EULAR Sjögren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjögren's syndrome

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► Additional data are published online only. To view these files please visit the journal online (http://ard.bmj.com).

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Accepted 9 June 2009
Published Online First 28 June 2009

ABSTRACT

Objective To develop a disease activity index for patients with primary Sjögren's syndrome (SS): the European League Against Rheumatism (EULAR) Sjögren's syndrome disease activity index (ESSDAI).

Methods Thirty-nine SS experts participated in an international collaboration, promoted by EULAR, to develop the ESSDAI. Experts identified 12 organ-specific 'domains' contributing to disease activity. For each domain, features of disease activity were classified in three or four levels according to their severity. Data abstracted from 96 patients with systemic complications of primary SS were used to generate 702 realistic vignettes for which all possible systemic complications were represented. Using the 0–10 physician global assessment (PhGA) scale, each expert scored the disease activity of five patient profiles and 20 realistic vignettes. Multiple regression modelling, with PhGA used as the dependent variable, was used to estimate the weight of each domain.

Results All 12 domains were significantly associated with disease activity in the multivariate model, domain weights ranged from 1 to 6. The ESSDAI scores varied from 2 to 47 and were significantly correlated with PhGA for both real patient profiles and realistic vignettes ($r=0.61$ and $r=0.58$, respectively, $p<0.001$). Compared with 57 (59.4%) of the real patient profiles, 468 (66.7%) of the realistic vignettes were considered likely or very likely to be true.

Conclusion The ESSDAI is a clinical index designed to measure disease activity in patients with primary SS. Once validated, such a standardised evaluation of primary SS should facilitate clinical research and be helpful as an outcome measure in clinical trials.

Primary Sjögren's syndrome (SS) is a systemic disorder characterised by lymphocytic infiltration and progressive destruction of exocrine glands. The inflammatory process can, however, affect any organ. As a result, clinical features can be divided into two facets: (1) benign but disabling manifestations such as dryness, pain and fatigue, affecting almost all patients; and (2) severe systemic manifestations that affect 20–40% of patients.

Evidence-based therapy for SS is largely limited to treatments that improve sicca features.[1] Clinical trials of disease-modifying therapies have used a variety of ad hoc outcome measures mainly based on glandular features or patient symptoms, but not systemic features.[2–6] Valid activity indices are needed[7–9] to assess the effectiveness of new therapies, such as B-cell targeted therapies that have shown promising results for both severe systemic[10 11] and glandular features.[12–15] Two disease activity indices have recently been proposed: the SS disease activity index (SSDAI)[16] and the Sjögren's systemic clinical activity index (SCAI).[17] The development of these indices was based on exploratory studies conducted in single countries, but they serve as the basis of the present collaborative project. The European League Against Rheumatism (EULAR) has thus promoted an international collaboration to develop consensus disease activity indices. Two indices are currently in development: (1) a patient-administered questionnaire to assess patient symptoms, the EULAR Sjögren's syndrome patient reported index (ESSPRI); and (2) a systemic activity index to assess systemic complications, the EULAR Sjögren's syndrome disease activity index (ESSDAI).

We now describe the development and initial validation of the ESSDAI. This index was developed with the help of a worldwide panel of primary SS experts using physician global assessment (PhGA) scale of disease activity as an external criterion. The aim is for the ESSDAI to be used as outcome criteria to evaluate primary SS in a standardised way in both clinical trials and daily practice.

METHODS

This paper results from a collaboration of experts identified through their involvement in the primary SS field, headed by a steering committee of seven physician experts in SS (HB, SJB, JEG, XM, ET, AT, CV), a clinical epidemiologist (PR) and a rheumatologist, fellow in clinical epidemiology (RS). The research protocol was endorsed by EULAR (project code CLI 010).

The steps of the development of the ESSDAI are summarised below; the entire methodology is available in appendix 1, available online only.

Selection of relevant domains and definition of items

Domains of organ-specific involvement relevant to assess disease activity were selected in these steps. For each domain, the different clinical manifestations were ranked by level of activity (ie, items). For selection of domains relevant to disease activity and a definition of items for each domain, steering committee members prepared a preliminary

proposal on the basis of their clinical experience, literature review and previous work.[16 17] The preliminary selection of domains and items were successively submitted to the expert panel. Experts had to rate the importance of each domain or suggest any additional domains or changes to proposed items. Intention-to-treat was used as a help for experts to define the different activity levels that ranged from no activity (requiring no treatment) to high activity (requiring high dose steroids or immunosuppressant). The experts' proposals were analysed, then discussed and voted on during a meeting.

Elaboration of clinical vignettes

In this step, realistic clinical vignettes were generated from real patient profiles.

Abstraction and standardisation of real patient profiles

Five members of the steering committee supplied 96 profiles of their patients with systemic complications of primary SS. Each profile had to contain sections on 'history' (demographic data and past medical history), 'today' (clinical symptoms and results of imaging examination) and 'laboratory' (biological features). Patient profiles included data from the baseline and two follow-up visits (3 and 6 months).

Abstraction of descriptions of items from real patient profiles

From patient profiles, 96 histories and 364 items, included in the 'today' and 'laboratory' sections, were extracted and standardised by the same investigator (RS). Descriptions of all ESSDAI items were obtained and entered in a database with their corresponding scoring (domain and activity level). Each item had a median of 8.5 (interquartile range 4–15) descriptions.

Generation of realistic clinical vignettes

Determination of construction rules

Data from primary SS patient cohorts of five members of the steering committee (SJB, XM, ET, AT, CV)[16–20] were used to construct a sample of vignettes with characteristics similar to European patient cohorts.

Generation of clinical vignettes

In total, 720 clinical vignettes were generated by a combination of 'history' and items from the 'today' and 'laboratory' sections, with respect to the domain and item distribution defined previously. However, because items in the database referred to only systemic features, descriptors of symptoms such as dryness, pain and fatigue were generated and assigned to 30% of the patient vignettes.

Assessment

The 96 real patient profiles and the 720 clinical vignettes were randomly assigned to the 40 experts. Each expert had to rate five real patient profiles (rated by two raters each) and 20 clinical vignettes (18 were 'unique' and two were 'common' to two raters). For the survey, an internet-secure relational database was constructed. Patient data were presented chronologically, and the responses could not be changed. For all visits of each profile or vignette, experts had to assess disease activity by use of the PhGA on a 0–10 numerical scale and a five-point scale (inactive, low, moderate, high, very high activity). For the first visit of each profile or vignette, they also had to evaluate the plausibility of each patient case with the use of a five-point scale (very unlikely, unlikely, possible, likely, very likely) by answering the following question: 'Please indicate, according to your clinical experience and knowledge of the disease, the likelihood that this patient scenario is a real case.'

Statistical methods

Determination of domain weights and construction of the ESSDAI

Realistic clinical vignettes were used to determine domain weights. Disease activity assessed by the PhGA was used as an external criterion. Bivariate analysis involved Pearson's correlation between PhGA and each domain separately; for each domain, scores ranged from 0 'no activity' to 3 'high activity'. All domains were entered into multivariate models; the PhGA was used as a dependant variable and each domain was an explanatory variable. Two models were evaluated: a multiple linear regression model and a robust regression model with the least-median-of-squares method with a modified maximum likelihood estimator.[21 22] The weights assigned to each domain were derived from the regression coefficients of the multivariate model and rounded to form simplified indices. The weight of each item was obtained by multiplying the weight of the domain by the level of activity.

Preliminary validation

The ESSDAI was then calculated for all real patient profiles and realistic clinical vignettes. Construct validity was assessed by the strength of correlation between the ESSDAI score and the PhGA.

Sensitivity analyses

To evaluate the stability/robustness of the domain weight estimation, other models were tested: a logistic regression model with the five-point scale used as an external criterion and different multiple linear regression models after pooling items that clustered.

Patient profile plausibility

Evaluation of patient profile plausibility of realistic clinical vignettes was compared with that of real patient profiles by a Cochran–Armitage trend test.

Reliability of disease activity scoring

The evaluation of clinical vignettes common to two raters was used to assess interrater reliability:

- For the 0–10 PhGA: intraclass correlation coefficient (ICC) and Bland and Altman graphical analysis[23 24]
- For the five-point scale: global agreement and kappa statistics[25 26]

The evaluation of real patient profiles was used to assess intrarater reliability by the ICC, if at the first follow-up visit, the physician considered the disease activity unchanged. ICC CI were estimated with bootstrapping methods, with 1000 replications.[27]

For all statistical analyses, a p value less than 0.05 was considered statistically significant. All statistical analyses involved the use of SAS release 9.1 and R release 2.2.1 statistical software packages.

RESULTS

Characteristics of expert panel

Of 40 invited primary SS experts, 39 took part in the study (35 Europeans from 13 countries and four North Americans). The median age of experts was 49 years (interquartile range 46–58); 35 were rheumatologists, three were internists and one was an oral medicine practitioner. All but two (94.9%) had 10 or more years of experience in managing primary SS. All were involved in clinical research, and 23 (59.0%) were also involved in basic science research into primary SS.

Selection of domains and definition of items

All 10 domains (constitutional and lymphadenopathy, glandular, articular, cutaneous, pulmonary, renal, muscular, peripheral nervous system, central nervous system, haematological) proposed by the steering committee were included. Experts decided to divide the 'constitutional and lymphadenopathy' domain into two domains and to add a biological domain but not add a hepatic domain (considered to result from damage). The definition of the different activity levels (items) of each domain was obtained by consensus after discussion during meetings of the steering committee and experts.

Characteristics of real patient profiles and realistic vignettes

Thirty-nine of the 40 experts completed the rating of the 96 real patient profiles and 702 of the 720 clinical vignettes (table 1). Real patient profiles, selected for the extent of systemic involvement, had a significantly higher number of involved organs than did realistic clinical vignettes (2.83±1.46 vs 2.14±1.08; p<0.001).

Determination of domain weights and derivation of the ESSDAI

All domains, except haematological, glandular, articular and biological domains, showed a significant positive correlation with the PhGA score (table 2). All domains were entered in two multivariate regression models. Multiple linear and least-median-of-squares regression models provided similar results (R^2=0.29 and R^2=0.30, respectively). In both models, all domains were significantly associated with disease activity (PhGA), and the weight estimation was similar. The weights derived from the regression coefficients were rounded to obtain a simple index (tables 2 and 3).

Table 1 Demographic characteristics for the 96 real patient profiles and 702 realistic clinical vignettes

	Real patient profiles (n=96)	Realistic clinical vignettes (n=702)
Age	55.92±15.13	55.85±14.21
Female sex	89 (92.71%)	647 (92.17%)
Disease duration	8.58±7.25	8.46±7.04
Oral dryness	90 (93.75%)	641 (91.31%)
Ocular dryness	82 (85.42%)	599/697 (85.94%)
Objectively assessed dryness	63/63 (100%)	456/456 (100%)
Anti-Ro/SSA antibodies	82 (86.42%)	595 (84.76%)
Anti-La/SSB antibodies	56 (58.33%)	399 (56.84%)
Lymphocytic sialadenitis with focus score ≥1	70/74 (94.59%)	490/525 (93.33%)
Organ involvement		
Constitutional symptoms	14 (14.58%)	76 (10.83%)
Lymphadenopathy	9 (9.38%)	80 (11.40%)
Lymphoma	8 (8.33%)	35 (4.99%)
Glandular	27 (28.12%)	270 (38.46%)
Articular	36 (37.5%)	396 (56.14%)
Cutaneous	29 (30.21%)	74 (10.54%)
Pulmonary	22 (22.92%)	90 (12.82%)
Renal	14 (14.58%)	37 (5.27%)
Muscular	2 (2.08%)	22 (3.13%)
Peripheral nervous system	15 (15.62%)	64 (9.12%)
Central nervous system	7 (7.29%)	20 (2.85%)
Haematological	25 (26.04%)	72 (10.26%)
Biological markers of B-cell activation	64 (66.67%)	268 (38.18%)

Data are presented as number (%) or mean±SD.

Preliminary validation of the ESSDAI in real patient profiles and realistic vignettes

The mean ESSDAI scores were 15.48±9.16 and 9.04±6.43 for real patient profiles and realistic vignettes, respectively. ESSDAI scores were significantly correlated with the PhGA score (r=0.58 for realistic vignettes and r=0.61 for real patient profiles, p<0.001; figure 1). The maximum theoretical ESSDAI score is 123; only 25% of realistic vignettes and the real patient profiles had a score of 13 or more and 21 or more, respectively. The highest score was 42 and 47 for the realistic vignettes and real profiles, respectively (figure 1).

Sensitivity analyses

Other models for testing sensitivity analyses led to similar domain weights and similar correlation with the PhGA score.

Patient profile plausibility

Overall, experts considered 468 (66.7%) of the 702 vignettes likely or very likely to be true, compared with 57 (59.4%) of the 96 real patient profiles (p=0.09).

Reliability of disease activity scoring

Interrater reliability assessed by the ICC on 76 common vignettes was 0.41 (0.18–0.60) for the PhGA. Bland and Altman graphical analysis revealed no systematic errors (mean difference −0.16) but a variability of rating among experts (95% agreement interval; −4.92 to +4.61). The ratings of the same vignette by two different experts differed by 1 or less points for 37 vignettes (48.7%), by 2 to 3 points for 30 (39.5%) and by over 3 points for nine (11.8%). The weighted kappa statistic for disease activity rating by the five-point scale was 0.32 (0.18–0.47). When grouping the highest activity scores (high and very high activity) and the lowest scores (inactive, low and moderate activity), the observed agreement was 72.4% and the kappa coefficient was 0.42 (0.21–0.63).

Intrarater reliability of the PhGA for 20 real patient profiles with unchanged activity at the first follow-up visit as assessed with the ICC was 0.86 (0.68–0.94).

DISCUSSION

The ESSDAI is a consensus clinical index designed to measure disease activity in patients with systemic complications of primary SS. This index is modelled on physicians' judgement of disease activity. It results from a large collaboration of European and North American experts in primary SS. Compared with the PhGA, the ESSDAI performed satisfactorily for an evaluation of disease activity in primary SS.

In the absence of an available 'gold standard' or true understanding of the disease process, the most accurate and meaningful method of disease activity assessment is to attempt to model the physicians' judgement. Any scale quantifying physicians' judgement of disease activity is a simplification of a complex mental process. For that purpose, two main gold standards have been used in the development of disease activity indices: (1) the PhGA[28–30] and (2) the intention-to-treat approach.[31 32] The PhGA was used for the development of the systemic lupus disease activity index (SLEDAI) in systemic lupus erythematosus (SLE),[28–30] whereas the intention-to-treat approach was used for the development of the British Isles lupus assessment group (BILAG) for SLE[31] and the DAS for rheumatoid arthritis.[32] However, unlike rheumatoid arthritis that quasi-exclusively affects the articular system and in which therapeutic decisions are reproducible, the multisystemic nature of primary

Table 2 Correlation between domains and disease activity, as assessed by the PhGA scale, and regression coefficients and domain weights obtained with the least-median-of-squares robust regression model with an MM estimator

	Bivariate analysis		Multivariate modelling: Least median of square with MM estimator			
Domains	Correlation with PhGA	p Value	Regression coefficient	Standard error	Weight	p Value
Constitutional	0.106	0.005	0.704	0.163	3	<0.001
Lymphadenopathy	0.134	<0.001	0.817	0.089	4	<0.001
Glandular	0.067	0.078	0.407	0.091	2	<0.001
Articular	0.063	0.095	0.489	0.068	2	<0.001
Cutaneous	0.156	<0.001	0.559	0.097	3	<0.001
Pulmonary	0.170	<0.001	1.066	0.115	5	<0.001
Renal	0.125	<0.001	1.090	0.170	5	<0.001
Muscular	0.156	<0.001	1.193	0.191	6	<0.001
PNS	0.197	<0.001	0.944	0.117	5	<0.001
CNS	0.159	<0.001	0.936	0.157	5	<0.001
Hematological	0.041	0.277	0.361	0.126	2	0.004
Biological	0.073	0.053	0.206	0.080	1	0.010

For bivariate analysis, Pearson's correlation coefficient (r) were obtained between the physician global assessment (PhGA) scale and each domain; for each domain, scores ranged from 0 'no activity' to 3 'high activity'. All domains were entered in multivariate regression with the least-median-of-squares model with an MM estimator. R^2=0.30 for the model. All domains were significantly associated with disease activity (as defined by the 0–10 PhGA numerical scale) in the multivariate model. The weights were derived from the regression coefficient of the multivariate model.
CNS, central nervous system; MM, modified maximum likelihood; PNS, peripheral nervous system.

Table 3 The EULAR Sjögren's syndrome disease activity index (ESSDAI): domain and item definitions and weights

Domain [weight]	Activity level	Description
Constitutional [3] Exclusion of fever of infectious origin and voluntary weight loss	No = 0	Absence of the following symptoms
	Low = 1	Mild or intermittent fever (37.5–38.5°C)/night sweats and/or involuntary weight loss of 5–10% of body weight
	Moderate = 2	Severe fever (>38.5°C)/night sweats and/or involuntary weight loss of >10% of body weight
Lymphadenopathy [4] Exclusion of infection	No = 0	Absence of the following features
	Low = 1	Lymphadenopathy ≥1 cm in any nodal region or ≥2 cm in inguinal region
	Moderate = 2	Lymphadenopathy ≥2 cm in any nodal region or ≥3 cm in inguinal region, and/or splenomegaly (clinically palpable or assessed by imaging)
	High = 3	Current malignant B-cell proliferative disorder
Glandular [2] Exclusion of stone or infection	No = 0	Absence of glandular swelling
	Low =1	Small glandular swelling with enlarged parotid (≤3 cm), or limited submandibular or lachrymal swelling
	Moderate = 2	Major glandular swelling with enlarged parotid (>3 cm), or important submandibular or lachrymal swelling
Articular [2] Exclusion of osteoarthritis	No = 0	Absence of currently active articular involvement
	Low = 1	Arthralgias in hands, wrists, ankles and feet accompanied by morning stiffness (>30 min)
	Moderate = 2	1–5 (of 28 total count) synovitis
	High = 3	≥6 (of 28 total count) synovitis
Cutaneous [3] Rate as 'no activity' stable long-lasting features related to damage	No = 0	Absence of currently active cutaneous involvement
	Low =1	Erythema multiforma
	Moderate = 2	Limited cutaneous vasculitis, including urticarial vasculitis, or purpura limited to feet and ankle, or subacute cutaneous lupus
	High = 3	Diffuse cutaneous vasculitis, including urticarial vasculitis, or diffuse purpura, or ulcers related to vasculitis
Pulmonary [5] Rate as 'no activity' stable long-lasting features related to damage, or respiratory involvement not related to the disease (tobacco use, etc)	No =0	Absence of currently active pulmonary involvement
	Low = 1	Persistent cough or bronchial involvement with no radiographic abnormalities on radiography Or radiological or HRCT evidence of interstitial lung disease with no breathlessness and normal lung function test
	Moderate = 2	Moderately active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath on exercise (NHYA II) or abnormal lung function tests restricted to 70%>DL_{CO}≥40% or 80%>FVC≥60%
	High = 3	Highly active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath at rest (NHYA III, IV) or with abnormal lung function tests DL_{CO}<40% or FVC<60%
Renal [5] Rate as 'no activity' stable long-lasting features related to damage and renal involvement not related to the disease. If biopsy has been performed, please rate activity based on histological features first	No = 0	Absence of currently active renal involvement with proteinuria <0.5 g/day, no haematuria, no leucocyturia, no acidosis, or long-lasting stable proteinuria due to damage
	Low = 1	Evidence of mild active renal involvement, limited to tubular acidosis without renal failure or glomerular involvement with proteinuria (between 0.5 and 1 g/day) and without haematuria or renal failure (GFR ≥60 ml/min)
	Moderate = 2	Moderately active renal involvement, such as tubular acidosis with renal failure (GFR <60 ml/min) or glomerular involvement with proteinuria between 1 and 1.5 g/day and without haematuria or renal failure (GFR ≥60 ml/min) or histological evidence of extra-membranous glomerulonephritis or important interstitial lymphoid infiltrate
	High = 3	Highly active renal involvement, such as glomerular involvement with proteinuria >1.5 g/day or haematuria or renal failure (GFR <60 ml/min), or histological evidence of proliferative glomerulonephritis or cryoglobulinaemia-related renal involvement

Continued

Table 3 Continued

Domain [weight]	Activity level	Description
Muscular [6] Exclusion of weakness due to corticosteroids	No = 0	Absence of currently active muscular involvement
	Low = 1	Mild active myositis shown by abnormal EMG or biopsy with no weakness and creatine kinase (N<CK≤2N)
	Moderate = 2	Moderately active myositis confirmed by abnormal EMG or biopsy with weakness (maximal deficit of 4/5), or elevated creatine kinase (2N<CK≤4N)
	High = 3	Highly active myositis shown by abnormal EMG or biopsy with weakness (deficit ≤3/5) or elevated creatine kinase (>4N)
PNS [5] Rate as 'no activity' stable long-lasting features related to damage or PNS involvement not related to the disease	No = 0	Absence of currently active PNS involvement
	Low = 1	Mild active peripheral nervous system involvement, such as pure sensory axonal polyneuropathy shown by NCS or trigeminal (V) neuralgia
	Moderate = 2	Moderately active peripheral nervous system involvement shown by NCS, such as axonal sensorimotor neuropathy with maximal motor deficit of 4/5, pure sensory neuropathy with presence of cryoglobulinamic vasculitis, ganglionopathy with symptoms restricted to mild/moderate ataxia, inflammatory demyelinating polyneuropathy (CIDP) with mild functional impairment (maximal motor deficit of 4/5 or mild ataxia) Or cranial nerve involvement of peripheral origin (except trigeminal (V) neralgia)
	High = 3	Highly active PNS involvement shown by NCS, such as axonal sensorimotor neuropathy with motor deficit ≤3/5, peripheral nerve involvement due to vasculitis (mononeuritis multiplex, etc), severe ataxia due to ganglionopathy, inflammatory demyelinating polyneuropathy (CIDP) with severe functional impairment: motor deficit ≤3/5 or severe ataxia
CNS [5] Rate as 'no activity' stable long-lasting features related to damage or CNS involvement not related to the disease	No = 0	Absence of currently active CNS involvement
	Low = 1	Moderately active CNS features, such as cranial nerve involvement of central origin, optic neuritis or multiple sclerosis-like syndrome with symptoms restricted to pure sensory impairment or confirmed cognitive impairment
	High = 3	Highly active CNS features, such as cerebral vasculitis with cerebrovascular accident or transient ischaemic attack, seizures, transverse myelitis, lymphocytic meningitis, multiple sclerosis-like syndrome with motor deficit
Haematological [2] For anaemia, neutropenia, and thrombopenia, only autoimmune cytopenia must be considered Exclusion of vitamin or iron deficiency, drug-induced cytopenia	No = 0	Absence of auto-immune cytopenia
	Low = 1	Cytopenia of auto-immune origin with neutropenia (1000<neutrophils<1500/mm^3), and/or anaemia (10<haemoglobin<12 g/dl), and/or thrombocytopenia (100000<platelets<150000/mm^3) Or lymphopenia (500<lymphocytes<1000/mm^3)
	Moderate = 2	Cytopenia of auto-immune origin with neutropenia (500≤neutrophils≤1000/mm^3), and/or anaemia (8≤haemoglobin≤10 g/dl), and/or thrombocytopenia (50000≤platelets≤100000/mm^3) Or lymphopenia (≤500/mm^3)
	High = 3	Cytopenia of auto-immune origin with neutropenia (neutrophils <500/mm^3), and/or or anaemia (haemoglobin <8 g/dl) and/or thrombocytopenia (platelets <50000/mm^3)
Biological [1]	No = 0	Absence of any of the following biological features
	Low = 1	Clonal component and/or hypocomplementaemia (low C4 or C3 or CH50) and/or hypergammaglobulinaemia or high IgG level between 16 and 20 g/l
	Moderate = 2	Presence of cryoglobulinaemia and/or hypergammaglobulinaemia or high IgG level >20 g/l, and/or recent onset hypogammaglobulinaemia or recent decrease of IgG level (<5 g/l)

CIDP, chronic inflammatory demyelinating polyneuropathy; CK, creatine kinase; CNS, central nervous system; DL_{CO}, diffusing CO capacity; EMG, electromyogram; EULAR, European League Against Rheumatism; FVC, forced vital capacity; GFR, glomerular filtration rate; Hb, haemoglobin; HRCT, high-resolution computed tomography; IgG, immunoglobulin G; NCS, nerve conduction studies; NHYA, New York Heart Association classification; Plt, platelet; PNS, peripheral nervous system.

SS makes therapeutic decisions more variable. In addition, the evidence-based therapeutic management of SLE is currently more advanced than in primary SS. Moreover, in BILAG, this approach was used to define, in each domain, the different classes (A, B, C, D, E) and not as a gold standard to determine domain weights. Therefore, in the absence of effective treatment or consensual therapeutic management and because of the variability of physician habits, the intention-to-treat approach might be more difficult to apply as a gold standard for primary SS at this time.

In addition, the extent to which each organ involvement or patient symptoms of fatigue and pain can influence the physicians' evaluation of disease activity, in such a polymorphous disease, is extremely variable, as demonstrated by the limited reliability of the PhGA. These discrepancies among physicians' views, even among disease experts, justify the necessity for a more objective and standardised scoring system to homogenise the assessment of disease activity in different settings, by different physicians, experts but also less experienced physicians. Similar to the correlation of SCAI scores with the PhGA,[17] that of ESSDAI scores with the PhGA was approximately 0.60. These correlations were lower than those from other studies evaluating DAS for various systemic disorders.[16 29 33] However, in most of those studies, the experts involved were trained to the rating of the PhGA and the different activity tools to improve reliability and homogeneity of this scoring. In the present study, to be closer to usual practice, we decided not to perform a training exercise.

The ESSDAI was developed by a large panel of primary SS experts and attempted to reflect their thought process. This may have ensured the content validity of the ESSDAI, including all relevant determinants of disease activity. The validity of the ESSDAI was further confirmed by the significant association of all domains with disease activity in our model. Previous primary SS activity indices have been developed with the use of cohorts in which approximately half of the patients had inactive or weakly active disease.[16 17] Our strategy was to use data from selected patients with systemic features to generate realistic clinical vignettes. This methodology enabled us to obtain a large number of vignettes (more than would have been possible with real patients) representing all possible systemic disease involvement (ie, items). We then evaluated the extent to which each item influenced the evaluation of disease activity, which had not been possible in previous studies that did not include all organ-specific features.[16 17] As in all global scoring systems,[16 29] similar ESSDAI scores (same disease activity) may reflect different domains involved. As a further component of this project we will also

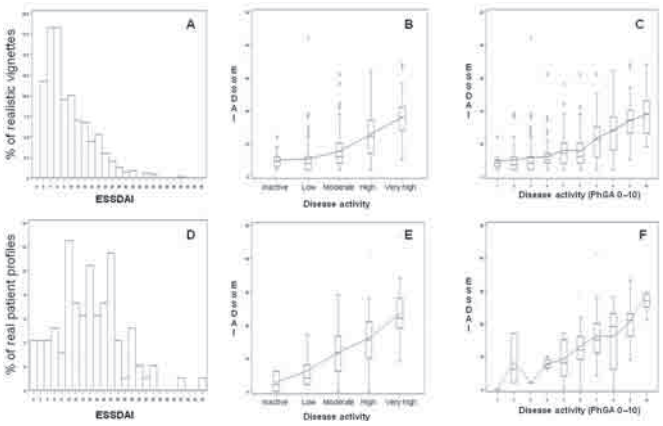

Figure 1 Distribution of EULAR Sjögren's syndrome disease activity index (ESSDAI) scores and correlation with disease activity in real patient profiles and realistic vignettes. (A), (B) and (C) refer to the 702 realistic clinical vignettes, and (D), (E) and (F) refer to the 96 real patient profiles. Distribution of ESSDAI scores in (A) realistic vignettes and (D) real patient profiles; (B and E) ESSDAI score for each level of global activity as defined by physicians on the five-point scale; and (C and F) correlation between ESSDAI scores and physicians' ratings of disease activity by the physician global assessment (PhGA) scale (0–10 scale). For box plots of ESSDAI scores, the boxes represent the 25th and 75th percentiles; the lines within the box represent the median; the dot inside the box, linked by a line, represents the mean; and the whiskers extend to the most extreme data point, which is no more than 1.5 times the interquartile range (difference between the 75th and 25th percentiles) from the box. Values that are more extreme were considered outliers and are plotted individually (dots). EULAR, European League Against Rheumatism.

be evaluating the most common patient-reported symptoms, such as dryness, pain and fatigue in a patient-completed questionnaire, the ESSPRI.

A major challenge in designing a systemic index is distinguishing between damage and disease activity. The most frequent approach, to avoid scoring damage, is to consider manifestations as active only if 'new' or 'worsening'. Under these scoring systems, when patients are evaluated at two time points, a persistent manifestation will not be rated at the second time point, which may cause an erroneous interpretation of improvement even though the patient's condition has not changed. To avoid this, all ESSDAI items were defined without reference to a previous assessment, but with an advice not to rate as active stable long-lasting features related to damage.

The ESSDAI is a systemic disease activity index developed to allow a standardised evaluation of disease activity in primary SS patients. Further studies are needed to assess the reliability and sensitivity to change of the ESSDAI. Once validated, if uniformly applied, the ESSDAI might enable comparison between studies and facilitate clinical research into primary SS. After the development of the patient-completed questionnaire (ESSPRI), the use of both the ESSDAI and ESSPRI for outcome assessment in randomised controlled trials should allow for assessing all facets of the disease.

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Acknowledgements The authors would like to thank Maxime Dougados and Alan Tyndall for their guidance and support. They thank the EULAR house in Zurich for their hospitality and outstanding organisation (Ernst Isler, Anja Schönbächler and their associates). The authors also thank the expert panel for their active and fruitful participation.

Funding This project was supported by a grant from the European League Against Rheumatism (EULAR).

Competing interests None.

Ethics approval This study was conducted with the approval of the institutional review board of GHU Paris Nord (no IRB0006477).

Provenance and peer review Not commissioned; externally peer reviewed.

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EULAR Sjögren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjögren's syndrome

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Ann Rheum Dis 2010 69: 1103-1109 originally published online June 28, 2009
doi: 10.1136/ard.2009.110619

Corrections

Raphaèle Seror, Philippe Ravaud, Simon J Bowman, *et al.* EULAR Sjögren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjögren's syndrome. *Ann Rheum Dis* 2010;**69**:1103–09. doi:10.1136/ard.2009.110619. In the published table 3 the activity level of the central nervous system (CNS) should read: No=0, Moderate=2 and High=3. There is no low activity in this domain. The corrected table 3 appears below:

Domain [Weight]	Activity level	Description
CNS [5]	No = 0	Absence of currently active CNS involvement
Rate as "No activity" stable long-lasting features related to damage or CNS involvement not related to the disease	Moderate = 2	Moderately active CNS features, such as cranial nerve involvement of central origin, optic neuritis or multiple sclerosis-like syndrome with symptoms restricted to pure sensory impairment or proven cognitive impairment
	High = 3	Highly active CNS features, such as cerebral vasculitis with cerebrovascular accident or transient ischemic attack, seizures, transverse myelitis, lymphocytic meningitis, multiple sclerosis-like syndrome with motor deficit.

Ann Rheum Dis 2011;**70**:880. doi:10.1136/ 2009.110619corr1