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Burden of systemic lupus erythematosus in clinical practice: baseline data from the SLE Prospective Observational Cohort Study (SPOCS) by interferon gene signature

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ABSTRACT

Objective The longitudinal Systemic Lupus Erythematosus Prospective Observational Cohort Study (SPOCS) aims to assess SLE disease course overall and according to type I interferon 4 gene signature (IFNGS). Here, we describe SPOCS patient characteristics by IFNGS and baseline disease activity.

Methods SPOCS (NCT03189875) is an international study of patients with SLE according to Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) criteria. Enrolled patients from 135 centres in 8 countries were followed biannually for ≤3 years from June 2017 to November 2022. Baseline demographics, disease characteristics, organ system involvement/damage and flares were analysed descriptively according to SLE Disease Activity Index-2000 score (SLEDAI-2K <10/≥10) and IFNGS status (high/low).

Results The study population (n=823) was 93.2% female, with mean (SD) age 45.3 (13.9) years and 11.1 (9.2) years since diagnosis; 52.4% had baseline SLICC/ACR Damage Index score ≥1. Patients with SLEDAI-2K scores ≥10 (241 of 584, 41.3%) vs <10 were younger (mean 42.8 (13.7) vs 46.6 (14.2) years; nominal p=0.001), had shorter SLE duration (10.4 (8.6) vs 12.4 (9.6) years; nominal p=0.012) and more severe flares (12.9% vs 5.3%; nominal p=0.001). IFNGS-high patients (522 of 739, 70.6%) were younger than IFNGS-low patients at first SLE manifestation (30.0 (12.7) vs 36.8 (14.6) years; nominal p<0.001). Proportions of IFNGS-high patients differed according to race (nominal p<0.001), with higher proportions among Asian (83.3%) and black (86.5%) versus white patients (63.5%). Greater proportions of IFNGS-high versus IFNGS-low patients had haematological (12.6% vs 4.1%), immunological (74.4% vs 45.6%) or dermal (69.7% vs 62.2%) involvement.

Conclusions We identified key characteristics of patients with high disease activity and/or elevated type I IFN signalling, populations with SLE with high unmet needs. Baseline SLEDAI-2K ≥10 was associated with shorter disease duration and more severe flares. IFNGS-high patients were younger at diagnosis and had distinct patterns of organ involvement, compared with IFNGS-low patients.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Type I interferons (IFNs) play a central role in the pathogenesis of SLE. IFN gene signature (IFNGS)-high/low subpopulations may differ with respect to SLE disease characteristics.

WHAT THIS STUDY ADDS

⇒ The Systemic Lupus Erythematosus Prospective Observational Cohort Study (SPOCS) will characterise disease activity treatment patterns, clinical outcomes, patient-reported health outcomes and healthcare resource utilisation in patients with moderate-to-severe SLE across eight countries on three continents.

⇒ Here, we describe the baseline demographic and clinical characteristics of the SPOCS cohort according to baseline disease activity and IFNGS status.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The capacity of SPOCS to generate and analyse real-world data obtained across patients with varied demographics, clinical characteristics and treatment regimens will advance our understanding of SLE and potentially inform clinical practice.

⇒ Exploring longitudinal changes according to patients' IFNGS status with well-characterised baseline disease will provide insights into disease pathogenesis and clinical outcomes.

INTRODUCTION

SLE is an autoimmune disease whose incidence has been shown to vary with sex, ethnicity and global region.[1 2] The aetiology of SLE remains incompletely understood, but genetic, immunological, hormonal and environmental factors impact the disease.[1–4] SLE can affect essentially all organ systems, including

the musculoskeletal, neurological, cardiorespiratory, renal and mucocutaneous systems; fatigue is also a prominent feature.[1] The burden of SLE is substantial, as patients with SLE have lower health-related quality of life compared with healthy controls or the general population.[1 2 5 6] Current therapies for SLE include antimalarials, glucocorticoids, immunosuppressive agents and biologics.[7 8]

Type I interferons (IFNs) play a central role in the pathogenesis and disease course of SLE.[9] Although these cytokines are produced by innate immune cells to activate the immune system and defend against viral and bacterial infections,[9] overexpression of type I IFNs occurs in patients with SLE and other autoimmune diseases,[9 10] and activation of the IFN pathway has been associated with increased SLE disease activity.[11–13] Type I IFN-inducible gene expression, measured using the IFN gene signature (IFNGS), provides a method to assess type I IFN pathway activation in individual patients.[14] IFNGS testing in patients with SLE has revealed a bimodal distribution of transcript scores,[15] suggesting that IFNGS-high and IFNGS-low subpopulations may differ with respect to SLE disease characteristics. A better understanding of these differences may reveal insights into disease pathogenesis and ultimately lead to improved clinical outcomes.

The Systemic Lupus Erythematosus Prospective Observational Cohort Study (SPOCS; NCT03189875) was designed to longitudinally analyse clinical features, disease activity, damage, treatment patterns, clinical outcomes, patient-reported health outcomes and healthcare resource utilisation in patients with moderate-to-severe SLE, according to IFNGS status.[16]

Here, we describe the baseline demographics and clinical characteristics of the SPOCS cohort overall and according to baseline disease activity (assessed using SLE Disease Activity Index-2000 (SLEDAI-2K)) and IFNGS status.

METHODS

Study design and patients

SPOCS (NCT03189875) is an international, multicentre, prospective, observational cohort of patients with moderate-to-severe SLE. Patients were enrolled from June 2017 through December 2019 and followed for up to 3 years with planned biannual study visits ending in November 2022. The study protocol has been published.[16] All treatment was based on the patient's and treating physician's decision only and not influenced by the SPOCS protocol. Demographic, clinical and laboratory data were collected from patients enrolled in eight countries in North America (Canada and USA), Europe (France, Germany, Italy, Spain and the UK) and Australia. The study was designed to be broad in enrolment. To be included in the study, patients must have been ≥18 years of age and provided written informed consent. All patients met American College of Rheumatology (ACR) or Systemic Lupus International Collaborating Clinics (SLICC) SLE classification criteria, had current or previous serology of ANA or anti-double-stranded DNA antibodies, received a minimum of 6 months of systemic treatment (beyond non-steroidal anti-inflammatory drugs and analgesics) for active SLE, and were classified as having moderate-to-severe SLE (SLEDAI-2K score ≥6 points, or modified SLEDAI-2K ≥4 points, where modified SLEDAI-2K is the SLEDAI-2K score without inclusion of points attributable to lupus headache or laboratory results included in the renal, immunological or haematology domains). While SPOCS was designed to enrol a diverse population, patients were excluded if they had active severe lupus nephritis at screening, were currently enrolled in interventional trials involving investigational agents or were unable to complete study measures. The inclusion criteria were thus similar to those of non-renal SLE trials.[17 18] Patients who developed severe active lupus nephritis or severe central nervous system disease during the study were allowed to remain in the study.

The planned sample size of 1500 patients was amended to 900 due to slow accrual of eligible patients; accordingly, using an event of interest incidence rate of 1 event per 100 person-years in a 2-year follow-up in 25% of patients, endpoint precision estimates for the incidence rate were adjusted from 1.6 (95% CI: 0.42 to 2.01) to 2.1 (0.30 to 2.44).[16]

SPOCS is being conducted in accordance with the principles of the Declaration of Helsinki and is consistent with the International Council for Harmonisation Good Clinical Practices, Good Pharmacoepidemiology Practice and applicable legislation according to the study classification in each country. All patients enrolled in SPOCS provided written informed consent.

Data collection

Data for patients enrolled in SPOCS were collected as previously described.[16] Baseline data included patient demographics (eg, age, sex and race (American Indian or Alaska Native, Asian, black or African American, Indigenous Australian, Native Hawaiian or Other Pacific Islander, white or other) or ethnicity (Hispanic or Latino, not Hispanic or Latino) as permitted by local regulations), body mass index, SLE disease characteristics including date of first diagnosis, SLEDAI-2K and modified SLEDAI-2K scores, organ system involvement and organ damage according to SLICC/ACR Damage Index (SDI) score, number and severity of SLE flares (mild/moderate or severe) according to Safety of Estrogens in Lupus National Assessment-SLEDAI Flare Index, Physician Global Assessment of disease activity, comorbidities, along with SLE treatments and concomitant medications. Blood samples were collected to determine IFNGS.

IFNGS testing

During routine blood sample collections, an additional blood sample was collected in a PAXgene tube and sent to a central laboratory for processing. Each patient's baseline mRNA expression of four type I IFN-inducible

genes (IFI27, IFI44, IFI44L and RSAD2) relative to three housekeeping genes (ACTB, 18S and GAPDH) was determined using the QIAGEN therascreen IFN-IFI gene expression Rotor-Gene Q reverse transcriptase PCR System. This expression score was compared with a pre-established cut-off to classify each patient as IFNGS-high or IFNGS-low.[14 18] Patients and physicians were not notified of the IFNGS status before the end of the study.

Statistical analysis

Demographics, clinical characteristics and SLE medications were summarised overall in the SPOCS population, and according to SLEDAI-2K categories (<10 vs ≥10), IFNGS status (high vs low) and countries. A SLEDAI-2K score of 10 has been previously identified as a threshold for high disease activity.[8 19 20] Continuous variables were reported as arithmetic mean and SD, median, first and third quartiles, and range, as appropriate. Categorical variables were summarised as number and percentages of patients with non-missing values in each category. This was a descriptive study in which patient subgroups were compared using unadjusted Mann-Whitney U test, X^2 test, Kruskal-Wallis test or Fisher's exact test. As no adjustments for multiplicity were made, all p values presented are nominal. All calculations and analyses were performed in R V.4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Patient and public involvement

No patients or members of the public were involved in the design of this trial.

RESULTS

Baseline patient characteristics

Between June 2017 and December 2019, 1050 patients were screened; 823 patients were enrolled from North America (n=389) and Europe or Australia (n=434). Most enrolled patients (93.2%, 767 of 823) were female, and the mean (SD) age at study entry was 45.3 (13.9) years (table 1). Overall, 9.1% (71 of 779) of enrolled patients were Asian, 16.4% (128 of 779) were black, 69.5% (541 of 779) were white and 5.0% (39 of 779) of patients identified with a different race. The mean (SD) years since

Table 1 Baseline demographics and patient characteristics of the SPOCS population by SLEDAI-2K and IFNGS category

		SLEDAI-2K			IFNGS		
	Overall (N=823)	<10 (n=343)	≥10 (n=241)	Nominal p value	High (n=522)	Low (n=217)	Nominal p value
Age, years	n=823	n=343	n=241	0.001	n=522	n=217	<0.001
Mean±SD	45.3±13.9	46.6±14.2	42.8±13.7		43.1±13.6	50.7±12.9	
Median (IQR)	45.0 (34.0–55.0)	47.0 (36.0–57.0)	41.0 (33.0–51.0)		42.0 (32.0–54.0)	51.0 (42.0–59.0)	
Age >40 years, n (%)	503 (61.1)	229 (66.8)	121 (50.2)	<0.001	283 (54.2)	168 (77.4)	<0.001
Male, n (%)	56 (6.8)	28 (8.1)	14 (5.8)	0.278	33 (6.3)	15 (6.9)	0.767
Race, n (%)	n=779	n=321	n=229	0.892	n=483	n=213	<0.001
Asian	71 (9.1)	34 (10.6)	20 (8.7)		50 (10.4)	10 (4.7)	
Black	128 (16.4)	53 (16.5)	39 (17.0)		96 (19.9)	15 (7.0)	
White	541 (69.5)	217 (67.6)	159 (69.4)		311 (64.4)	179 (84.0)	
Other	39 (5.0)	17 (5.3)	11 (4.8)		26 (5.4)	9 (4.2)	
Ethnicity, n (%)	n=722	n=279	n=217		n=449	n=196	
Hispanic or Latino	113 (15.7)	49 (17.6)	36 (16.6)	0.776	87 (19.4)	20 (10.2)	0.004
BMI kg/m^2	n=727	n=297	n=221	0.017	n=458	n=195	<0.001
Mean±SD	27.1±6.8	27.5±7.1	26.1±6.5		26.6±6.5	29.0±7.3	
Median (IQR)	26.1 (22.0–30.8)	26.3 (22.3–31.1)	24.9 (21.0–29.3)		25.4 (21.8–29.8)	27.8 (23.5–32.7)	
BMI category, n (%)	n=727	n=298	n=221	0.190	n=458	n=195	0.005
Underweight	33 (4.5)	16 (5.4)	15 (6.8)		25 (5.5)	4 (2.1)	
Normal	284 (39.1)	106 (35.7)	96 (43.4)		186 (40.6)	63 (32.3)	
Overweight	212 (29.2)	88 (29.6)	60 (27.2)		136 (29.7)	58 (29.7)	
Obese	198 (27.2)	87 (29.3)	50 (22.6)		111 (24.2)	70 (35.9)	

All p values are nominal; there have been no adjustments for multiplicity. Subgroups do not total overall population n due to missing data.
BMI, body mass index; IFNGS, type I interferon gene signature; SLEDAI-2K, SLE Disease Activity Index-2000; SPOCS, SLE Prospective Observational Cohort Study.

Table 2 Clinical characteristics of the SPOCS population at baseline, by SLEDAI-2K and IFNGS category

		SLEDAI-2K			IFNGS		
	Overall (N=823)	<10 (n=343)	≥10 (n=241)	Nominal p value	High (n=522)	Low (n=217)	Nominal p value
Years since diagnosis of SLE	n=814	n=340	n=238	0.012	n=517	n=215	0.052
Mean±SD	11.1±9.2	12.4±9.6	10.4±8.6		11.7±9.6	10.2±8.6	
Median (IQR)	9.0 (4.0–17.0)	10.0 (5.0–19.0)	8.0 (3.0–17.0)		9.0 (4.0–18.0)	8.0 (3.0–16.0)	
Age at SLE first manifestation, years	n=732	n=309	n=223	0.522	n=473	n=186	<0.001
Mean±SD	32.0±13.9	31.6±13.9	30.8±13.4		30.0±12.7	36.8±14.6	
Median (IQR)	30.0 (22.0–41.0)	30.0 (20.2–42.0)	29.0 (22.0–37.0)		28.0 (21.0–37.0)	37.5 (25.5–47.0)	
Age at SLE first manifestation, years, n (%)	n=732	n=309	n=223	0.548	n=473	n=186	<0.0001
<18	105 (14.3)	52 (16.8)	30 (13.5)		73 (15.4)	17 (9.1)	
18–29	245 (33.5)	101 (32.7)	83 (37.2)		181 (38.3)	43 (23.1)	
30–49	297 (40.6)	123 (39.8)	90 (40.4)		182 (38.5)	89 (47.9)	
50+	85 (11.6)	33 (10.7)	20 (9.0)		37 (7.8)	37 (19.9)	
SLE diagnosis age, years, n (%)	n=815	n=341	n=238	0.297	n=517	n=216	<0.001
<18	114 (14.0)	57 (16.7)	32 (13.5)		81 (15.7)	18 (8.3)	
18–29	231 (28.3)	91 (26.7)	77 (32.4)		180 (34.8)	31 (14.4)	
30–49	350 (42.9)	144 (42.2)	103 (43.3)		206 (39.8)	112 (51.9)	
50+	120 (14.7)	49 (14.4)	26 (10.9)		50 (9.7)	55 (25.5)	
SLEDAI-2K	n=584	n=343	n=241	<0.001	n=386	n=135	0.101
Mean±SD	9.8±4.6	6.8±1.3	13.9±4.5		9.8±4.3	9.1±4.9	
Median (IQR)	8.0 (6.0–12.0)	7.0 (6.0–8.0)	12.0 (10.0–16.0)		8.0 (6.0–12.0)	8.0 (6.0–10.0)	
SLEDAI-2K ≥10, n (%)	241 (41.3)	0 (0.0)	241 (100.0)	<0.001	164 (42.5)	45 (33.3)	0.062
Modified SLEDAI-2K*	n=817	n=343	n=241	<0.001	n=519	n=217	0.174
Mean±SD	6.5±3.4	4.8±1.9	8.5±4.2		6.2±3.2	6.6±3.4	
Median (IQR)	6.0 (4.0–8.0)	4.0 (4.0–6.0)	8.0 (6.0–10.0)		6.0 (4.0–8.0)	6.0 (4.0–8.0)	
Physician Global Assessment	n=820	n=340	n=241	<0.001	n=520	n=217	0.127
Mean±SD	1.5±0.6)	1.4 (0.6)	1.7 (0.6)		1.5 (0.6)	1.5 (0.6)	
Median (IQR)	1.5 (1.1–2.0)	1.4 (1.0–2.0)	1.9 (1.3–2.0)		1.5 (1.1–2.0)	1.5 (1.0–2.0)	
SDI total score	n=811	n=336	n=237	0.100	n=512	n=217	0.181
Mean±SD	1.2±1.6	1.1±1.4	1.3±1.7		1.1±1.6	1.3±1.6	
Median (IQR)	1.0 (0.0–2.0)	0.5 (0.0–2.0)	1.0 (0.0–2.0)		0.0 (0.0–2.0)	1.0 (0.0–2.0)	
SDI group, n (%)				0.599			0.135
0	386 (47.6)	168 (50.0)	109 (46.0)		258 (50.4)	92 (42.4)	
1	190 (23.4)	70 (20.8)	56 (23.6)		116 (22.7)	55 (25.3)	
2+	235 (29.0)	98 (29.2)	72 (30.4)		138 (27.0)	70 (32.3)	
Any organ damage†, n (%)	425 (52.4)	168 (50.0)	128 (54.0)	0.344	254 (49.6)	125 (57.6)	0.048
Annualised flare rate‡	n=822	n=343	n=241	0.005	n=522	n=216	0.666
Mean±SD	1.5±2.2	1.3±2.0	1.9±2.4		1.5±2.2	1.6±2.4	
Median (IQR)	2.0 (0.0–2.0)	2.0 (0.0–2.1)	2.0 (0.0–2.0)		2.0 (0.0–2.0)	2.0 (0.0–2.0)	
≥1 flare§, n (%)	445 (54.1)	175 (51.0)	155 (64.3)	0.001	287 (55.0)	113 (52.3)	0.508
≥1 mild flare§, n (%)	187 (22.8)	95 (27.7)	43 (17.8)	0.006	124 (23.8)	44 (20.4)	0.318

Continued

Table 2 Continued

		SLEDAI-2K			IFNGS		
	Overall (N=823)	<10 (n=343)	≥10 (n=241)	Nominal p value	High (n=522)	Low (n=217)	Nominal p value
≥1 moderate flare§, n (%)	155 (18.9)	62 (18.1)	59 (24.5)	0.060	93 (17.8)	42 (19.4)	0.603
≥1 severe flare§, n (%)	64 (7.8)	18 (5.3)	31 (12.9)	0.001	35 (6.7)	22 (10.2)	0.107
Conditions or comorbidities, n (%)	n=822	n=342	n=241		n=522	n=217	
Any comorbidity	687/823 (83.5)	273/343 (79.6)	205 (85.1)	0.091	426 (81.6)	192 (88.5)	0.022
Joint disease (SLE/non-SLE)	514 (62.5)	201 (58.8)	159 (66.0)	0.078	306 (58.6)	157 (72.4)	<0.001
CVD/stroke risk factors	276 (33.6)	102 (29.8)	74 (30.7)	0.820	160 (30.7)	92 (42.4)	0.002
Cancer	47 (5.7)	23 (6.7)	12 (5.0)	0.382	27 (5.2)	15 (6.9)	0.352
Renal disease (ESRD)	96 (11.7)	43 (12.6)	30 (12.5)	0.964	74 (14.2)	14 (6.5)	0.003
CNS disorders	86 (10.5)	24 (7.0)	34 (14.1)	0.005	51 (9.8)	26 (12.0)	0.370
Diabetes mellitus (all)	63 (7.7)	31 (9.1)	14 (5.8)	0.147	32 (6.1)	28 (12.9)	0.002
Metabolic syndrome	20 (2.4)	8 (2.3)	6 (2.5)	0.907	6 (1.1)	13 (6.0)	<0.001
Family history of autoimmune disease	224/805 (27.7)	91/327 (27.8)	72/239 (30.1)	0.551	148/510 (29.0)	59/213 (27.7)	0.720

All p values are nominal; there have been no adjustments for multiplicity. Subgroups do not total overall population n due to missing data.
*Modified SLEDAI-2K score was defined as the SLEDAI-2K assessment score without the inclusion of points attributable to lupus headache or laboratory results included in the renal, immunological or haematology domains.
†SDI >0.
‡The annualised flare rate is calculated by dividing the number of flares by the follow-up time in days and multiplying by 365.25.
§Physician-reported flares within 6 months of study entry.
ACR, American College of Rheumatology; CNS, central nervous system; CVD, cardiovascular disease; ESRD, end-stage renal disease; IFNGS, type I interferon gene signature; SDI, SLICC/ACR Damage Index; SLEDAI-2K, SLE Disease Activity Index-2000; SLICC, Systemic Lupus International Collaborating Clinics; SPOCS, SLE Prospective Observational Cohort Study.

SLE diagnosis was 11.1 (9.2) years (table 2). At baseline, 80.4% (662 of 823) of patients were receiving an antimalarial agent, 53.8% (443 of 823) were receiving immunosuppressants and 20.2% (166 of 823) were receiving biologics (table 3). Oral glucocorticoids were in use or used in the past year by 61.5% (506 of 823) of patients.

When stratified by baseline disease activity scores, 241 patients had SLEDAI-2K scores ≥10 and 343 had SLEDAI-2K <10. Patients with a SLEDAI-2K score ≥10 vs <10 were younger (mean (SD): 42.8 (13.7) years vs 46.6 (14.2) years; nominal p=0.001) (table 1). No difference in mean age at SLE first manifestation was observed between patients with a SLEDAI-2K ≥10 vs <10 (table 2). Race distribution was similar in patients with a baseline SLEDAI-2K ≥10 vs a SLEDAI-2K <10 (white: 69.4% (159 of 229) vs 67.6% (217 of 321), black: 17.0% (39 of 229) vs 16.5% (53 of 321) and Asian: 8.7% (20 of 229) vs 10.6% (34 of 321); nominal p=0.89) (table 1). At baseline, the mean (SD) duration of SLE was shorter in patients with a SLEDAI-2K ≥10 vs a SLEDAI-2K <10 (10.4 (8.6) years vs 12.4 (9.6) years; nominal p=0.012) (table 2).

Among the patients receiving oral glucocorticoids, mean cumulative and daily doses were similar regardless of SLEDAI-2K category and there were no differences in any other baseline treatments between the baseline SLEDAI-2K groups (all nominal p≥0.5) (table 3).

Approximately two-thirds of patients had IFNGS-high status, while one-third was IFNGS-low (70.6% (522 of 739) vs 29.4% (217 of 739)) (table 1). The proportions of patients of each race differed across IFNGS categories (p<0.001). The relative proportions of patients who were IFNGS-high were higher among Asian (83.3% (50 of 60)) and black patients (86.5% (96 of 111)) compared with white patients (63.5% (311 of 490)). The percentage of IFNGS-high patients ranged from 64% to 83% across countries (figure 1). Overall baseline data by country are provided in the online supplemental tables 1 and 2. The IFNGS-high group was younger than the IFNGS-low group (mean (SD) age: 43.1 (13.6) years vs 50.7 (12.9) years; nominal p<0.001) (table 1). A greater percentage of patients in the IFNGS-high group were <30 years of age at SLE diagnosis compared with the IFNGS-low group (50.5% vs 22.7%) (table 2). Patients in the IFNGS-high group were younger at SLE first manifestation than those in the IFNGS-low group (mean (SD): 30.0 (12.7) years vs 36.8 (14.6) years; nominal p<0.001), with 53.7% of

Table 3 SLE medications in the SPOCS population at baseline, by SLEDAI-2K and IFNGS category

		SLEDAI-2K			IFNGS		
	Overall (N=823)	<10 (n=343)	≥10 (n=241)	Nominal p value	High (n=522)	Low (n=217)	Nominal p value
Number of medication classes (±AM)	n=823	n=343	n=241	0.777	n=522	n=217	<0.001
Mean±SD	1.3±0.8	1.3±0.8	1.3±0.8		1.4±0.8	1.1±0.8	
Median (IQR)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)		1.0 (1.0–2.0)	1.0 (0.0–2.0)	
Level of therapy, n (%)				0.920			<0.001
None (±AM)	139 (16.9)	61 (17.8)	38 (15.8)		71 (13.6)	55 (25.3)	
Monotherapy (±AM)	323 (39.3)	131 (38.2)	97 (40.3)		196 (37.5)	93 (42.9)	
Dual (±AM)	313 (38.0)	131 (38.2)	92 (38.2)		218 (41.8)	61 (28.1)	
Triple (±AM)	48 (5.8)	20 (5.8)	14 (5.8)		37 (7.1)	8 (3.7)	
AMs, n (%)	662 (80.4)	277 (80.8)	193 (80.1)	0.839	407 (78.0)	189 (87.1)	0.004
Immunosuppressants*, n (%)	443 (53.8)	187 (54.5)	137 (56.9)	0.577	303 (58.0)	95 (43.8)	<0.001
Biologics†, n (%)	166 (20.2)	64 (18.7)	40 (16.6)	0.522	99 (19.0)	45 (20.7)	0.580
Glucocorticoids‡	506 (61.5%)	211 (61.5%)	155 (64.3%)	0.491	354 (67.8%)	107 (49.3%)	<0.001
Cumulative glucocorticoids§, g	n=491	n=204	n=148	0.613	n=344	n=104	0.665
Mean±SD	2.5±3.1	2.7±3.2	2.5±3.0		2.5±3.1	2.3±2.9	
Total glucocorticoids¶, mg/day				0.613			0.665
Mean±SD	6.8±8.5	7.3±8.9	6.8±8.2		6.8±8.5	6.4±7.8	
Cumulative glucocorticoids§, g (including 0 mg)	n=808	n=336	n=234	0.863	n=512	n=214	0.014
Mean±SD	1.5±2.7	1.6±2.8	1.6±2.7		1.7±2.8	1.1±2.3	
Total glucocorticoids¶, mg/day (including 0 mg)				0.863			0.014
Mean±SD	4.1±7.4	4.4±7.8	4.3±7.3		4.6±7.7	3.1±6.3	
Total glucocorticoids daily dose¶, n (%)				0.829			<0.001
No glucocorticoids	317 (39.2)	132 (39.3)	86 (36.8)		168 (32.8)	110 (51.4)	
Dose ≤7.5 mg	353 (43.7)	142 (42.3)	103 (44.0)		248 (48.4)	73 (34.1)	
Dose >7.5 mg	138 (17.1)	62 (18.5)	45 (19.2)		96 (18.8)	31 (14.5)	

All p values are nominal; there have been no adjustments for multiplicity. Subgroups do not total overall population n due to missing data.
*Cytotoxic or immunosuppressive agents included cyclophosphamide, methotrexate, mycophenolate mofetil/mycophenolic acid, azathioprine, tacrolimus, mizoribine, leflunomide or ciclosporin.
†Belimumab or rituximab.
‡Number of patients with at least one ongoing glucocorticoid prescription or at least one prescription recorded in the previous year.
§The sum of all glucocorticoids received in the past 365 days, standardised to g/year.
¶Cumulative glucocorticoids divided by 365 to convert to daily dose and group patients into daily dose groups.
AM, antimalarial; IFNGS, type I interferon gene signature; SLEDAI-2K, SLE Disease Activity Index-2000; SPOCS, SLE Prospective Observational Cohort Study.

patients <30 years of age at first manifestation, compared with 32.3% of the IFNGS-low group.

More patients categorised as IFNGS-high versus IFNGS-low received immunosuppressants (58.0% (303 of 522) vs 43.8% (95 of 217); nominal p<0.001) and oral glucocorticoids (67.8% (354 of 522) vs 49.3% (107 of 217); nominal p<0.001), whereas fewer patients in the IFNGS-high versus IFNGS-low group received antimalarials (78.0% (407 of 522) vs 87.1% (189 of 217); nominal p=0.004) (table 3). Higher percentages of patients in the IFNGS-high versus IFNGS-low group were receiving immunosuppressants, regardless of concurrent antimalarial use (online supplemental table 4).

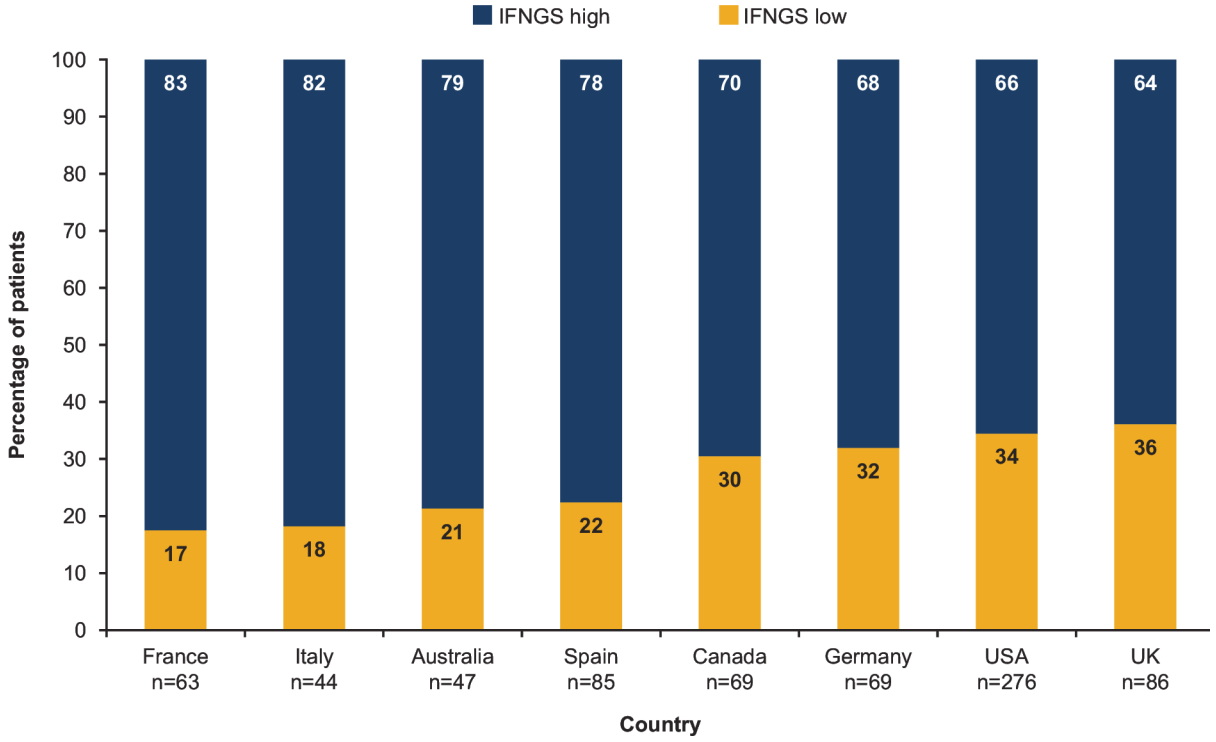

Figure 1 IFNGS status by country at baseline. The number of patients categorised as IFNGS-low and IFNGS-high is presented by country, with countries presented in order from smallest to largest percentage of IFNGS-low patients. IFNGS, type I interferon gene signature.

Baseline SLE disease activity and damage

In the overall SPOCS cohort, patients most often had musculoskeletal (75.3%), dermal (67.6%) or immunological (66.4%) organ system involvement at baseline (online supplemental figure 1A). The mean (SD) SLEDAI-2K score was 9.8 (4.6) and median (IQR: 25th–75th percentile) score was 8.0 (6.0–12.0) (table 2).

On average, modified SLEDAI-2K scores, SLEDAI-2K scores and the percentage of patients with SLEDAI-2K scores ≥10 were not different between IFNGS-high and IFNGS-low patients. More patients in the IFNGS-high group had haematological (12.6% vs 4.1%), immunological (74.4% vs 45.6%) or dermal (69.7% vs 62.2%) SLEDAI-2K domain involvement than in the IFNGS-low group (all nominal p<0.05) (figure 2). Conversely, fewer IFNGS-high patients had central nervous system (5.8% vs 11.1%; nominal p=0.012) and musculoskeletal (72.6% vs 81.6%; nominal p=0.010) involvement than patients in the IFNGS-low group. Renal involvement among patients in the IFNGS-high group was 20.2% vs 16.3% in the IFNGS-low group (nominal p=0.299).

The mean (SD) SDI score was 1.2 (1.6), and approximately half of all patients had organ damage (52.4%, 425 of 811) at baseline (table 2). The proportion of patients with any organ damage was greater in the IFNGS-low group (57.6%) versus the IFNGS-high group (49.6%; nominal p=0.048); the difference in the presence of organ damage between the IFNGS groups was not affected by years since SLE diagnosis (≤5 or >5 years; nominal p=0.3896).

Flares

Approximately half of all patients (54.1%, 445 of 822) had experienced ≥1 flare within the 6 months prior to the baseline visit (table 2); organ system involvement was generally similar between those who had and had not experienced flare (online supplemental figure 1B). Compared with patients with baseline SLEDAI-2K scores <10, those with SLEDAI-2K scores ≥10 had higher mean (SD) annualised flare rate in the year before enrolment (1.9 (2.4) vs 1.3 (2.0), nominal p=0.005) and severe flares were more common (12.9% vs 5.3%; p=0.001) (table 2). In contrast, the IFNGS groups did not differ in the percentages of patients who experienced ≥1 flare in the 6 months prior to baseline visit (IFNGS-high vs IFNGS-low: 55.0%, 287 of 522 vs 52.3%, 113 of 216), their greatest flare severity (IFNGS-high vs IFNGS-low: mild, 23.8%, 124 of 522 vs 20.4%, 44 of 216; moderate, 17.8%, 93 of 522 vs 19.4%, 42 of 216; severe, 6.7%, 35 of 522 vs 10.2%, 22 of 216) or in annualised flare rates (mean (SD), IFNGS-high vs IFNGS-low: 1.5 (2.2) vs 1.6 (2.4)) (nominal p=NS for all).

DISCUSSION

SPOCS is a prospective, observational study designed to analyse clinical outcomes over time of a large, real-world cohort of patients with moderate-to-severe SLE. Overall, this study identified substantial clinical burden in a broadly representative group of patients with moderate-to-severe SLE in a real-world setting, including long disease

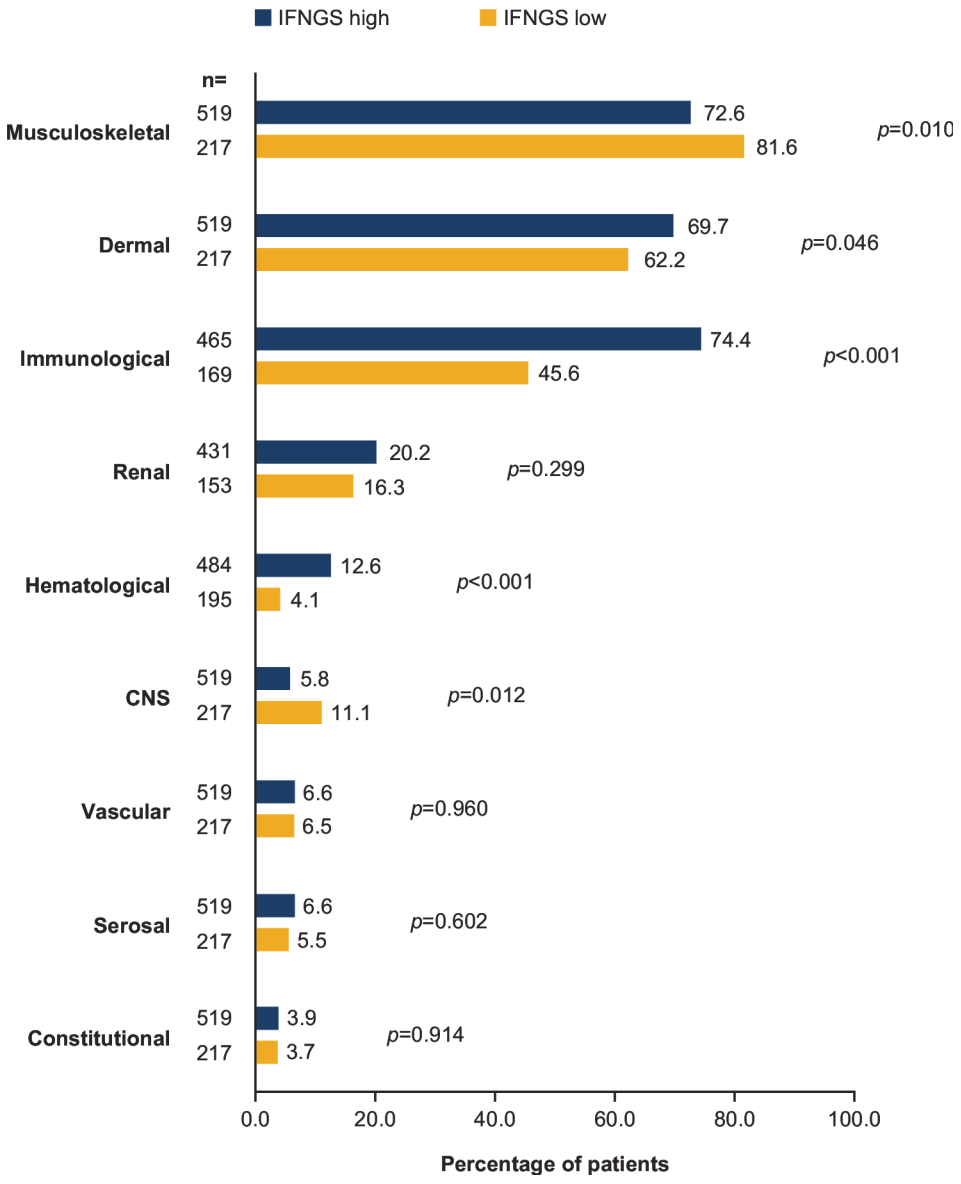

Figure 2 Baseline clinical manifestations by organ system involvement in the SPOCS population by IFNGS. All p values are nominal; there have been no adjustments for multiplicity. CNS, central nervous system; IFNGS, type I interferon gene signature; SPOCS, SLE Prospective Observational Cohort Study.

duration and presence of organ damage in more than half of patients. Additionally, we characterised patients with high disease activity and those with elevated IFN signalling according to IFNGS-high status to gain insight into two subgroups of patients with higher medical needs.

Patients with higher SLE disease activity tend to experience greater clinical, social and economic burdens than those with low disease activity.[6 21 22] In the SPOCS SLE cohort, approximately 41% of patients had high disease activity (SLEDAI-2K scores ≥10[8 19 20]) at baseline. Patients with SLEDAI-2K ≥10 were younger and had shorter SLE duration than those with SLEDAI-2K <10. At baseline, SPOCS patients with higher baseline SLEDAI-2K scores experienced more flares and more severe flares than patients with lower baseline scores, consistent with other real-world studies.[23] Of note, there were no differences in therapies between the baseline SLEDAI-2K groups.

Baseline IFNGS status was associated with differences in patient characteristics. Patients in the IFNGS-high group tended to be younger at SLE first manifestation than those in the IFNGS-low group, with the percentage of patients in the IFNGS-high group under 30 years old at SLE diagnosis being twice that of the IFNGS-low group. Conversely, the IFNGS-low group had twice the proportion of patients with 'late-onset' SLE (ie, patients diagnosed with SLE at ≥50 years old). Age of onset, here identified as 'age of SLE diagnosis', has been associated with differences in clinical outcomes and disease progression. For example, late-onset SLE less frequently presents with organ-specific manifestations and tends to be more indolent.[24]

In addition to age, the IFNGS subgroups also differed according to organ involvement, as IFNGS-high patients were more likely to have haematological, immunological

and dermal involvement than IFNGS-low patients. Haematological manifestations are common in patients with SLE and include abnormalities in blood cell counts.[25] Blood cell counts have been shown to associate with IFNGS status and disease activity[26] and can impact patient outcomes. For example, low lymphocyte count and lymphopenia are associated with damage accrual and glucocorticoid use in patients with SLE.[27 28]

Conversely, we identified less musculoskeletal involvement in IFNGS-high versus IFNGS-low patients in our real-world study; similar findings were identified in IFNGS-high versus IFNGS-low patients with moderate-to-severe SLE in a clinical trial setting.[29] Slightly more IFNGS-low versus IFNGS-high patients had organ damage according to SDI in our study, which is likely a function of the older age of the IFNGS-low patients, as evidenced by their more frequent comorbidities. More patients in the IFNGS-high group than in the IFNGS-low group received immunosuppressants and/or oral glucocorticoids, consistent with more severe disease overall in this subset of patients.

Notably, the relative proportions of patients who were IFNGS-high versus IFNGS-low were higher among black and Asian patients compared with white patients, which supports findings in other populations with moderate-to-severe SLE.[29] Three of the four genes included in the SPOCS IFNGS assay (IFI27, IFI44L and RSAD2) have been associated with African ancestry[30]; in the same meta-analysis (which adjusted for the presence of lupus nephritis and hydroxychloroquine use), only IFI27 expression was associated with disease activity.[30] Knowledge of IFNGS status and detailed baseline disease information could aid in understanding the contribution of genetic versus environmental factors driving differences in SLE disease incidence among patients of different ethnicities.

While SPOCS was designed to be broad in enrolment, the exclusion of patients with active lupus nephritis at screening may have reduced the baseline levels of kidney involvement in this population compared with unselected populations with SLE and is a limitation of the study. Similarly, the recruitment of only patients with moderate-to-severe SLE disease activity at baseline may limit generalisability of our results to this specific population with SLE and may have concealed other differences in clinical activity between IFNGS-high and IFNGS-low populations. Furthermore, although a SLEDAI-2K score of 10 was previously identified as a threshold for high disease activity,[8 19] severe involvement of single or even multiple domains may not yield an overall score that exceeds this threshold, and so some patients with severe organ involvement would not be captured as having high disease activity. Differences in the baseline characteristics of disease activity and IFNGS subgroups in the SPOCS cohort were analysed descriptively, which is a limitation of this study.

In conclusion, this descriptive analysis confirms that there are distinct baseline characteristics according to disease activity and IFNGS status. As longitudinal outcomes are analysed in this study in the future, this will allow for a powerful investigation of how different baseline characteristics, including IFNGS levels, impact longitudinal outcomes in patients with SLE being treated in the real-world setting.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study involves human participants and the committee/institutional review board/independent ethics committee at each study site approved the SPOCS protocol prior to study initiation (protocol number: D3461R00001, V.3.0, 26 June 2019). Participants gave informed consent to participate in the study before taking part.

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