Functional impairment of systemic scleroderma patients with digital ulcerations: results from the DUO Registry

L. Guillevin[1], E. Hunsche[2], C.P. Denton[3], T. Krieg[4], B. Schwierin[2], D. Rosenberg[2]
M. Matucci-Cerinic[5], for the DUO Registry Group

[1]Department of Internal Medicine, Centre de Référence pour les Vascularites Nécrosantes et la Sclérodermie Systémique, Hôpital Cochin, Assistance Publique-Hôpitaux de Paris, Université Paris Descartes, Sorbonne Paris Cité, France; [2]Actelion Pharmaceuticals Ltd., Allschwil, Switzerland; [3]Centre for Rheumatology and Connective Tissue Diseases, Royal Free Hospital, London, UK; [4]Department of Dermatology, University of Köln, Köln, Germany; [5]Department of Rheumatology AVC, Department of Biomedicine, Division of Rheumatology AOUC, Department of Medicine, Denothe Centre, University of Florence, Florence, Italy.

Loïc Guillevin, MD
Elke Hunsche, PhD
Christopher P. Denton, PhD, FRCP
Thomas Krieg, MD
Barbara Schwierin, PhD
Daniel Rosenberg, PhD
Marco Matucci-Cerinic, MD

Please address correspondence to:
Loïc Guillevin, MD,
Hôpital Cochin,
27 rue du Faubourg Saint-Jacques,
75014 Paris, France.
E-mail: loic.guillevin@cch.aphp.fr

Received on May 31, 2013; accepted in revised form on June 20, 2013.

Clin Exp Rheumatol 2013; 31 (Suppl. 76): S71-S80.

Key words: scleroderma, systemic, skin ulcer, burden of illness, absenteeism, activities of daily living, self-report

Funding: see Acknowledgements, p. S-77.

Competing interests: L. Guillevin, C.P. Denton, and M. Matucci-Cerinic have received consultancy and speaker fees from Actelion. T. Krieg has received consultancy and speaker fees and research grants from Actelion. E. Hunsche, D. Rosenberg and B. Schwierin are employees of Actelion and own stock and options in Actelion.

ABSTRACT

Objective. *Digital ulcers (DUs) are frequent manifestations of systemic scleroderma (SSc). This study assessed functional limitations due to DUs among patients enrolled in the Digital Ulcer Outcome (DUO) Registry, an international, multicentre, observational registry of SSc patients with DU disease.*

Methods. *Patients completed at enrolment a DU-specific functional assessment questionnaire with a 1-month recall period, measuring impairment in work and daily activities, and hours of help needed from others. Physician-reported clinical parameters were used to describe the population. For patients who completed at least part of the questionnaire, descriptive analyses were performed for overall results, and stratified by number of DUs at enrolment.*

Results. *This study included 2327 patients who completed at least part of the questionnaire. For patients with 0, 1–2, and ≥3 DUs at enrolment, mean overall work impairment during the prior month among employed/self-employed patients was 28%, 42%, and 48%, respectively. Across all included patients, ability to perform daily activities was impaired on average by 35%, 54%, and 63%, respectively. Patients required a mean of 2.0, 8.7, and 8.8 hours of paid help and 17.0, 35.9, and 63.7 hours of unpaid help, respectively, due to DUs in the prior month. Patients with DUs had more complications and medication use than patients with no DUs.*

Conclusion. *With increasing number of DUs, SSc patients reported more impairment in work and daily activities and required more support from others.*

Introduction

Systemic scleroderma (SSc) is a rare multisystem autoimmune disorder with an estimated prevalence of approximately 2 per 10,000 adults (1, 2). SSc is commonly classified into two major subtypes on the basis of clinical features: diffuse cutaneous SSc is characterised by rapidly progressive fibrosis of the skin and internal organs, whereas limited cutaneous SSc is typified by vascular manifestations, with limited skin and organ fibrosis (1). Digital ulcers (DUs) on the fingertips, finger creases, or extensor surfaces of joints are a frequent complication in both SSc subsets (3). DUs occur in 36%–58% of SSc patients over the disease course (3-5); they are a major factor of morbidity by leading to infection, gangrene, and need for amputation or sympathectomy (4, 6).

Although few studies have investigated the effect of SSc-related DUs on patient disability, available evidence shows that DUs contribute to limiting hand function and the ability to perform housekeeping tasks, work, and have a normal personal and professional life (7-11). Prior studies have assessed the association between DUs and work or daily activities in patients with DUs compared with patients with no DUs (7-9), or among patients with different degrees of DU disease severity (10, 11), but no studies were multi-country, of large sample size, nor distinguished between patients with no DUs, a few DUs and patients with many DUs on their hands.

In this analysis from the multinational, European DUO Registry, SSc patients are categorised in three groups of DU severity, as measured by number of DUs at enrolment: patients with no DU (0 DU), those with a few (1–2) DUs, and those with many (≥3) DUs at enrolment. In order to assess the association between number of DUs and patients' ability to function in normal daily life, patients are described in terms of their self-reported ability to work, to perform daily activities and their need

for paid and unpaid help – all related to the last month prior to enrolment. In addition, clinical characteristics at enrolment are reported.

Materials and methods

Design and patients

The Digital Ulcer Outcome (DUO) Registry is a multicentre, prospective, observational cohort study of patients in Europe with a history of DU associated with SSc. The DUO Registry, sponsored by Actelion Pharmaceuticals Ltd., is a post-approval commitment for bosentan to the European Medicines Agency (EMA) and was started in April 2008. Actelion and an independent Scientific Committee of SSc experts were responsible for designing the DUO Registry protocol, Case Report Form (CRF), and analysis plan. Data collection and statistical analyses were performed by Actelion. The Scientific Committee was included in the review of the data. Actelion and the Scientific Committee were jointly involved in the decision to publish these analyses.

Eligible patients are those presenting with SSc and a history of DU disease in the past and/or DUs at time of enrolment into the registry, regardless of treatment. The DUO Registry collects data on DU disease history, severity at enrolment, and disease course, irrespective of treatment regimen (Actelion trial ID: AC-052-514) (12). The DUO Registry protocol defines DU as a denuded area with defined border and loss of epithelialisation, loss of epidermis and dermis, excluding fissures, paronychia, extrusion of calcium, or ulcers over the metacarpo-phalangeal joints.

The goal of the present analysis from the DUO Registry was to describe the association between the number of DUs and work, daily activities, and help needed in patients with SSc. Patients who were enrolled up to 19 November 2011 and completed at least part of the functional assessment questionnaire at their enrolment visit were considered for this analysis. Patients were recruited from Austria, the Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, the Netherlands, Norway, Portugal, Slovakia, Slovenia, Spain, Sweden, Switzerland, and the UK. The registry protocol, the patient informed consent form, and other relevant information were submitted to the health authorities, data protection agencies, and the relevant independent ethics committees, according to national requirements and in compliance with local laws (12). Ethical approval was granted by the institutional ethics committees of participating centres when applicable or required. At participating centres, all SSc patients with DU who had given written consent were enrolled.

Data collection

In the DUO Registry, patients undergo clinical assessments and receive standard medical care as determined by their physicians, with no protocol-driven visits or tests. All components of the CRF, including patients' socio-demographic and clinical features as well as data from patient-completed functional assessment questionnaires, are recorded in a Web-based electronic data capture system.

At the enrolment visit, the following data are collected by the investigator: demographic characteristics (including patient age, gender, body weight, and height), SSc disease classification, dates of first Raynaud and non-Raynaud manifestations and DU, presence or absence and type (if present) of internal organ SSc manifestations, number of DUs, DU complications, and medications.

Functional assessment

At the enrolment visit, patients are asked to complete a functional assessment questionnaire that was specifically designed for the DUO Registry based on the existing, validated Work Productivity and Activity Impairment Questionnaire (WPAI) (13). The WPAI was adapted together with the Scientific Committee and amended (including questions on help needed) taking into account design features of the DUO Registry. The questionnaire was translated into the various languages used in the participating countries. Patients are not compensated for completing the questionnaire. The questionnaire solicits patient-reported evaluations of the extent to which problems associated with ulcers of the fingers (*i.e.* DU-associated problems) affected their ability to work and perform regular daily activities, and their need for help from others. Work impairment is determined based on employment status, work days or hours missed, normal working hours per week, and productivity impairment while working. Patients score their productivity impairment using a scale from 0 (DU-associated problems had no effect on work) to 10 (DU-associated problems completely prevented work). Impairment of daily activities other than work is also scored from 0 (DU-associated problems had no effect on daily activities) to 10 (DU-associated problems completely prevented doing daily activities). The need for help is quantified as days or hours of paid and unpaid help needed. For all functional assessment questions, the recall period is the month prior to enrolment. To analyse responses to the questions on productivity and daily activity impairment, scores on the scales from 0 to 10 were transformed to impairment percentages. Work time missed was expressed as the percentage of actual hours missed during the past month out of the expected number of hours normally worked during the past month. Overall work impairment (expressed as a percentage) was calculated as the sum of work time missed and lost productivity at work (*i.e.* work time attended multiplied by the work impairment percentage).

Statistical analysis

Data were summarised by counts and percentages, means and 95% confidence intervals. Patients were categorised according to number of DUs on fingers at the enrolment visit: either 0 DU, 1–2 DUs, or ≥3 DUs. To avoid the risk of spurious results among the large number of comparisons, p values were not calculated for between-category comparisons (14). In order to quantify the precision of estimated levels of impairment, 95% confidence intervals were calculated.

Missing values were not imputed except if "work hours missed" was not reported but "productivity impairment

Table I. Demographic and disease characteristics by number of digital ulcers.

	0 DU (n=747)	1–2 DUs (n=981)	≥3 DUs (n=592)	All* (n=2327)
Female, n/N† (%)	620/747 (83)	831/980 (85)	496/592 (84)	1954/2326 (84)
Age at enrolment visit, years				
N†	747	979	592	2325
Mean (95% CI)	55.8 (54.8, 56.8)	54.5 (53.6, 55.4)	52.8 (51.7, 54.0)	54.5 (53.9, 55.1)
Age at first DU, years				
N†	545	812	485	1846
Mean (95% CI)	48.0 (46.8, 49.3)	47.1 (46.1, 48.1)	43.8 (42.4, 45.1)	46.5 (45.8, 47.2)
Age at first Raynaud's phenomenon (years)				
N†	650	882	533	2070
Mean (95% CI)	41.1 (40.0, 42.3)	39.2 (38.2, 40.2)	37.6 (36.3, 38.8)	39.4 (38.7, 40.1)
Body Mass Index (kg/m^2)				
N†	618	825	514	1963
Mean (95% CI)	24.6 (24.0, 25.3)	24.0 (23.0, 24.9)	23.5 (22.8, 24.2)	24.1 (23.6, 24.5)
Raynaud's phenomenon, n/N† (%)	728/729 (100)	968/970 (100)	577/583 (99)	2279/2288 (100)
Non-Raynaud CTD manifestation, n/N† (%)	700/711 (99)	950/959 (99)	567/579 (98)	2223/2256 (99)
Disease classification, n/N† (%)				
Diffuse SSc	254/738 (34)	367/974 (38)	289/586 (49)	914/2304 (40)
Limited SSc	382/738 (52)	523/974 (54)	242/586 (41)	1148/2304 (50)
Overlap/mixed CTD	66/738 (9)	64/974 (7)	41/586 (7)	171/2304 (7)
Other specified‡	36/738 (5)	14/974 (1)	11/586 (2)	62/2304 (3)
Other not specified	–	6/974 (1)	3/586 (1)	9/2304 (0)
Internal organ SSc disease, n/N† (%)§				
Lung fibrosis	281/747 (38)	418/981 (43)	313/592 (53)	1015/2327 (44)
PAH	135/747 (18)	139/981 (14)	103/592 (17)	377/2327 (16)
Kidney	43/747 (6)	36/981 (4)	33/592 (6)	112/2327 (5)
Gastrointestinal tract	401/747 (54)	542/981 (55)	343/592 (58)	1288/2327 (55)
Heart	81/747 (11)	98/981 (10)	85/592 (14)	264/2327 (11)
Not specified‖	3/747 (0)	7/981 (1)	–	10/2327 (0)

*Includes 7 patients with missing information on number of DUs; †Number of patients with data on characteristic/manifestation/classification; ‡SSc, systemic lupus erythematosus, undifferentiated connective tissue disease, pre-scleroderma, antiphospholipid syndrome, Buerger's disease, dermatomyositis, gangrene and necrosis of the feet, Jo-1 syndrome, or Sicca syndrome; §Patients can appear in multiple categories; percentages will not sum to 100%; ‖Question on internal organ SSc disease manifestations was answered "Yes", but no organ was selected; CI: confidence interval; CTD: connective tissue disease; DU: digital ulcer; PAH: pulmonary arterial hypertension; SSc: systemic scleroderma.

due to DU was reported, then "work hours missed" was imputed to be 0. If hours of paid or unpaid help were not reported but the question whether the patient needed help was answered, missing hours of either paid or unpaid help were imputed to be 0.

To exclude outlying values that could yield unrealistic results, the maximum possible number of monthly work hours and monthly work hours missed was fixed at 42 per week multiplied by 4.3, based on the longest legal working week in any European country in the DUO Registry. Analyses were performed using SAS® version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

As of the data extraction taken on 19 November 2011, 3383 patients were enrolled in the DUO Registry. Of these, 2327 (69%) patients from 286 centres in 18 European countries completed at least one part of the functional assessment questionnaire at the time of enrolment and were included in this analysis set. Five countries accounted for more than 80% of patients: France, Germany, Italy, Spain, and the UK.

Patient socio-demographic and clinical characteristics

The majority of patients (84%) were female, and the mean DU disease duration (as measured by time from first DU to enrolment visit) was approximately 8 years (Table I). Compared with questionnaire completers, patients who did not complete any part of the functional assessment questionnaire had similar socio-demographics (data not shown).

When patient characteristics were stratified by the number of DUs at enrolment, patients with more DUs had an earlier start of disease symptoms (as reflected by age at onset of first Raynaud's phenomenon and age at first DU), and were younger at enrolment (Table I). Patients with ≥3 DUs had a higher proportion of diffuse SSc and a higher prevalence of lung fibrosis, when compared with those who had no DUs (Table I).

As expected, DU complications were reported more frequently in patients with DUs than among those with no DUs (Table II). Compared with patients with no DUs, a higher proportion of those with DUs were using analgesics and anti-inflammatory agents, systemic antibiotics, endothelin receptor antagonists, calcium channel blockers, prostacyclines, and topical DU treatments (Table II).

Functional assessment

Association between number of DUs and work impairment

Of the 784 (34%) respondents who were employed/self-employed, 576 (73%) completed the work-related

Table II. Complications on fingers associated with digital ulcers and medication use at enrolment.

	0 DU (n=747)	1–2 DUs (n=981)	≥3 DUs (n=592)	All* (n=2327)
Complications, n/N† (%)				
At least one	46/740 (6)	316/976 (32)	211/587 (36)	574/2307 (25)
Critical digital ischemia‡	27/488 (6)	145/619 (23)	116/338 (34)	289/1449 (20)
Gangrene	4/740 (1)	91/973 (9)	68/582 (12)	163/2299 (7)
Autoamputation	3/734 (0)	28/965 (3)	31/576 (5)	62/2279 (3)
Soft tissue infection requiring systemic antibiotics	16/740 (2)	157/968 (16)	99/580 (17)	272/2292 (12)
Osteomyelitis	3/737 (0)	12/971 (1)	15/582 (3)	30/2294 (1)
Medication use, n/N (%)				
Analgesics and anti-inflammatories	347/747 (47)	567/981 (58)	366/592 (62)	1283/2327 (55)
Immunosuppressants	248/747 (33)	292/981 (30)	213/592 (36)	754/2327 (32)
Systemic antibiotics	33/747 (4)	207/981 (21)	133/592 (23)	374/2327 (16)
Endothelin receptor antagonists	344/747 (46)	452/981 (46)	326/592 (55)	1125/2327 (48)
Calcium channel blockers	297/747 (40)	471/981 (48)	277/592 (47)	1049/2327 (45)
Prostacyclines	233/747 (31)	457/981 (47)	277/592 (47)	968/2327 (42)
Phosphodiesterase-5 inhibitors	45/747 (6)	53/981 (5)	31/592 (5)	129/2327 (6)
Topical DU treatments	54/747 (7)	325/981 (33)	195/592 (33)	577/2327 (25)

*Includes 7 patients with missing information on number of DUs; †Number of patients with data on complication; ‡Defined in the CRF as follows: "This is not a Raynaud's phenomenon. It is a prolonged severe persistent reduction in digital tissue perfusion without re-warming"; DU, digital ulcer.

Table III. Work status and impairment due to digital ulcers in the prior month.

	0 DU (n=747)	1–2 DUs (n=981)	≥3 DUs (n=592)	All* (n=2327)
Employed/self-employed, n (%)	247 (33)	336 (34)	198 (33)	784 (34)
Patients completing work part of questionnaire, n†	195	239	140	576
Normal working hours per week, mean (95% CI)	32.1 (30.7, 33.4)	30.2 (28.9, 31.5)	30.9 (29.2, 32.6)	31.0 (30.2, 31.8)
Work hours missed due to DUs, during prior month, mean (95% CI)	2.8 (1.5, 4.0)	4.7 (3.5, 5.9)	5 (3.3, 6.7)	4.1 (3.4, 4.9)
Work time missed due to DUs, % (95% CI)‡	3.0 (1.4, 4.6)	4.4 (3.0, 5.9)	5.4 (3.2, 7.6)	4.3 (3.3, 5.2)
Impairment due to DUs while working, % (95% CI)§	26.5 (22.5, 30.5)	39.9 (36.2, 43.7)	45.4 (40.5, 50.3)	36.7 (34.2, 39.2)

*Includes 7 patients with missing information on number of DUs; †Number of employed/self-employed patients who gave information about working hours missed, normal working hours, and productivity impairment; ‡100×[Hours missed during month]÷[4.3×Normal working hours per week]; §Converted from original scale: 0–10; CI: confidence interval; DU, digital ulcer.

section of the questionnaire. When patients were stratified by number of DUs at enrolment, the percentage of employed/self-employed patients, and average weekly working hours for employed/self-employed patients, were both similar (Table III). The number of work hours missed due to DUs and productivity impairment due to DUs while working, both related to the past month, increased with number of DUs (1–2 and ≥3 *vs*. 0). Considering work time missed and productivity impairment, the mean overall work impairment due to DUs in the prior month was 38% among the 576 employed/self-employed patients who completed the work section of the questionnaire (Fig. 1). Mean overall work impairment due to DUs increased with number of DUs, from 27.8% in patients with 0 DUs to 41.7% in those with 1–2 DUs and to 47.5% in those with ≥3 DUs.

Association between number of DUs and daily activity impairment

Responses to the daily activity question revealed that DUs had a considerable impact during the prior month. On average, the 2179 patients who completed the daily activity section of the questionnaire reported that DUs had impaired their ability to perform their regular daily activities by 50% (Fig. 2). Mean daily activity impairment worsened with number of DUs, from 34.5% in patients with 0 DUs to 53.7% in those with 1–2 DUs and to 62.7% in those with ≥3 DUs.

Association between number of DUs and need for help

DUs were responsible for patients needing help from others. The 2226 patients who completed the help due to DU disease section of the questionnaire reported they required 6.6 (95% CI = 5.2, 7.9) mean hours of paid help and 36.7 (95% CI = 32.9, 40.5) mean hours of unpaid help in the prior month (Fig. 3). Mean hours of paid help needed increased with the number of DUs, from 2.0 hours in patients with 0 DUs to 8.7 hours in those with 1–2 DUs and to 8.8 hours in those with ≥3 DUs. Mean hours of unpaid help also increased with the number of DUs, from 17.0 hours in patients with 0 DUs to 35.9 hours in those with 1–2 DUs and to 63.7 hours in those with ≥3 DUs.

Discussion

The present results are based on assessments from the DUO Registry, the largest DU-specific registry currently available (15). These analyses comprised 2327 patients from 18 European countries. Previous studies that evaluated the impact of DUs in SSc patients in clinical practice included fewer patients, and each study was conducted in a single country (5-7, 10, 11, 16-19).

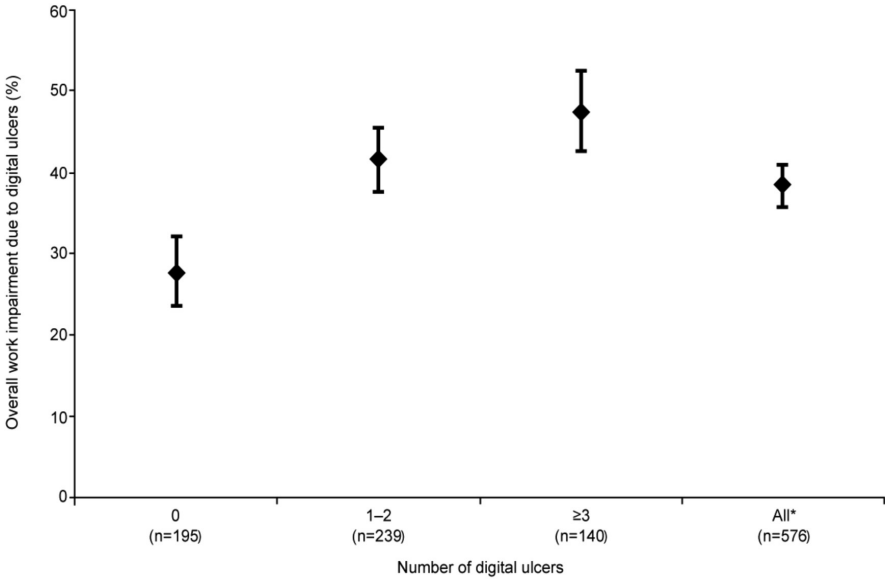

Fig. 1. Mean overall work impairment due to digital ulcers (DUs) in the prior month. Results are reported by number of DUs, for employed/self-employed patients. Error bars are 95% confidence intervals. Overall work impairment due to DU is pro-rated by the number of hours the patient normally works. *Includes 2 employed/self-employed patients with missing information on number of DUs.

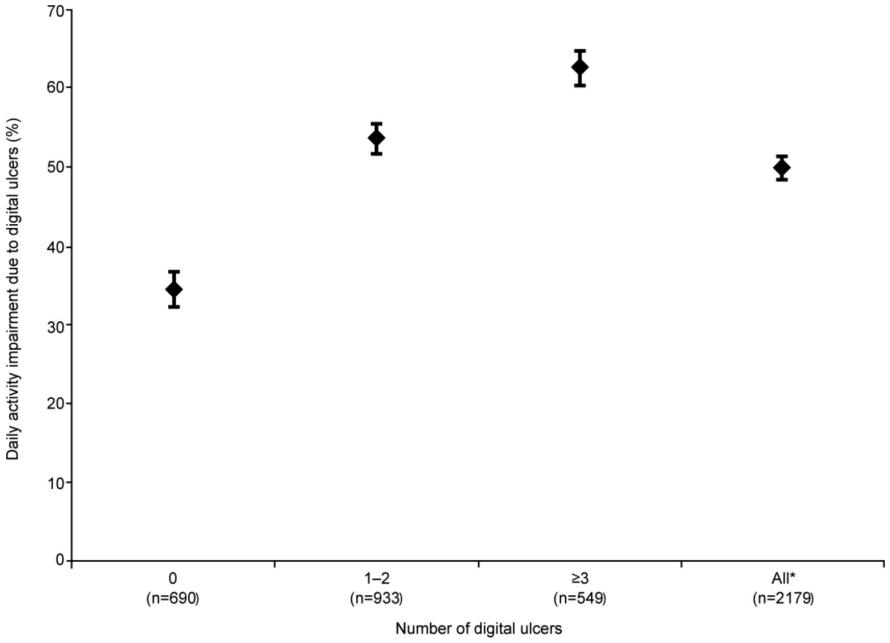

Fig. 2. Mean daily activity impairment due to digital ulcers (DUs) in the prior month. Results are reported by number of DUs. Percentages are converted from the original scale (0–10). Error bars are 95% confidence intervals. *Includes 7 patients with missing information on number of DUs.

The present analyses extend prior investigations—none of which assessed functional correlates of DUs by categorising patients by number of DUs – by establishing that the number of DUs (0, 1–2, or ≥3) was related to impairment of SSc patients' general ability to work and perform daily activities, and their requirement for daily support. Additionally, patient burden, as measured by rates of complications and use of SSc-related medications (including prostacyclin and analgesics), mostly increased with number of DUs.

Patients' self-completed functional assessments in the DUO Registry pointed to a major impact of DUs on work, supporting findings from earlier studies (7, 10, 11). Among 113 patients with SSc who were in the workforce, Bérezné *et al*. found a mean self-reported productivity decrease of 1.4 on the 0–10 scale from the questionnaire (developed by Actelion for DU, which was provided to Bérezné *et al*. for use in their study) (7). This estimate cannot be compared directly with the DUO Registry findings because Bérezné *et al*. included a high proportion (40%) of SSc patients with no past or current DUs, which may have contributed to the apparently low work impairment in their study. In addition, the study by Bérezné *et al*. was conducted in a single country only, whereas the DUO Registry comprises many European countries. The impact of disease on work impairment is expected to vary depending on the social security system and other characteristics of the country in question.

In the DUO Registry, work hours missed, productivity impairment while working, and overall work impairment all increased with number of DUs. On average, overall work impairment was approximately 20% higher (in absolute percentage terms) among patients with ≥3 DUs than among those with none. Two prior studies investigated the relationship between different measures of DU severity and work disability: Sandqvist et al. described 48 patients of working age with SSc and found that self-rated DU symptoms (such as pain, fatigue, and impaired hand function) were significantly associated with ability to work (11). Toffolo *et al*. measured ulcer dimensions and administered the Disabilities of the Arm, Shoulder, and Hand (DASH) Questionnaire to 24 patients with SSc, revealing increasing work impairment with larger ulcer dimensions (10).

As in previous investigations (7, 19), the present analysis found no effect of DUs on the percentage of employed/self-employed patients. However, the presence of DU, alone or associated with other clinical manifestations, is directly associated with disability because of pain and limited possibilities to perform the most simple tasks in daily life, such as housekeeping, or any work involving the hands (11). Thus, DUs may have an impact on employment and influence the types of work done over the course of the disease,

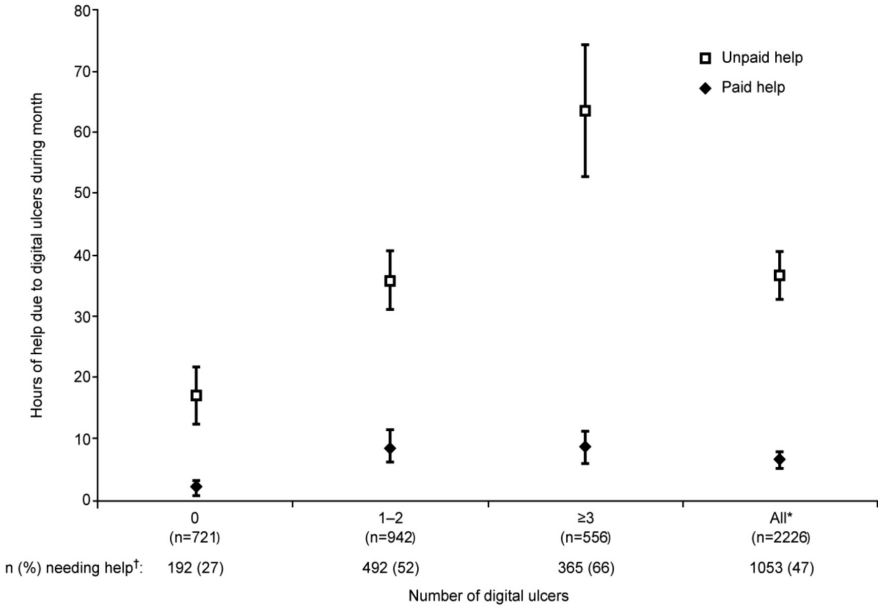

Fig. 3. Mean hours of help needed due to digital ulcers (DUs) in the prior month. Results are reported by number of DUs. Error bars are 95% confidence intervals. *Includes 7 patients with missing information on number of DUs. †Patients needing help due to DUs.

but the study design and assessments in this and previous analyses may have been unable to address such differences.

Present results demonstrate that DUs severely impair SSc patients' ability to perform daily activities. The average impairment of 50% found in this analysis, across all three DU categories (34.5%, 53.7%, and 62.7% in patients with 0, 1–2, and ≥3 DUs, respectively), was similar to that reported for 60 patients with DUs in the previously discussed study by Bérezné *et al*., who estimated a mean impairment of daily activities of 48% (7). Findings are also broadly consistent with recent data for patients with SSc from the Canadian Scleroderma Research Group Registry who reported at least sometimes experiencing DUs. Of these patients, 91% said that DUs had at least moderate impact on their daily activities (impact response options: no impact, minimal, moderate, severe and extremely severe) (9).

Moreover, mean daily activity impairment in the DUO Registry was 1.5 times higher among patients with 1–2 DUs and nearly twice as high in those with ≥3 DUs, compared with patients with no DUs. Toffolo *et al*. also reported that daily activity impairment (assessed using the DASH) correlated significantly with severity of DUs as measured by diameter and area of DUs (10).

Data from the DUO Registry indicate that the need for help from others due to DUs increases with number of DUs. Compared with patients with no DUs, those with ≥3 DUs reported requiring approximately 6.8 and 46.7 more hours of paid and unpaid help, respectively. Bérezné *et al*. also found that a high proportion of patients with DUs needed both paid and unpaid household help due to DUs, though their data were not stratified by number of DUs (7). The 59 patients with DUs assessed by Bérezné *et al*. needed a mean of 3.8 hours per month of paid help and 15.0 hours per month of unpaid help. This represents less paid and unpaid help than the average in the present study (6.6 hours of paid help and 36.7 hours of unpaid help). The findings by Bérezné et al. are more similar to the results for patients with no DUs in the DUO Registry (*i.e*. 2.0 hours of paid help and 17.0 hours of unpaid help). Nevertheless, both studies point to a substantial need for help by patients with DUs associated with SSc.

This study is subject to a number of limitations. Different types of bias may have impacted results. Recall bias may be present, since patients had to remember and quantify their functioning during the previous month. Selection bias also cannot be excluded, because patients who did not complete at least one part of the functional assessment questionnaire differed in certain clinical and demographic aspects from questionnaire completers. In addition, social security systems vary among the countries included in the DUO Registry, which may have influenced results (*e.g*. due to level of payment in case of absence from work, and payment of home help).

Observed differences between categories based on number of DUs at enrolment could be due to differences in risk factors, SSc treatment, or SSc severity, rather than number of DUs per se. For example, patients with more DUs may have had higher overall SSc severity, which could have confounded the apparent association of some functional impairment measures with number of DUs. Supporting this possibility, the results indicated that patients with a higher number of DUs present at enrolment were younger, and had earlier disease symptoms. In the DUO Registry, the functional assessment questionnaire asks patients to indicate their functional limitations due to their DUs, thus the study design limits our ability to assess the contribution of the underlying SSc to functional impairment. It should be noted that although the questionnaire asks patients to report the impact of their DU on work, daily activities, and need for help, they may not always be able to attribute these to their DU disease, as opposed to their underlying SSc or their comorbidities. For example, in a recent survey of 556 SSc patients in Canada, 317 (57%) patients self-reported one or more of the following symptoms resulting in moderate or greater impact: hand stiffness, difficulty in making a fist, holding objects, opening their hand, and/or using a faucet (20). The DUO Registry was not designed to address the important question of whether employment rates differs between the general population and patients with DU disease, or to assess the impact of DU disease on employability, the type of work performed, or the need to change work.

Nearly 70% of the patients enrolled in the DUO Registry answered the functional assessment questions, thus implying good representativeness of the results. However, the ability to generalise results from this study is limited by the fact that the DUO Registry aims for high coverage of bosentan-treated patients with DUs associated with SSc, so the registry may have a higher proportion of bosentan-treated patients than the overall population seen in clinical practice. However, baseline demographic, clinical, and antibody characteristics of patients enrolled in the DUO Registry are similar to those in previously reported cohorts (12).

In conclusion, the present results reveal the heavy burden that DU disease imposes on patients with SSc, with respect to its association with work, daily activities, and need for paid and unpaid help, and also in terms of complications and need for medications. Greater patient morbidity and medication use, higher impairment of work and daily activities, and increased help received from others were reported in patients with increasing number of DUs. These results demonstrate that number of DUs is a clinically relevant endpoint assessing severity of DU disease and burden on patients. The ability of the DU-specific measures employed in the DUO Registry to detect differences in patient-relevant outcomes supports previous calls for the development of clinician- and patient-reported instruments of high specificity to the clinical impact of DUs for future studies of DU associated with SSc (21). In addition, results highlight the importance of predictive tools, such as videocapillaroscopy (22), to identify SSc patients at high risk for developing DU, as well as effective treatments to reduce the number of DUs in order to improve functioning and to reduce the disease burden in patients with SSc.

Acknowledgements

This work was supported by Actelion Pharmaceuticals Ltd., which funded the Digital Ulcer Outcomes (DUO) Registry, the statistical analyses for the present study, and the drafting and publication of this paper, including the page charge. We gratefully acknowledge all physicians who participated in this study. Statistical analyses were performed by Mariabeth Silkey, Actelion Pharmaceuticals Ltd. and Michelle Palmer, Numerus Ltd., funded by Actelion Pharmaceuticals Ltd. Medical writing support was provided by W. Mark Roberts, Montréal, Québec, Canada, funded by Actelion Pharmaceuticals Ltd.

DUO Registry investigators

Austria

Allgemeines Krankenhaus Linz, Linz, B Raffier; Hanusch-Krankenhaus, Wien, M Hirschl; Karl Landsteiner Gesellschaft - Landesklinikum Pölten, St Pölten, F Trautinger, P Schmidt; Klinikum Mostviertel-Amstetten, Amstetten, M Stetter; Klinikum Wels-Grieskirchen, Wels, M Hundstorfer, V Reinhart; Krankenanstalt Rudolfstiftung, Wien, B Monshi, D Pirkhammer, L Richter; Krankenhaus der Elisabethinen Linz, Linz Oberösterreich, N Hamberger, S Metz; Krankenhaus Hietzing, Wien, R Feldmann; Landesklinikum Wiener Neustadt, Wiener Neustadt, K Semmelweis; Landeskrankenhaus Feldkirch, Feldkirch, K Lackner, N Tomi; Landeskrankenhaus Klagenfurt, Kärnten, H Kolle; Medizinische Universität Graz, Graz, F Hafner, M Brodmann; Medizinische Universität Innsbruck, Innsbruck, M Kuen-Spiegel; Medizinische Universität Wien, Wien, G Minmair, PM Heil; Rheuma-Zentrum Wien-Oberlaa, Wien, H Broll; Universitätsklinik für Dermatologie, Wien, G Holzer; Universitätsklinik für Dermatologie, Landeskrankenhaus Salzburg, X Illmer; Weinviertel Stockerau, Stockerau, B Rintelen, J Sautner; Wilhelminenspital, Wien, M Takacs, M Thun

Czech Republic

Faculty Hospital Bulovka, Prague, I Zemanova; Faculty Hospital Hradec Kralove, Hradec Kralove, T Soukup; Faculty Hospital Olomouc, Jesenik, A Smrzova; Faculty Hospital U svate Anny Brno, Brno, J Bohmova, L Prochazkova, P Nemec; General Hospital Brno, Brno, Z Fojtik; General Hospital Plzen, Plzen, D Suchy; Institute of Rheumatology Prague, Prague, R Becvar

Denmark

Arhus University Hospital, Arhus C, AB Olsen, KH Sondergaard

Finland

Helsinki University Central Hospital, Helsinki, R Luosujärvi; Tampere University Hospital, Tampere, K-L Vidqvist

France

Centre hospitalier d'Albi, Albi, Médecine Interne, S Madaule; Centre Hospitalier de Le Mans, Le Mans, Dermatologie, N Beneton, H Maillard; Centre Hospitalier de Lille, Hôpital Claude Huriez, Lille, Médecine Interne, H Charlanne, F Granel-Brocard, E Hachulla, PY Hatron, N Jourdain, M Lambert, D Launay, S Morell, G Woijtasik; Centre Hospitalier de Perpignan, Hôpital Saint-Jean Roussillon, Perpignan, Médecine Interne, O Cartry; Centre hospitalier de Valence, Valence, Dermatologie, F Skowron, Médecine Interne, T Zenone; Centre Hospitalier Universitaire d'Amiens, Amiens, Dermatologie, A Dadban, C Lok; Centre Hospitalier Universitaire de Besançon, Hôpital Jean Minjoz, Besançon, Médecine Interne, D Ferrandiz, N Magy-Bertrand, MP Moiton; Centre Hospitalier Universitaire de Bordeaux, Hôpital Saint-André, Bordeaux, Dermatologie, A Taieb, S Balquiere, E Belin, C Droitcourt, S Julien, S Prey, Médecine Interne, C Boulon, J Constans; Centre Hospitalier Universitaire de Bordeaux, Hôpital du Haut-Lévesque, Pessac, Dermatologie, MS Doutre, E Kostrzewa; Centre Hospitalier Universitaire de Bordeaux, Hôpital Pellegrin, Bordeaux, Rhumatologie, C Richez; Centre Hospitalier Universitaire de Brest, Hôpital Morvan-Dermatologie, Brest, M Greco, L Misery, B Sassolas; Centre Hospitalier Universitaire de Dijon, Hôpital du Bocage, Dijon, Médecine Interne, E Collet, S Berthier, V Leguy-Seguin; Centre Hospitalier Universitaire de Grenoble, Hôpital Michallon, La Tronche, Médecine Vasculaire, B Imbert, P Carpentier, S Blaise; Centre Hospitalier Universitaire de Limoges, Hôpital Dupuytren, Limoges, Dermatologie, A Couraud, V Doeffel-Hantz, A Spars, Médecine Interne, H Bezanahary, N Boussely, S Dumonteil, AL Fauchais, G Goudran, V Loustaud-Ratti, P Manea, E Vidal; Centre Hospitalier Universitaire de Lyon, Hôpital Edouard Herriot, Lyon, Médecine Interne, B Coppere, H Desmurs-Clavel, MH Girard-Madoux, A Hot, J Ninet; Centre Hospitalier Universitaire de Marseille, Hôpital-Nord, Marseille, Médecine Interne, B Granel; Centre Hospitalier Universitaire de Montpellier, Hôpital Lapeyronie, Montpellier, Rhumatologie, JD Cohen; Centre Hospitalier Universitaire de Montpellier, Hôpital Saint-Eloi, Montpellier, Médecine Interne, A Keynote, A Khau van Kien, A Le Quellec, S Riviere, P Rullier, Dermatologie, D Bessis; Centre Hospitalier Universitaire de Nancy, Hôpital Central, Nancy, Médecine Interne, C Farcas; Centre Hospitalier Universitaire de Nancy, Hôpital de Brabois, Nancy, Médecine Vasculaire, Vandoeuvre-les-Nancy, V Bravetti, T Moline, D Wahl, S Zuily; Centre Hospitalier Universitaire de Nancy, Hôpital Maringer, Nancy,

Dermatologie, F Granel-Brocard; Centre Hospitalier Universitaire de Nantes, Hôtel-Dieu, Nantes, Médecine Interne, C Agard, Médecine Vasculaire, C Durant; Centre Hospitalier Universitaire de Nice, Hôpital de l'Archet, Nice, Médecine Interne, JG Fuzibet, V Queyrel; Centre Hospitalier Universitaire de Paris, AP-HP, Hôpital Cochin, Paris, Médecine Interne, A Berezne, L Guillevin, L Mouthon; Centre Hospitalier Universitaire de Paris, Hôpital St Antoine, Paris, Médecine Interne, J Cabane, K Tiev, C Tolédano; Centre Hospitalier Universitaire de Paris, Hôpital St-Joseph, Paris, Médecine Vasculaire, I Lazareth, U Michon-Pasturel, P Priollet; Centre Hospitalier Universitaire de Reims, Hôpital Robert Debré, Reims, Dermatologie, Z Reguiai; Centre Hospitalier Universitaire de Rennes, Hôpital Sud, Rennes, Médecine Interne,C Cazalets-Lacoste, O Decaux, P Jégo, A Letrémy, A Perlat; Centre Hospitalier Universitaire de Rouen, Rouen, Dermatologie, O Deboves, AB Duval-Modeste; Centre Hospitalier Universitaire de Strasbourg, Hôpital Hautepierre, Strasbourg, Rhumatologie, E Chatelus, H Chiffot, J Sibillia, C Sordet; Centre Hospitalier Universitaire de Toulouse, Hôpital Purpan, Toulouse, Médecine Interne, D Adoue, B Couret, G Moulis, G Pugnet, L Sailler; Centre Hospitalier Universitaire de Tours, Hôpital Bretonneau, Tours, Médecine Interne, E Diot; Hôpital Joseph Ducuing, Toulouse, Médecine Interne, F Gaches; Hôpital St-Louis Paris, Paris, Médecine Interne, D Farge, H Keshtmand; Hôpital Tenon, Paris, Dermatologie, C Frances

Germany

Asklepios Klinik Altona, Wedel, A von Elling, D Boro, J Ebel, K Ahmadi-Simab; Bezirksklinikum Obermain, Ebensfeld, E Klein, K Hahn; Charité Campus Benjamin Franklin, Berlin, K Schulze; Charité Campus Mitte, Berlin, C Rasche, G Riemekasten, HH Lee, K Deuschle, K Mattat, M Becker, M Worm; Dermatologisches Ambulatorium Hamburg-Alstertal, Hamburg, C Mensing, D Klings, H Mensing, J Messall, R Zuper; Endokrinologikum Frankfurt, Frankfurt, P Eilbacher, P Saar; Fachärztepraxis Innere Medizin in Bad Abbach, Bad Abbach, P Kaufmann; Fachklinik Hornheide, Münster, C Hallermann, K Schmidt; Fachkliniken Wangen, Wangen/Allgau, H Wahn, K Schildt; Fachpraxis Rheumatologie, Winsen, T Schuart; Gefässpraxis im Tal, München, A Kaczmarczyk, C Kellner, J von Oelhafen, P Baron von Bildering, S Kunze; Helios-Klinikum Berlin Buch, Berlin, HJ Kleiner; HSK Dr. Horst Schmidt Klinik, Wiesbaden, B Alsheimer, N Schuetz, E Märker-Hermann; Internistische Gemeinschaftspraxis Dr. med. K-H. Göttl / Dr. med. O. Adjan, Passau, E Weiss, N Reischel, S Kern, KH Goettl; J.-W.-Goethe-Universitätsklinikum, Frankfurt, A Himsel, U Henkemeier; Johannes Gutenberg Universität Mainz, Bad Kreuznach, A Schwarting, A Hazenbiller, V Nichelmann; Kerckhoff-Klinik Bad Nauheim, Bad Nauheim, C Rumbaur, I Boesenberg, T Schmeiser, U Mueller-Ladner; Klinikum Augsburg, Augsburg, A Unholzer, H Starz, J Welzel, K Plaumann; Klinikum Darmstadt, Darmstadt, F Stoeckl, S Sperling; Klinikum Darmstadt, Darmstadt, M Podda, N Wagner, H Rapprich; Klinikum der Universität München LMU, München, A Niedermeier, G Messer, M Sardy, V Bekou; Klinikum Lüdenscheid, Lüdenscheid, D Dill-Müller, M Wlodarz; Klinikum rechts der Isar der Technischen Universität München, München, B Belloni, B Huettig, M Ziai, R Hein; Klinikum Südstadt Rostock, Rostock, C Kneitz, I Federow, K Schneider, M Semmler, S Hapke; Krankenhaus Barmherzige Brüder, Regensburg, C Metzler; Krankenhaus Bassum, Bassum, T Stein; Krankenhaus Dresden-Friedrichstadt, Dresden, M Enderlein, M Kayser; Krankenhaus Porz am Rhein, Köln, M Werthmann; Krankenhaus Waltershausen-Friedrichroda, Friedrichsroda, CU Guenther, S Neul; Kreiskrankenhaus Plochingen, Plochingen, B Hellmich, C Loeffler, J Pflugfelder, P Karaenke; Medizinische Poliklinik Würzburg, Würzburg, C Mueglich, HP Tony, P Marina, M Popp; Praxis Dr. M. Mittag, Leipzig, M Mittag; Praxis Dr. med. C. Baumann, Plauen, C Baumann; Praxis Dr. med. E. G. Scheibl, Paderborn, EG Scheibl, H Brand; Praxis Dr. med. H. U. Wilhelm, Stuttgart, HU Wilhelm; Praxis Dr. med. J. Böhm, Erlangen, J Dyballa, J Boehm; Praxis Dr. med. J. Taggeselle, Markkleegerg, J Taggeselle; Praxis Dr. med. K. Lüthke, Dresden, I Wuerzburg, K Lüthke; Praxis Dr. med. K. Niefanger, Straubing, K Niefanger; Praxis Dr. med. Lothar Mayer, Bad Staffelstein, L Mayer, J Drabek; Praxis Dr. med. W. Harmuth, Marktredwitz, W Harmuth; Praxis Dr. med. S. Dietl, Weiden, D Moritz, S Dietl; Praxis Prof. Dr. med. A. Gause, Hamburg, A Gause; Praxis Prof. Dr. med. M. Gaubitz, Münster, A Hallecker, M Gaubitz; Praxisgemeinschaft Dres. med. Rumpel, Regensburg, E Krupp, H Rumpel; Rheumaklinik Bad Bramstedt, Bad Bramstedt, F Moosig, P Frey, S Kahl; Rheumapraxis Augsburg-Land, Stadtbergen, M Linke; Rheumapraxis Bad Aibling, Bad Aibling, B Merk, HH Bloching; Rheuma-Praxis Bayreuth, Bayreuth, W Ochs; Rheumapraxis Dr. med. R. Kurthen, Aachen, R Kurthen; Rheumapraxis Neuss, Neuss, E Eiden, I Guertler; Rheumatologie im Struensee-Haus, Hamburg, PM Aries, S Kirchberg; Rheumatologische Schwerpunktpraxis am EVK, Düsseldorf, K Jahnke, S Mettler, S Toeller, S Zwenger, HE Langer; Rheumatologische Schwerpunktpraxis Würzburg, Wurzburg, F Deininger, F Hartmann; Rheumazentrum Prof. Dr. med. G. Neeck, Hohenfelde, G Neek, H Wernitzsch; Rheumpraxis Hofheim, Hofheim, L Meier, U Herr, U Meier; Sana Rheumazentrum Rheinland-Pfalz, Bad Kreuznach, W Flaig, A Schwarting; Schön Klinik Hamburg-Eilbek, Hamburg, L Bruckner, N Sheikh, J Wollenhaupt; SRH Klinikum Karlsbad-Langensteinbach, Karlsbad, B Krog, E Wollersdorfer, R Holl, C Diehm; St. Josef-Hospital - Katholisches Klinikum Bochum, Bochum, C Tiggers, J Peters, J Kirschke, A. Kreuter; Uni-Klinikum Campus Kiel, Kiel, JO Schroeder, R Zeuner, S Uhlig, S Barth; Universitätshautklinik Kiel, Kiel, R Huegel, R Glaeser; Universitätsklinik Bonn, Bonn, C Schaefer, M Monshausen, T Mengden; Universitätsklinik Heidelberg, Heidelberg, A Funkert, N Blank, S Lupaschko; Universitätsklinikum Aachen, Aachen, B Voss, M Megahed; Universitätsklinikum Bonn, Bonn, F Sadeghlar, M Seidel, JC Wasmuth; Universitätsklinikum des Saarlandes, Homburg, G Aßmann, J Vosswinkel; Universitätsklinikum des Saarlandes, Homburg, C Pfoehler; Universitätsklinikum Düsseldorf, Düsseldorf, A Gerber, M Haust, NP Hoff, R Mota, S Akanay-Diesel, B Homey; Universitätsklinikum Erlangen, Erlangen, A Katzemich, C Erfurt-Berge, M Sticherling; Universitätsklinikum Erlangen, Erlangen, C Beyer, J Distler; Universitätsklinikum Essen, Essen, A Mitchell, C Freundlieb, U Rushentsova; Universitätsklinikum Göttingen, Göttingen, G Hermanns, S Blaschke; Universitätsklinikum Greifswald, Greifswald, M Fiene; Universitätsklinikum Hamburg-Eppendorf, Hamburg, C Wessel; Universitätsklinikum Jena, Jena, J Norgauer; Universitätsklinikum Köln, Köln, B Rabe, J Schuster, J Scholz, K Kremer, M Robakidze-Torbahn, P Moinzadeh; Universitätsklinikum Lübeck, Lübeck, A Dohse, A Muhlack, L Schultz, S Schult, Y Frambach, S Kruse; Universitätsklinikum Mainz, Mainz, A Kettenbach, I Fell, K Schweda, K Steinbrink, M Podobinska; Universitätsklinikum Tübingen, Tübingen, G Fierlbeck, S Schanz; Universitätsklinkum Ulm, Ulm, C Pfeiffer, R Hassel; Westfälische Wilhelms-Universität Münster, Münster, I Herrgott, C Sunderkoetter; Zentrum für Endokrinologie & Diabetologie & Rheumatologie (Hansakontor), Dortmund, J Guenzel

Greece

Agios Pavlos General Hospital, Thessaloniki, P Athanassiou; Ahepa University Hospital, Thessaloniki, L Settas, T

Dimitroulas; Herakleio University Hospital, Herakleio/Creta, I Kritikos; Ioannina University Hospital, Ioannina, N Tsifetaki; Ippokrateio Garyfallos, Thessaloniki, A Garyfallos; Ippokrateion Athens, Athens, D Vasilopoulos; Ippokrateion Hospital Boura, Thessaloniki, P Boura, S Kamali; Ippokrateio Hospital Aslanidis, Thessaloniki, S Aslanidis; Laiko General Hospital of Athens, Athens, P Vlachoyannopoulos; Papageorgiou General Hospital, Thessaloniki, V Galanopoulo; University Hospital of Larisa, Larisa, L Sakkas, A Koutroubas; Asklipoieio Voulas Hospital, Athens, T Elezoglou; Alexandroupoli University Hospital, Alexandroupoli, N Galanopoulos

Ireland

St Vincent's Hospital Dublin, Dublin, A Grier, M Murray, M O'Rourke

Italy

Azienda Ospedaliera Istituto Ortopedico Gaetano Pini, Milan, N Del Papa, W Maglione, S Zeni; Azienda Ospedaliera Vittorio Emanuele, Catania, R Foti, A Benenati; Clinica di Reumatologia Azienda Ospedaliero – Universitaria di Udine, Udine, S De Vita; Clinica di Reumatologia Università Cattolica, Roma, G Ferraccioli; Clinica Reumatologica ASL 5 Ospedale Murri, Jesi, W Grassi, R de Angeli; Clinical Medica Azienda Ospedaliero-Universitaria, Ancona, G Pomponio; Dermatologia Clinica IFO – Istituto Dermatologico San Gallicano, Rome, A Mussi; II Divisione Dermatologica-IDI, Roma, L Colonna; Immunologia Clinica Spitali Civili, Brescia, P Airo, S Zingarelli; Immunologia Clinica-Policlinico Maggiore, Milan, R Scorza, A Serverino; Immunologia Ospedale San Martino, Genova, F Puppo, S Negrini; Immunologia Policlinico Umberto I, Roma, F Salsano; Istituto di Clinica Medica Azienda Ospedaliera Policlinico Paolo Giaccone, Palermo, G Triolo; Medicina Generale Catanzaro, Catanzaro, S Mazzuca; Medicina Interna Obassano - Torino, Orbassano-Torino, R Carignola; Medicina Riabilitativa Passirana, Passirana di Rho, S Gatti; Ospedale Policlinico "Giambattista Rossi" - Borgo Roma, Verona, G Lunardi; Policlinico Umberto I, Roma, V Riccieri; Reumatologia Arcispedale S. Maria Nuova Pad. Spallanzani, Reggio Emilia, C Salvarani, G Bajocchi; Reumatologia Azienda ASL 2 – Castrovillari, Mormanno, G Varcasia; Reumatologia Humanitas-Rozzano, Milan, B Marasini, L Belloll; Reumatologia Ospedale Careggi - Firenze, Firenze, M Matucci-Cerinic, R de Luca; Reumatologia Ospedale G. Rummo Pad., Benevento, S Stisi, S Bellissimo; Reumatologia Ospedale Le Molinette, Turin, E Fusaro; Reumatologia Ospedale Mauriziano Umberto I, Turin, R Pellerito; Reumatologia Ospedale Padova, Padua, F Cozzi, M Rizzo; Reumatologia Ospedale Sant' Anna-Ferrara, Ferrara, A Bartoluzzi, F Trotta; Reumatologia Ospedali Riuniti, Foggia, F Cantatore, A Corrado; Reumatologia Policlinico Modena, Modena, C Ferri, M Colaci; Reumatologia Policlinico Sant'Orsola Malpighi, Bologna, N Malavolta, R Mulè; Reumatologia Policlinico Siena, Siena, M Galeazzi; Reumatologia Policlinico Universitario Bari, Bari, G Lapadula; Reumatologia-Cagliari, Cagliari, A Mathieu, A Vacca; Reumatologia-Coppito, L'Aquila, R Giacomelli, P Cipriani; Reumatologia-Policlinico San Matteo, Pavia, C M Montecucco, V Codullo; Servizio di Reumatologia Ospedali Riuniti di Foggia, Foggia, R Bucci; Unità Operativa Semplice di Reumatologia A.R.N.A.S. Garibaldi, Catania, E Battaglia; Universita Di Napoli, Napoli, G Valentini, G Cuomo; UO Reumatologia Azienda Ospedaliera Policlinico Bari, Bari, N Terlizzi, L Serafino; UO Reumatologia Ospedale Pisa, Pisa, S Bombardieri, A Della Rossa, M Doveri; UOC Servizio di Reumatologia - Policlinico Tor Vergata, Roma, R Perricone, M de Mattia; V Divisione Dermatologica-IDI, Roma, S Pallotta

Netherlands

Franciscus Ziekenhuis, Roosendaal, JHLM Groenendael, P Seys; Haga Ziekenhuis Leyenburg, Den Haag, RJ Goekoop; Maasstad Ziekenhuis, Rotterdam, KH Han, M Wlarvens, F. Bonte-Mineur; Medisch Centrum Haaglanden, Den Haag, MHW de Bois, WM de Beus; Sint Franciscus Gasthuis Rotterdam, Rotterdam, D van Zeben; UMC St Radboud Nijmegen, Nijmegen, M Vonk, HKA Knaapen; Universitair Medisch Centrum Groningen, Groningen, A Smit, H Bootsma; Universitair Medisch Centrum Utrecht, Utrecht, E Ton; VU Medisch centrum Amsterdam, Amsterdam, A Voskuyl; Zienkenhuis Gelderse Vallei, Ede, EAJ Dutmer, JN Stolk

Norway

Helse Bergen Haukeland universitetssjukehus, Bergen, T-M Madland; Universitetssykehuset Nord-Norge, Tromso, M Seip; Oslo universitetssykehus, Rikshospitalet, Oslo, AM Hoffmann-Vold, O Midtvedt; Sorlandet Sykehus, Kristiansand, H Bitter; St. Olavs Hospital, Universitetssykehuset i Trondheim, Trondheim, R Stocklund Thomsen

Portugal

Centro Hospitalar Lisboa Norte, EPE - Hospital Santa Maria, Lisbon, C Resende, C Ponte; CHC - Centro Hospitalar Coimbra, EPE - Hospital dos Covões, S. Martinho do Bispo Coimbra, F Silva; CHVNG/E - Centro Hospitalar de Vila Nova Gaia/Espinho, EPE, Vila Nova de Gaia, P Ferreira; HCC - Hospital Curry Cabral, EPE, Lisboa, A Grilo, N Riso; HDS - Hospital Distrital Santarém, EPE, Santarem, C Santos, I Camara, J Costa; HFF- Hospital Fernando Fonseca, EPE, Amadora, J Alves, S Oliveira; HGSA - Centro Hospitalar do Porto, EPE, Porto, I Almeida, I Silva; Hosptial Garcia de Orta, EPE, Almada, A Cordeiro; IPR-Instituto Portugues Reumatologia, Lisboa, P Coelho

Slovakia

National Institute of Rheumatic Diseases, Piestany, J Lukac

Slovenia

Department of Rheumatology, University Medical Centre, Ljubljana, AS Dolnicar

Spain

Hospital Clínic Provincial de Barcelona - Autoinmu, Barcelona, G Espinosa, JC Mejía, M Ramos, MA Plasin Rodriguez; Hospital Clínico Universitario de Santiago de Compostela - Reuma, Santiago, A Mera, JS Blanco, JJ Diaz, L Losada, E Pérez, JR Maneiro, M Caamano, S Fernández, SA Insua; Hospital Clínico Universitario de Valladolid, Valladolid, J Barbado; Hospital de Cabueñes, Gijón, EM Fonseca, FJ Nuño; Hospital de la Santa Creu i Sant Pau - Reuma, Barcelona, I Castellví; Hospital de Madrid Norte Sanchinarro, Madrid, P García de la Pena; Hospital General Ciudad Real, Ciudad Real, D Bellido, M Paulino, PV García, V Salas, MD Mínguez, MA Sánchez; Hospital General de Segovia, Segovia, C Urrego; Hospital General Juan Ramón Jiménez, Huelva, I Martín; Hospital General Universitari de Valencia, Valencia, A Rueda, J Calvo; Hospital Infanta Sofía, Madrid, MM Ripoll; Hospital provincial de Ávila, Ávila, MC Torres, M Corteguera; Hospital Provincial de Pontevedra - Reuma, Pontevedra, F Maceiras, J Cruz, JA Mosquera; Hospital San Agustín, Avilés, R Gómez, B Arca, I Carrio; Hospital Universitari de Bellvitge - Interna, Hospitalet, M Rubio; Hospital Universitari de Bellvitge - Reuma, Hospitalet, I Castellví Barranco, P Santos; Hospital Universitari Vall D'Hebron - Interna, Barcelona, CP Simeón, V Fonollosa; Hospital Universitario Cruces, Barakaldo, MV Egurbide; Hospital Universitario de La Princesa, Madrid, R García de Vicuña, E Vicente; Hospital Universitario de Móstoles, Móstoles, V Villaverde, C Fernández, E García, J Usón, R Miguélez; Hospital Universitario de San Cecilio, Granada, JL Callejas, N Ortego; Hospital Universitario Doctor Peset, Valencia, J Román, JJ Alegre-Sancho; Hospital Universitario La Paz, Madrid, A Robles, JJ Ríos, MG Bonilla; Hospital Universitario Lucus Augusti - Reuma, Lugo, A Sánchez-Andrade, TR Vázquez, JA Miranda; Hospital Universitario Miguel Servet,

Zaragoza, L Sáez; Hospital Universitario Ramón y Cajal, Madrid, A Zea, C De la Puente; Hospital Universitario Reina Sofía, Córdoba, FG Martínez, MA Aguirre; Hospital Universitario Severo Ochoa, Leganés, P Collado, A Cruz, M Crespo; Hospital Universitario Virgen del Rocío, Sevilla, J Sánchez-Román, MJ Castillo; Hospital Virgen de la Salud, Toledo, AM García, G Muñiz

Sweden

Falu Lasarett, Falun, PJ Hedin; Helsingborgs Lasarett, Helsingborg, C Stahl Hallengren; Blekingesjukhuset, Karlskrona, Karlskrona, T Bracin; Karolinska universitetssjukhuset, Huddinge, Stockholm, A Nordin, K Albertsson, Y Rydvald; Spenshult sjukhus, Oskarstrom, C Thorsson; Universitetssjukhuset i Linköping, Linköping, E Hermansson

Switzerland

Rheumaklinik und Institut für Physikalische Medizin Universitätsspital Zürich, Zürich, B Maurer, D Verner, O Distler, R Schmidt-Bosshard

United Kingdom

Addenbrooke's Hospital, Cambridge, F Hall, K Murphy; Aintree University Hospital, Liverpool, J Lamb, M Anderson, R Moots; Chapel Allerton Hospital Leeds, Leeds, M Buch, L Bissell; Glasgow Royal Infirmary, Glasgow, R Madhok, R Hampson; Guy's and St Thomas' Hospital, London, D D'Cruz, LM Choong; King's College Hospital, London, P Gordon, J Dobson, R Salerno; Queens Hospital, Burton on Trent, M Nisar, C Williams, L Wilcox; Royal Free Hospital, London, C Denton, R Ochiel, T Ngcozana, L Parker, R Vincent; Royal National Hospital for Rheumatic Diseases, Bath, N McHugh, S Cole, S Brown, J James; Salford Royal University Teaching Hospital, Manchester, A Herrick, J Manning, T Moore; Solihull Hospital - Heart of England NHS Trust, Birmingham, A Faizal; Southport and Formby District General Hospital, Southport, H Skyes; The Ulster Hospital, Belfast, A Smythe, A Hamilton

References

1. LE GUERN V, MAHR A, MOUTHON L, JEANNERET D, CARZON M, GUILLEVIN L: Prevalence of systemic sclerosis in a French multi-ethnic county. *Rheumatology* (Oxford) 2004; 43: 1129-37.
2. MAYES MD, LACEY JV, JR., BEEBE-DIMMER J *et al*.: Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. *Arthritis Rheum* 2003; 48: 2246-55.
3. WALKER UA, TYNDALL A, CZIRJAK L *et al*.: Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. *Ann Rheum Dis* 2007; 66: 754-63.
4. STEEN V, DENTON CP, POPE JE, MATUCCI-CERINIC M: Digital ulcers: overt vascular disease in systemic sclerosis. *Rheumatology* (Oxford) 2009; 48 (Suppl. 3): iii19-24.
5. KHIMDAS S, HARDING S, BONNER A, ZUMMER B, BARON M, POPE J: Associations with digital ulcers in a large cohort of systemic sclerosis: results from the Canadian Scleroderma Research Group registry. *Arthritis Care Res* (Hoboken) 2011; 63: 142-9.
6. NIHTYANOVA SI, BROUGH GM, BLACK CM, DENTON CP: Clinical burden of digital vasculopathy in limited and diffuse cutaneous systemic sclerosis. *Ann Rheum Dis* 2008; 67: 120-3.
7. BÉREZNÉ A, SEROR R, MORELL-DUBOIS S *et al*.: Impact of systemic sclerosis on occupational and professional activity with attention to patients with digital ulcers. *Arthritis Care Res* (Hoboken) 2011; 63: 277-85.
8. MERKEL PA, HERLYN K, MARTIN RW *et al*.: Measuring disease activity and functional status in patients with scleroderma and Raynaud's phenomenon. *Arthritis Rheum* 2002; 46: 2410-20.
9. BASSEL M, HUDSON M, TAILLEFER SS, SCHIEIR O, BARON M, THOMBS BD: Frequency and impact of symptoms experienced by patients with systemic sclerosis: results from a Canadian National Survey. *Rheumatology* (Oxford) 2011; 50: 762-7.
10. TOFFOLO SR, FURTADO RN, KLEIN A, WATANABE S, ANDRADE LE, NATOUR J: Measurement of upper limb ulcers in patients with systemic sclerosis: reproducibility and correlation with pain, function, and quality of life. *Nurs Res* 2008; 57: 84-92.
11. SANDQVIST G, SCHEJA A, HESSELSTRAND R: Pain, fatigue and hand function closely correlated to work ability and employment status in systemic sclerosis. *Rheumatology* (Oxford) 2010; 49: 1739-46.
12. DENTON CP, KRIEG T, GUILLEVIN L *et al*.: Demographic, clinical and antibody characteristics of patients with digital ulcers in systemic sclerosis: data from the DUO Registry. *Ann Rheum Dis* 2012; 71: 718-21.
13. REILLY MC, ZBROZEK AS, DUKES EM: The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993; 4: 353-65.
14. VANDENBROUCKE JP, VON ELM E, ALTMAN DG *et al*.: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Ann Intern Med* 2007; 147: W163-94.
15. GALLUCCIO F, MATUCCI-CERINIC M: Registry evaluation of digital ulcers in systemic sclerosis. *Int J Rheumatol* 2010; 2010: 363679.
16. MOUTHON L, MESTRE-STANISLAS C, BÉREZNÉ A *et al*.: Impact of digital ulcers on disability and health-related quality of life in systemic sclerosis. *Ann Rheum Dis* 2010; 69: 214-7.
17. POOLE JL, WATZLAF VJ, D'AMICO F: A five-year followup of hand function and activities of daily living in systemic sclerosis (scleroderma). *J Hand Ther* 2004; 17: 407-11.
18. MALCARNE VL, HANSDOTTIR I, MCKINNEY A *et al*.: Medical signs and symptoms associated with disability, pain, and psychosocial adjustment in systemic sclerosis. *J Rheumatol* 2007; 34: 359-67.
19. SHARIF R, MAYES MD, NICASSIO PM *et al*.: Determinants of work disability in patients with systemic sclerosis: a longitudinal study of the GENISOS cohort. *Semin Arthritis Rheum* 2011; 41: 38-47.
20. BASSEL M, HUDSON M, BARON M *et al*.: Physical and occupational therapy referral and use among systemic sclerosis patients with impaired hand function: results from a Canadian national survey. *Clin Exp Rheumatol* 2012; 30: 574-7.
21. MATUCCI-CERINIC M, SEIBOLD JR: Digital ulcers and outcomes assessment in scleroderma. *Rheumatology* (Oxford) 2008; 47 (Suppl. 5): v46-47.
22. SEBASTIANI M, MANFREDI A, LO MONACO A *et al*.: Capillaroscopic Skin Ulcers Risk Index (CSURI) calculated with different videocapillaroscopy devices: how its predictive values change. *Clin Exp Rheumatol* 2013: 31 (Suppl. 76); S115-S117.