continuation of the special interest group meeting for SSc, the following plans were laid for the next 2 years, in preparation for OMERACT 8:

1. The validation of the GI SSc HRQOL instruments will be completed, an attempt will be made to discern the minimally clinically important difference using this questionnaire, and work will begin to ascertain the relationship between the GI SSc questionnaire and other GI measurements (e.g., endoscopy, radiologic techniques).
2. Validation of tools to measure renal function in SSc will be completed (not including definition and measurement of scleroderma renal crisis, which was not deemed necessary to develop further). It was further agreed that examination of the frequency and definition of chronic renal failure in SSc was necessary.
3. Careful consideration of methods to measure vascular change, and both the occurrence and healing of digital ulcerations will require significant time, and perhaps the development of additional approaches.
4. The development of a skin score for pediatric SSc patients remains an important and high priority issue and one deserving collaborative and concentrated attention.

It was also decided that work from OMERACT 7 could be completed in time for OMERACT 8. Specifically:

1. Skin scoring in adults, previously validated for the mRSS, will continue to be tested using additional skin scoring systems.
2. Pulmonary function measures in SSc, already validated in outline, will be further tested and developed, including functional measures such as the 6 minute walking distance, imaging techniques such as the high-resolution computerized tomographic scan, and histological/immunological based approaches, such as bronchoalveolar lavage, etc.
3. An overarching goal that must remain: validation of a composite measure of response, analogous to the American College of Rheumatology 20% response criteria or Disease Activity Score 28, to encompass multiple organ systems and reflect response of the whole patient to therapeutic interventions.

REFERENCES

1. Boers M, Brooks P, Strand CV, Tugwell P. The OMERACT filter for Outcome Measures in Rheumatology. J Rheumatol 1998;25:198-9.
2. Merkel PA, Clements PJ, Reveille JD, Suarez-Almazor ME, Valentini G, Furst DE. Current status of outcome measure development for clinical trials in systemic sclerosis. Report from OMERACT 6. J Rheumatol 2003;30:1630-47.
3. Bombardieri S, Medsger TA Jr, Silman AJ, Valentini G. The assessment of the patient with systemic sclerosis. Clin Exp Rheumatol 2003;21 Suppl 29:S2-4.
4. Clements PJ. Systemic sclerosis (scleroderma) and related disorders: clinical aspects. Baillieres Best Pract Res Clin Rheumatol 2000;14:1-16.
5. Sjogren RW. Gastrointestinal features of scleroderma. Curr Opin Rheumatol 1996;8:569-75.
6. Guyatt G, Mitchell A, Irvine EJ, et al. A new measure of health status for clinical trials in inflammatory bowel disease. Gastroenterology 1989;96:804-10.
7. Manterola C, Munoz S, Grande L, Bustos L. Initial validation of a

questionnaire for detecting gastroesophageal reflux disease in epidemiological settings. J Clin Epidemiol 2002;55:1041-5.
8. Groll D, Vanner SJ, Depew WT, et al. The IBS-36: a new quality of life measure for irritable bowel syndrome. Am J Gastroenterol 2002;97:962-71.
9. Kingdon EJ, Knight CJ, Dustan K, et al. Calculated glomerular filtration rate is a useful screening to identify scleroderma patients with renal impairment. Rheumatology Oxford 2003;42:26-33
10. Hallan S, Asberg A, Lindberg M, Johnsen H. Validation of the Modification of Diet in Renal Disease formula for estimating GFR with special emphasis on calibration of the serum creatinine assay. Am J Kidney Dis 2004;44:939; author reply 939-40.
11. Livi R, Pignone A, Miniati I, Matucci-Cerinic M. Renal involvement in systemic sclerosis. Long term follow up of scleroderma patients: Evidence for modification of blood pressure and glomerular filtration rate (submitted).
12. Furst DE, Clements PJ, Wong WK, et al. Effects of the American College of Rheumatology systemic sclerosis trial guidelines on the nature of systemic sclerosis patients entering a clinical trial. Rheumatology Oxford 2001;40:615-22.
13. Akesson A, Fiori G, Krieg T, et al. Assessment of skin, joint, tendon and muscle involvement. Clin Exp Rheumatol 2003;21 Suppl 29:S5-S8.
14. Sato S, Hasegawa M, Takehara K. Serum levels of interleukin-6 and interleukin-10 correlate with total skin thickness score in patients with systemic sclerosis. J Dermatol Sci 2001;27:140-6.