Real-world impact of flaring on patient-reported outcomes and healthcare resource utilisation in systemic lupus erythematosus

K.H. Costenbader[1], B. Hoskin[2], C. Atkinson[2], D. Bell[2], J. Pike[2], J.H. Lofland[3], P. Berry[3], C.S. Karyekar[3], Z. Touma[4]

[1]Brigham and Women's Hospital, Boston, MA, USA; [2]Adelphi Real World, Bollington, UK; [3]Global Commercial Strategy Organisation, Janssen, Horsham, PA, USA; [4]University of Toronto, Toronto, Canada.

Abstract

Objective

We investigated the association of SLE flares with patient-reported outcomes (PRO) and healthcare resource utilisation (HCRU) using real-world data.

Methods

Rheumatologists from the USA, France, Germany, Spain, Italy provided demographic, clinical, and HCRU data for patients with SLE, who provided PRO data. "Flaring" was defined as ≥1 rheumatologist-reported flare in the past 12 months. Demographic/clinical data were analysed descriptively, and findings compared statistically by flaring status. Logistic regression estimated a propensity score for flaring based on ethnicity, disease duration, and severity at diagnosis. Propensity score-matched flaring and non-flaring patients were compared for their HCRU, PROs, income loss and treatment satisfaction.

Results

Physicians (n=263) provided data for 1,278 patients (408 flaring/870 non-flaring); 729 patients (241 flaring/488 non-flaring) provided matched patient data. Patients had a mean 2.1 flares in the previous 12 months. Propensity score matched analyses indicated worse outcomes and greater HCRU in the past 12 months in flaring than non-flaring patients: EuroQoL 5D-3L Utility Index: 0.72 vs. 0.83; Functional Assessment of Chronic Illness Therapy-Fatigue scale: 30.06 vs. 36.48; Work Productivity and Activity Impairment Index: absenteeism 5.87% vs. 2.53% / presenteeism 33.44% vs. 19.16% / overall work impairment 35.98% vs. 20.66% / total activity impairment 42.47% vs. 30.23%; healthcare consultations (8.10 vs. 6.41), hospitalisations (24.26 vs. 7.63), emergency department visits (20.83 vs. 4.19), tests (46.59 vs. 38.90); current medications (2.76 vs. 2.19) (all p<0.001 except absenteeism, p=0.004).

Conclusion

Similar flaring SLE patients had worse PROs and higher HCRU than non-flaring patients, underscoring the need for more effective strategies and treatments to alleviate or prevent flaring.

Key words

flares, healthcare resource utilisation, lupus, patient-reported outcomes, real-world, systemic lupus erythematosus, unmet need

Karen H. Costenbader, MD, MPH
Ben Hoskin, MSc
Christian Atkinson, MRes
David Bell, BSc
James Pike, BSc, MPhil
Jennifer H. Lofland, PharmD, PhD, MPH
Pamela Berry, MSc
Chetan S. Karyekar, MD
Zahi Touma, MD, PhD

Please address correspondence to:
Ben Hoskin,
Adelphi Real World,
Adelphi Mill,
Grimshaw Lane,
Bollington SK10 5JB,
United Kingdom.
E-mail: ben.hoskin@adelphigroup.com

Received on July 7, 2021; accepted in revised form on November 15, 2021.

Funding: this study was funded by Janssen.

Competing interests: K.H. Costenbader collaborated with Janssen employees on this study, has acted as a consultant for AstraZeneca and Neutrolis, and has research collaborations with GlaxoSmithKline, Lilly, Exagen Diagnostics and Merck.
Z. Touma collaborated with Janssen employees on this study, has acted as a consultant for AstraZeneca, Biogen IDEC, EMD Serono, Pfizer Inc., GlaxoSmithKline, Janssen Inc., UCB, Eli Lilly and Sarkana Pharma.
P. Berry and C. Karyekar are full time employees and shareholders of Janssen Global Services LLC.
J. Lofland is a former employee of Janssen.
B. Hoskin, C. Atkinson and D. Bell are employed by Adelphi Real World.

Introduction

Systemic lupus erythematosus (SLE) is a disabling autoimmune disease in which autoantibodies are directed against nuclear antigens in various body organs (1, 2). In the USA and Europe, the incidence of SLE has been reported to range from 3 to 32 per 100,000 and the prevalence from 43 to 518 per 100,000, with incidence and prevalence higher in non-White than White individuals, and in women than in men (3–9). The mean age at diagnosis of SLE has been estimated to be 39–40 years (3–5). SLE is therefore common in women of childbearing age and has the potential to have major humanistic and economic impacts, with patients with greater disease severity and flares having a higher reported total medical cost (10).

The disease course of SLE includes unpredictable disease flares, in which a period of increased disease activity is followed by a return to pre-flare disease severity (11). The pathogenesis of SLE is not well understood, although environmental factors including ultraviolet light, infections, certain hormones, and drugs that affect the immune system, as well as medication non-adherence, may trigger flares, they often occur with no obvious cause (12, 13). Flares can lead to substantial organ damage (11) with consequent increased morbidity and mortality (14). Although prevention of flaring is a treatment goal recommended in SLE clinical guidelines (15, 16), current treatments have limited efficacy in preventing flaring (17). Maintenance treatment with immunosuppressive drugs and biologics, minimisation of medication non-adherence, and short-term use of glucocorticoid 'pulses' are the available treatment options (18, 19).

Studies from Hong Kong and Canada have shown an association of flaring with reduced health-related quality of life (HRQoL) (20) and increased healthcare resource utilisation (HCRU) and healthcare costs (21, 22). However, there are limited international real-world studies on the impact of flaring in SLE on patient-reported outcomes (PRO), HCRU and income. The objective of the current study was to investigate the association of flaring with health status, fatigue severity and its impact, work productivity and activity impairment, HCRU and income, using real world data from SLE patients and their physicians in the USA and Europe.

Materials and methods

Study design and data collection

The data were from the 2015 Adelphi Real World Lupus Disease Specific Programme™ (DSP), collected in the USA and Europe. The Lupus DSP is a real-world, non-interventional, point-in-time survey of rheumatologists and their patients with SLE, capturing current and historical data on patients' disease status and management, in a real-world clinical setting. A combination of physician- and patient-reported questionnaires was used to understand flaring status and how this impacted QoL from the patient's perspective, the full DSP methodology has been published and validated previously (23).

Rheumatologists from a broad geographical area in the USA and five European countries (France, Germany, Spain, Italy and the UK) were identified from publicly available lists and invited to participate in the DSP™ if they were actively managing patients with SLE and saw ≥5 patients with SLE in a typical month, with rheumatologists in our study cohort seeing a mean of 24.9 patients per month and managing a mean of 84.2 patients in total. After enrolling in the study, a total of 263 participating rheumatologists completed a patient record form for five consecutively consulting patients who were aged ≥18 years with SLE and not already taking part in a clinical trial on lupus. Data recorded on the form included patient diagnosis, demographic and clinical characteristics, SLE management history including treatment, healthcare utilisation during the 12 months prior to data collection (healthcare professional [HCP] consultations, hospitalisations, emergency department [ER] visits and number of tests to aid in the management of the patient's SLE), and satisfaction with current lupus medication. Information was obtained retrospectively by the rheumatologists through review of patients' medical records. Physician-completed data included a global as-

sessment of SLE disease activity (mild, moderate or severe) and satisfaction with lupus medications. Satisfaction was assessed by asking, 'Overall, how satisfied are you with this patient's current lupus medications?'; response options were: 'Very dissatisfied', 'Dissatisfied', 'Somewhat dissatisfied', 'Neither satisfied nor dissatisfied', 'Somewhat satisfied', 'Satisfied' 'Very satisfied'.

Patients for whom physicians completed a record form were invited by their physician to complete a patient self-completion form. The patient form included validated PRO questionnaires and patient satisfaction with lupus medications.

Patient HCRU was measured by the number of hospitalisations and visits to the rheumatologist and/or emergency department, within the last 12 months, these visits could be in relation to any aspect of their SLE and did not have to specifically concern a flare.

The PRO questionnaires included the three-level European Quality of Life questionnaire (EQ-5D-3L), a widely used generic measure of health status (24, 25) which includes a descriptive section assessing health in five dimensions (Mobility, Self-care, Usual Activities, Pain / Discomfort, and Anxiety / Depression), with three response levels (no problems, some problems, extreme problems / unable to do). Application of country-specific scoring algorithms result in a single health utility index, with a value of 1 indicating perfect health, a value of 0 indicating death, and a value of <0 indicating a health state worse than death (26, 27).

The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale assesses fatigue and its impact on daily activities and functioning in chronic disease (28, 29). The questionnaire includes 13 items such as tiredness, weakness, lack of energy, and the impact of these on daily functioning (*e.g.* sleeping, and social activities). The instrument uses a 5-point Likert response scale ranging from 0 (not at all) to 4 ("very much"). Each FACIT item is scored between 0 and 4 and all items contribute equally to the sum score. The worst possible sum score is 0 and the best possible score is 52, indicating no fatigue. The content validity and psychometric properties of the FACIT-fatigue scale have been established in numerous chronic conditions, including SLE (30–32).

The Work Productivity and Activity Impairment in Lupus questionnaire (WPAI-Lupus) assesses the impact of lupus on work productivity and activity impairment over the past 7 days (33). The questionnaire comprises six items, and provides scores for absenteeism, presenteeism, overall work impairment, and total activity impairment, each expressed as a percentage of work time missed or impairment.

Patient satisfaction was assessed by asking, 'Overall, how satisfied are you with your current lupus medications?' with seven levels of response ranging from *'Very dissatisfied' to 'Very satisfied'*.

The Disease Specific Programme (DSP) was conducted in accordance with the European Pharmaceutical Market Research Association (EphMRA) code of conduct, and as such, it did not require ethical review. All responses captured on the data collection forms were anonymised to preserve physician and patient confidentiality and therefore no personal identifiable information was collected. Patients provided informed consent for use of their anonymised and aggregated data for research.

Statistical analysis

Flares and disease severity and progression were defined based on the clinical judgement of the managing rheumatologists rather than according to a list of prescriptive criteria, and therefore reflect how physicians identify, classify and manage flares and disease progression in their SLE patients in a real-world clinical setting (23). Patients were considered as flaring if their rheumatologist reported that they had experienced ≥1 flare in the previous 12 months, and as not flaring if they had experienced no flares in the previous 12 months.

Descriptive analyses of patient demographics and clinical characteristics were performed for the total study population and stratified by flaring status. Means and standard deviations were calculated for continuous variables, and frequency counts and percentages for categorical variables. Results were compared using χ^2 tests for categorical variables, Fisher's exact test for 2-by-2 categorical variables, and t-tests for numeric variables.

To calculate the impact of flaring on income, each patient was assigned an appropriate salary (in US dollars for consistency) based on their country and age, and on their sex for patients from USA, Germany and the UK (salary information split by sex was not available for France, Italy or Spain) (34–39). Loss of income was calculated for each patient as the product of salary and patient-reported absenteeism, presenteeism, and overall work impairment (40). Mean income loss was then compared between flaring and non-flaring patients.

Due to the observational nature of the data, any observed significant difference in an outcome using a bivariate test between two groups (*e.g.* a t-test) may be due to confounding factors. Propensity score matching is a statistical matching technique that attempts to balance pre-specified covariates between patient groups through the use of the propensity score (a measure of how likely a patient is to belong to either group, based on the covariates used) (41). Analyses to compare HCRU, PRO scores and income loss in flaring versus non-flaring patients were conducted utilising propensity score matching. Flaring and non-flaring patient groups were matched overall on ethnicity, time since SLE diagnosis, and SLE disease severity at diagnosis (based on physician judgement: mild, moderate and severe). Propensity scores were estimated using a logistic regression model. Patients in the flaring group were matched 1:1, with replacement and allowing for ties, to patients in the non-flaring group. A caliper was not applied. The balance in covariates between groups, following propensity score matching, was assessed by calculating standardised mean differences (SMDs), with an SMD between -10% and 10% (not inclusive) taken to be indicative of adequate balance (42). The treatment effect, or difference in outcomes between groups, was computed by taking the average of the difference

between the outcomes in matched patients. The Abadie-Imbens standard error and the corresponding test statistic and associated *p*-value were also calculated (43). Propensity score matching was repeated three times, for analyses of the following groups of variables: 1) Physician-reported HCRU outcomes; 2) Patient-reported EQ-5D-3L utility index, FACIT-Fatigue scores and WPAI total activity impairment; 3) Patient-reported WPAI absenteeism, presenteeism, and overall work impairment (with their dollar adjusted equivalents).

All analyses were conducted in Stata version 16.0 (44).

Results

Patients

Rheumatologists provided data for 1,278 patients, 470 from the USA and 808 from Europe (France, n=172; Germany, n=174; Spain, n=156; Italy, n=136; UK, n=170). Of these, approximately one-third (408; 32%) were considered by their physicians to be flaring and approximately two-thirds (870; 68%) to be non-flaring.

Of the 1,278 patients with physician-reported data, 729 self-reported data, 257 from the USA and 472 from Europe (France, n=94; Germany, n=134; Spain, n=87; Italy, n=98; UK, n=59). Of these, approximately one-third (241; 33%) were reported by their physicians to be flaring and approximately two-thirds (488; 67%) were non-flaring.

Based on physician-reported data, flaring and non-flaring patients were comparable for age, proportions of each sex, and time since diagnosis (Table I). However, patients classified as flaring were less likely to be White than non-flaring patients ($p<0.001$), and lower proportions of flaring than non-flaring patients were considered by their physicians to have mild SLE, and higher proportions of flaring than non-flaring patients were considered by their physicians to have severe SLE ($p<0.0001$) (Table I). A mean of 2.1 flares/year was reported for flaring patients (Table I).

Patient-reported outcomes

Propensity score matching achieved balance for all variables, with an SMD in the range of -10% to 10%. In the non-flaring group post-matching compared with pre-matching, there was a lower proportion of White patients and a higher proportion of patients of African ancestry, time since SLE diagnosis was slightly longer, there was a lower proportion of patients with mild SLE and a higher proportion of patients with severe SLE (Supplementary Table S1).

Propensity score coefficients indicated an impact of flaring on all PRO variables (Fig. 1). Health status, as indicated by the EQ-5D-3L utility index, was worse in flaring compared with non-flaring patients, and flaring patients reported higher levels of fatigue than non-flaring patients (both $p<0.001$). WPAI absenteeism ($p=0.004$), presenteeism ($p<0.001$), overall work impairment ($p<0.001$), and total activity impairment ($p<0.001$) were all greater in flaring patients compared with non-flaring patients. The greatest differences were seen in percentage presenteeism and overall work impairment (both 1.75-fold higher in flaring than non-flaring patients).

Table I. Patient demographics and clinical characteristics.

	Total (n=1278)	Non-flaring (n=870)	Flaring (n=408)	*p*-value
Age, years				
n	1277	869	408	
Mean (SD)	42.2 (13.5)	42.4 (13.9)	41.8 (12.5)	0.4618
Range	18–85	18–85	18–79	
Sex, n (%)				
n	1276	869	407	
Female	1106 (86.7)	756 (87.0)	350 (86.0)	0.6587
Male	170 (13.3)	113 (13.0)	57 (14.0)	
Ethnicity, n (%)				
n	1278	870	408	
White	934 (73.1)	664 (76.3)	270 (66.2)	0.0002
African ancestry	173 (13.5)	97 (11.1)	76 (18.6)	
Other	171 (13.4)	109 (12.5)	62 (15.2)	
Time since diagnosis, years				
n	1278	870	408	
Mean (SD)	5.6 (6.1)	5.4 (6.1)	5.9 (6.2)	0.1654
Range	0.0–40.9	0.0–39.9	0.0–40.9	
Number of flares in past 12 months				
n	1272	870	402	
Mean (SD)	0.7 (1.2)	0.0 (0.0)	2.1 (1.3)	<0.0001
Range	0.0–10.0	0.0–0.0	1.0–10.0	
Current SLE disease severity, n (%)				
n	1271	863	408	
Mild	912 (71.8)	691 (80.1)	221 (54.2)	<0.0001
Moderate	318 (25.0)	159 (18.4)	159 (39.0)	
Severe	41 (3.2)	13 (1.5)	28 (6.9)	

Patients were considered as flaring if they had experienced ≥1 physician-defined flare in the 12 months prior to data collection and as not flaring if they had experienced no flares in the 12 months prior to data collection.
Current disease severity based on physician response to question "What is the current level of disease severity for this patient?"
SLE: systemic lupus erythematosus; SD: standard deviation.

Healthcare resource utilisation

Propensity score matching achieved balance for all variables, with an SMD in the range of -10% to 10%. Post-matching compared with pre-matching, in the non-flaring group, there were a lower proportion of White and a higher proportion of patients of African ancestry, a lower proportion of patients with mild SLE and a higher proportion of patients with severe SLE (Suppl. Table S2).

Propensity score coefficients indicated an impact of flaring on all aspects of HCRU (Fig. 2). The number of consultations with HCPs, hospitalisations, visits to the ER, and tests performed in the 12 months prior to data collection were all higher in flaring compared with non-flaring patients (all $p<0.001$). The greatest differences were seen in the mean numbers of hospitalisations (around three-fold higher in flaring than non-flaring patients) and ER visits (around five-fold higher in flaring than non-flaring patients). When con-

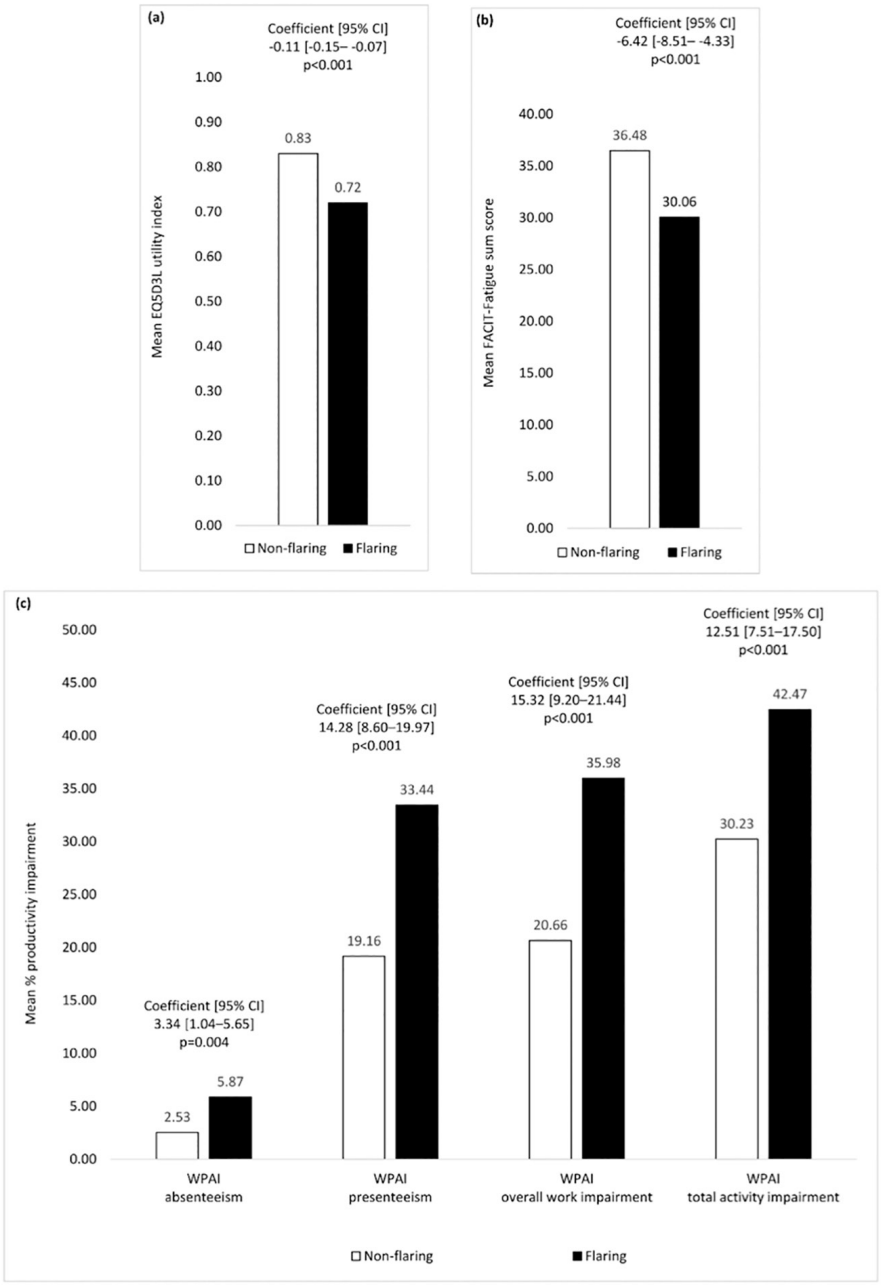

Fig. 1. Association of flaring with PROs (**a**) EQ-5D-3L, (**b**) FACIT-Fatigue, (**c**) WPAI
Patients were considered as flaring if they had experienced ≥1 physician-defined flare in the 12 months prior to data collection and as not flaring if they had experienced no flares in the 12 months prior to data collection
CI: confidence interval; EQ-5D-3L: EuroQoL 5D-3L; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; PRO: patient-reported outcome; WPAI: Work Productivity and Activity Impairment questionnaire.

sidering all classes of drugs, and regardless of dose, flaring patients were taking a greater number of medications for their SLE than non-flaring patients (p<0.001).

Loss of income

As loss of income was calculated based on WPAI-reported productivity impairment, patient characteristics before and after propensity score matching for PROs shown in Supplementary Table S1 also apply for income loss. The losses in annual income due to presenteeism and overall work impairment were both 1.8-fold higher in flaring than non-flaring patients (Fig. 3). Propensity score coefficients indicated an impact of flaring on income (Fig. 3). Loss of income associated with absenteeism (p=0.005), presenteeism (p<0.001), and overall work impairment (p<0.001) was greater in flaring compared with non-flaring patients.

Current SLE medication

A higher proportion of patients classified by their physicians as flaring versus non-flaring were receiving corticosteroids, immunosuppressants or biologics as treatment for their SLE (Table II). There were no differences in the proportions of flaring and non-flaring patients receiving other types of SLE medications.

Physicians were satisfied (based on physician responses of 'somewhat satisfied', 'satisfied' or 'very satisfied' on the PRF) with their patient's current medication for SLE in 86.6% of cases for non-flaring patients and 64.5% of cases for flaring patients. Propensity score coefficients indicated a higher level of satisfaction with current medication in non-flaring than flaring patients (coefficient [95% CI]: -0.22 [0.28–0.17]; p<0.001).

Patients were satisfied (based on patient responses of 'somewhat satisfied', 'satisfied' or 'very satisfied' on the patient self-complete form) with their current medication for SLE in 85.1% of cases for non-flaring patients and 69.3% of cases for flaring patients. Propensity score coefficients indicated a higher level of satisfaction with current medication in non-flaring than flaring patients (coefficient [95% CI]: -0.16 [0.24–0.08]; p<0.001).

Discussion

We investigated the association of flaring with PROs, HCRU, income loss, and physician and patient satisfaction with current lupus medication by analysis of a large dataset of real-world data from SLE patients and their physicians in the USA and five European countries. Patients' mean age was a little over 40 years, and >85% were female, reflecting the age and sex of SLE patients reported in the literature (7, 45). One-third of patients had experienced ≥1 flare in the previous 12 months. Our analysis showed no difference in SLE disease duration between flaring and non-flaring patients; longer disease duration in patients experiencing flaring compared with non-flaring patients has

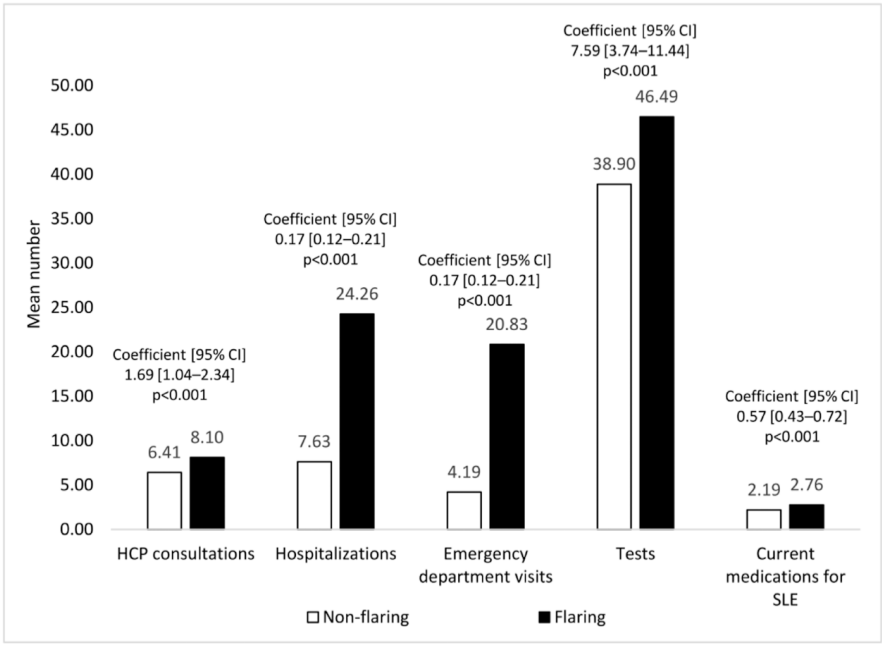

Fig. 2. Association of flaring with HCRU.
Patients were considered as flaring if they had experienced ≥1 physician-defined flare in the 12 months prior to data collection and as not flaring if they had experienced no flares in the 12 months prior to data collection. HCP consultations, hospitalisations, emergency department visits and tests in the past 12 months are reported; tests included x-rays, MRIs, CT scans, endoscopies, biopsies, renal/liver function tests, urinalysis, blood counts, inflammatory markers (ESR, CRP), rheumatoid factor.
CT: computerised axial tomography; CI: confidence interval; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HCP: healthcare professional; HCRU: healthcare resource utilisation; MRI: magnetic resonance imaging; SLE: systemic lupus erythematosus.

been reported in some studies in the literature (46, 45), although a higher rate of flaring in patients with shorter disease duration has also been reported (21).

Our analysis showed a significant and consistent association of flaring with a range of PROs in SLE patients. FACIT-Fatigue scores were significantly worse in flaring than in non-flaring patients, and for the flaring group, but not the non-flaring group, the mean score was more than 1 standard deviation below the US general population normative value of 43.6±9.4 (29). Levels of fatigue observed in our study (mean FACIT-Fatigue scores of 36.5 and 30.0 for non-flaring and flaring patients, respectively) were somewhat lower than those reported in other studies. SLE patients before and after treatment in a clinical trial had mean FACIT-Fatigue scores of 19.1 and 24.8, respectively (30), patients in a study to determine the minimal clinically important difference for a number of PRO instruments to assess fatigue in SLE had a mean FACIT-Fatigue score of 25.7 (48) and in third study on patient QoL patients had a mean score of 40 (49).

Flaring was also associated with worse health status and greater impairment of work productivity *versus* non-flaring. These findings reflect some findings reported in the literature, although we believe our analysis to be the first reported study comparing EQ-5D-3L, FACIT-Fatigue, and WPAI scores in flaring and non-flaring patients. One published study showed the presence of flare to be independently associated with lower scores, indicating poorer HRQoL, for all scales except bodily pain and mental health of the Medical Outcomes Survey Short Form 36 HRQoL questionnaire (20). The overall work impairment that we observed for flaring patients (42%) was similar to that observed in a European online survey of more than 2,000 SLE patients, which reported a range of impairments of 39–51%, depending on country (50). We observed a 1.8-fold greater overall work impairment and loss of income due to work impairment, in flaring than non-flaring patients. This indicates that even having an average of around two flares/year (in our analysis flaring patients had a mean of 2.1 flares in the previous 12 months) can have a major impact on income. We have been unable to identify any published reports on the association of work productivity impairment with flaring, although indirect costs related to productivity loss (including unemployment, sick leave, and days off from household work or other activities due to SLE) were shown to be greater in flaring than non-flaring patients in a retrospective cost-of-illness study of Chinese SLE patients in Hong Kong (21).

We identified strong associations of flaring status with HCRU, with flaring patients having higher numbers of HCP consultations, hospitalisations, visits to the ER, and tests in the 12 months prior to data collection, as well as receiving more medications for SLE at the time of data collection, compared with non-flaring patients. The numbers of hospitalisations and ER visits in flaring patients were about 3-fold and 5-fold (respectively) those in non-flaring patients. This indicates a larger burden on the health system for flaring than non-flaring patients and highlights an unmet need to control flaring in the management of SLE.

However, high levels of SLE-targeted medication were observed, with >50% of both flaring and non-flaring patients receiving anti-malarials, corticosteroids, and immunosuppressants, and corticosteroid, immunosuppressant and biologic use higher in flaring than non-flaring patients. Approximately 60% of patients were receiving anti-malarials, with similar levels of use in flaring and non-flaring patients. This would indicate that control of flares is an important aspect of disease management of SLE patients, as anti-malarials are known to reduce the occurrence of flares (51, 52). The higher utilisation of advanced therapies in the flaring group (19% of flaring patients were receiving biologics *versus* 10% of non-flaring patients) suggests that such therapies are either not effective or are not being used appropriately, and would also indicate that newer, more effective therapies are needed for controlling flares in SLE patients.

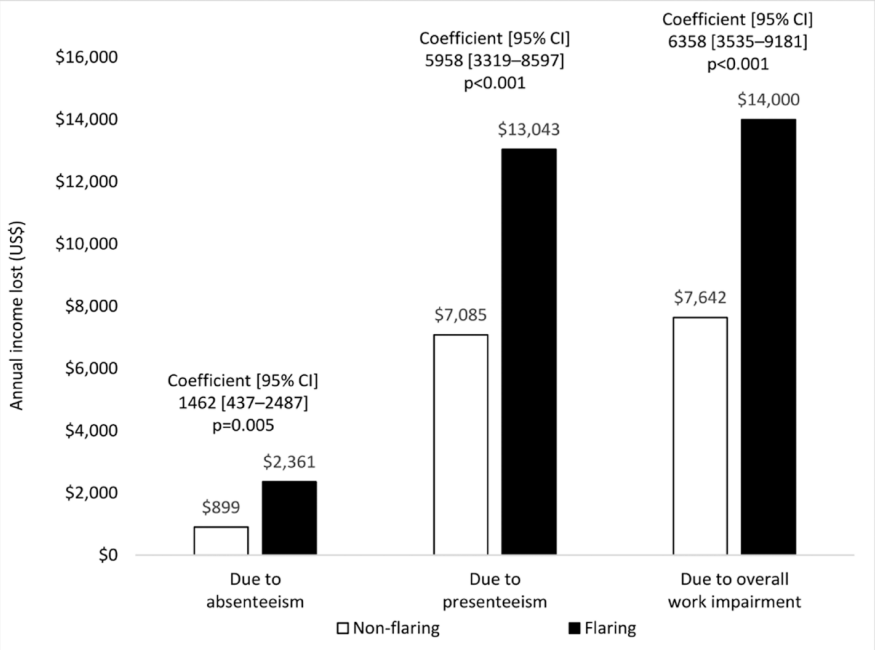

Fig. 3. Association of flaring with loss of income.
Patients were considered as flaring if they had experienced ≥1 physician-defined flare in the 12 months prior to data collection and as not flaring if they had experienced no flares in the 12 months prior to data collection.

Table II. Current treatment for SLE.

n (%)	Total (n=1265)	Non-flaring (n=857)	Flaring (n=408)	*p*-value
Anti-coagulant	28 (2.2)	17 (2.0)	11 (2.7)	0.4193
Anti-convulsant	3 (0.2)	3 (0.4)	0 (0.0)	0.5554
Antidepressant/anxiolytic	33 (2.6)	18 (2.1)	15 (3.7)	0.1295
Anti-malarial	784 (62.0)	533 (62.2)	251 (61.5)	0.8526
Biologic	162 (12.8)	83 (9.7)	79 (19.4)	<0.0001
Corticosteroid	880 (69.6)	537 (62.7)	343 (84.1)	<0.0001
COX2 inhibitor	71 (5.6)	46 (5.4)	25 (6.1)	0.6021
Immunosuppressant	713 (56.4)	437 (51.0)	276 (67.6)	<0.0001
NSAID	192 (15.2)	129 (15.1)	63 (15.4)	0.8671
Other topical non-steroids	16 (1.3)	11 (1.3)	5 (1.2)	1.0000
Other	4 (0.3)	1 (0.1)	3 (0.7)	0.1014

Patients were considered as flaring if they had experienced ≥1 physician-defined flare in the 12 months prior to data collection and as not flaring if they had experienced no flares in the 12 months prior to data collection. COX2: cyclooxygenase-2; NSAID: non-steroidal anti-inflammatory drug; SLE: systemic lupus erythematosus.

Few studies have examined the impact of SLE flares on HCRU, although a retrospective cost-of-illness study demonstrated that patients in Hong Kong experiencing flares had higher HCRU than those not experiencing flares (21). However, consistent with our findings, published analyses have shown healthcare costs (which clearly relate to HCRU) in Canada and Hong Kong to be 2-fold higher for SLE patients with flares than those without flares (21, 22), with direct healthcare costs highly correlated with the number of flares (p<0.0001 in both univariate and multivariate analyses) (21).

We observed that higher levels of satisfaction with treatment in non-flaring than flaring patients were reported by both physicians and patients. To our knowledge, this is the first study that reports the association of treatment satisfaction with flaring in SLE. The lower level of treatment satisfaction in the flaring group could be due to several reasons, including poor effectiveness, adverse effects, inconvenience of administration, and cost (53). In both of the analysis cohorts (flaring and non-flaring), a similar proportion of physicians and patients were satisfied with treatment. There appears to be a need for treatment options that are considered effective and tolerable by physicians and patients alike.

There were a number of potential limitations of this analysis. The inclusion of data for the next five consecutively consulting patients means that the study sample was pseudo-random, rather than truly random, and that patients who consulted their physician more frequently than average might be over-represented. As with all survey studies, the methodology relied on accurate reporting by physicians and patients; missing data are to be expected and may influence results. This was a cross-sectional rather than a longitudinal survey and data may be used to explore the association between factors but not to assess causality. Given the predominance of White patients in our study, findings may not be generalisable to a more racially- and ethnically-diverse patient population (7). This is particularly important as non-White SLE patients have been reported to be more likely to develop severe disease and have poorer clinical outcomes than White patients (6, 54). There were also limitations in using propensity score matching; while we chose matching variables that we thought to be imbalanced between the groups and that might affect the outcomes, with a finite sample size we had to use a limited set of variables so that matches may be found, and we were only able to match on observed variables, so any bias due to unused or unobserved/unobservable variables remained between the groups. We did not control for concomitant conditions as SLE is so heterogeneous that it is often hard to distinguish concomitant conditions from the condition itself, or indeed from actual manifestations that occur during flare.

Despite these limitations, this analysis provides novel and useful insights as it is based on a substantial body of real-world data from a large, international patient cohort.

A range of treatments is available for the treatment of SLE, with clinical

guidelines recommending low-dose hydroxychloroquine for all patients, minimised use of glucocorticoids to manage symptoms, immunosuppressants to assist with corticosteroid withdrawal, and add-on biologics if needed (15). Together with achievement of remission or low disease activity, prevention of flares is a recommended treatment goal in SLE (15). However, no treatment is currently available that successfully prevents flares, and as our findings indicated higher HCRU and significantly worse health status, fatigue, and work impairment in flaring compared with non-flaring patients, it may be concluded that there is a need for more effective treatments in patients to alleviate flaring in SLE, with consequent reduction in the humanistic and HCRU burden.

Acknowledgements

This study was funded by Janssen and data collection was designed and conducted by Adelphi Real World as part of an independent survey, entitled the Adelphi Real World Lupus DSP. Janssen did not influence the original survey through either contribution to the design of questionnaires or data collection. The analysis described here used data from the Adelphi Real World Lupus DSP. The DSP is a wholly owned Adelphi product. Janssen is one of multiple subscribers to the DSP.

Medical writing support under the guidance of the authors was provided by Carole Evans, PhD on behalf of Adelphi Real World, and was funded by Janssen, in accordance with Good Publication Practice (GPP3) guidelines (*Ann Intern Med* 2015;163:461-464).

References

1. LO MS, TSOKOS GC: Recent developments in systemic lupus erythematosus pathogenesis and applications for therapy. *Curr Opin Rheumatol* 2018; 30: 222-8. https://doi.org/10.1097/bor.0000000000000474
2. PALEY MA, STRAND V, KIM AH: From mechanism to therapies in systemic lupus erythematosus. *Curr Opin Rheumatol* 2017; 29: 178-86. https://doi.org/10.1097/bor.0000000000000369
3. SOMERS EC, MARDER W, CAGNOLI P *et al*.: Population-based incidence and prevalence of systemic lupus erythematosus: the Michigan Lupus Epidemiology and Surveillance program. *Arthritis Rheumatol* 2014; 66: 36978. https://doi.org/10.1002/art.38238
4. LIM SS, BAYAKLY AR, HELMICK CG, GORDON C, EASLEY K, DRENKARD C: The incidence and prevalence of systemic lupus erythematosus, 2002–2004: The Georgia Lupus Registry. *Arthritis Rheumatol* 2014; 66: 35768. https://doi.org/10.1002/art.38239
5. REES F, DOHERTY M, GRAINGE M, DAVENPORT G, LANYON P, ZHANG W: The incidence and prevalence of systemic lupus erythematosus in the UK, 1999–2012. *Ann Rheum Dis* 2016; 75: 13641. https://doi.org/10.1136/annrheumdis-2014-206334
6. LEWIS MJ, JAWAD AS: The effect of ethnicity and genetic ancestry on the epidemiology, clinical features and outcome of systemic lupus erythematosus. *Rheumatology* (Oxford) 2017; 56 (Suppl. 1): i67-i77. https://doi.org/10.1093/rheumatology/kew399
7. STOJAN G, PETRI M: Epidemiology of systemic lupus erythematosus: an update. *Curr Opin Rheumatol* 2018; 30: 144-50. https://doi.org/10.1097/bor.0000000000000480
8. GERGIANAKI I, BORTOLUZZI A, BERTSIAS G: Update on the epidemiology, risk factors, and disease outcomes of systemic lupus erythematosus. *Best Pract Res Clin Rheumatol* 2018; 32: 188-205. https://doi.org/10.1016/j.berh.2018.09.004
9. IZMIRLY PM, PARTON H, WANG L *et al*.: Prevalence of Systemic Lupus Erythematosus in the United States: estimates from a meta-analysis of the Centers for Disease Control and Prevention National Lupus Registries. *Arthritis Rheumatol* 2021; 73: 991-6. https://doi.org/10.1002/art.41632
10. DORIA, A, AMOURA Z, CERVERA R *et al*.: Annual direct medical cost of active systemic lupus erythematosus in five European countries. *Ann Rheum Dis* 2014; 73: 154-60. https://doi.org/10.1136/annrheumdis-2012-202443
11. GENSOUS N, MARTI A, BARNETCHE T *et al*.: Predictive biological markers of systemic lupus erythematosus flares: a systematic literature review. *Arthritis Res Ther* 2017; 19: 238. https://doi.org/10.1186/s13075-017-1442-6
12. FERNANDEZ D, KIROU KA: What causes lupus flares? *Curr Rheumatol Rep* 2016; 18: 14. https://doi.org/10.1007/s11926-016-0562-3
13. TRENTIN F, ZUCCHI D, SIGNORINI V, ELEFANTE E, BORTOLUZZI A, TANI C: One year in review 2021: systemic lupus erythematosus. *Clin Exp Rheumatol* 2021; 39: 231-41. https://doi.org/10.55563/clinexprheumatol/7gzsxp
14. WANG Z, LI M, WANG Y *et al*.: Long-term mortality and morbidity of patients with systemic lupus erythematosus: a single-center cohort study in China. *Lupus* 2018; 27: 864-9. https://doi.org/10.1177/0961203317751852
15. FANOURIAKIS A, KOSTOPOULOU M, ALUNNO A *et al*.: 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis* 2019; 78: 736-45. https://doi.org/10.1136/annrheumdis-2019-215089
16. GORDON C, AMISSAH-ARTHUR MB, GAYED M *et al*.; British Society for Rheumatology Standards, Audit and Guidelines Working Group. The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults. *Rheumatology* (Oxford) 2018; 57: e1-e45. https://doi.org/10.1093/rheumatology/kex286
17. MCELHONE K, ABBOTT J, HURLEY M *et al*.: Flares in patients with systemic lupus erythematosus. *Rheumatology* (Oxford) 2021; 60: 3262-7. https://doi.org/10.1093/rheumatology/keaa777
18. ADAMICHOU C, BERTSIAS G: Flares in systemic lupus erythematosus: diagnosis, risk factors and preventive strategies. *Mediterr J Rheumatol* 2017; 28: 4-12. https://doi.org/10.31138/mjr.28.1.4
19. RUIZ-IRASTORZA G, BERTSIAS G: Treating systemic lupus erythematosus in the 21st century: new drugs and new perspectives on old drugs. *Rheumatology* (Oxford) 2020; 59 (Suppl. 5): v69-v81. https://doi.org/10.1093/rheumatology/keaa403
20. ZHU TY, TAM LS, LEE VW, LEE KK, LI EK: Relationship between flare and health-related quality of life in patients with systemic lupus erythematosus. *J Rheumatol* 2010; 37: 568-73. https://doi.org/10.3899/jrheum.090876
21. ZHU TY, TAM LS, LEE VW, LEE KK, LI EK: The impact of flare on disease costs of patients with systemic lupus erythematosus. *Arthritis Rheum* 2009; 61: 1159-67. https://doi.org/10.1002/art.24725
22. CLARKE AE, UROWITZ MB, MONGA N, HANLY JG: Costs associated with severe and nonsevere systemic lupus erythematosus in Canada. *Arthritis Care Res* (Hoboken) 2015; 67: 431-6. https://doi.org/10.1002/acr.22452
23. ANDERSON P, BENFORD M, HARRIS N, KARAVALI M, PIERCY J: Real-world physician and patient behaviour across countries: Disease-Specific Programmes – a means to understand. *Curr Med Res Opin* 2008; 24: 3063-72. https://doi.org/10.1185/03007990802457040
24. EUROQOL GROUP: EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990; 16: 199-208. https://doi.org/10.1016/0168-8510(90)90421-9
25. RABIN R, DE CHARRO F: EQ-5D: a measure of health status from the EuroQol Group. *Ann Med* 2001; 33: 337-43. https://doi.org/10.3109/07853890109002087
26. HURST NP, KIND P, RUTA D, HUNTER M, STUBBINGS A: Measuring health-related quality of life in rheumatoid arthritis: validity, responsiveness and reliability of EuroQol (EQ-5D). *Br J Rheumatol* 1997; 36: 551-9. https://doi.org/10.1093/rheumatology/36.5.551
27. SZENDE A, OPPE M, DEVLIN N: 2007. EQ-5D Value Sets: Inventory, Comparative Review and User Guide. Netherlands: Springer.
28. YELLEN SB, CELLA D, WEBSTER K, BLENDOWSKI C, KAPLAN E: Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage* 1997; 13: 63-74. https://doi.org/10.1016/s0885-3924(96)00274-6
29. CELLA D, LAI JS, CHANG CH, PETERMAN A, SLAVIN M: Fatigue in cancer patients compared with fatigue in the general United States population. *Cancer* 2002; 94: 528-38. https://doi.org/10.1002/cncr.10245
30. LAI JS, BEAUMONT JL, OGALE S, BRUNETTA P, CELLA D: Validation of the functional assessment of chronic illness therapy-fatigue scale in patients with moderately to severely active systemic lupus erythematosus, participating in a clinical trial. *J Rheumatol* 2011; 38: 672-9.

https://doi.org/10.3899/jrheum.100799
31. KOSINSKI M, GAJRIA K, FERNANDES AW, CELLA D: Qualitative validation of the FAC-IT-Fatigue scale in systemic lupus erythematosus. *Lupus* 2013; 22: 422-30. https://doi.org/10.1177/0961203313476360
32. STRAND V, SIMON LS, MEARA AS, TOUMA Z: Measurement properties of selected patient-reported outcome measures for use in randomised controlled trials in patients with systemic lupus erythematosus: a systematic review. *Lupus Sci Med* 2020; 7: e000373. https://doi.org/10.1136/lupus-2019-000373
33. REILLY MC, ZBROZEK AS, DUKES EM: The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993; 4: 353-65. https://doi.org/10.2165/00019053-199304050-00006
34. Salary Explorer. Available at: http://www.salaryexplorer.com/. Accessed 4 June 2020.
35. Organisation for Economic Co-operation and Development (OECD): Available at: https://stats.oecd.org/. Accessed 4 June 2020.
36. Statista: Available at: https://www.statista.com/. Accessed 4 June 2020.
37. CNBC: Available at: https://www.cnbc.com/. Accessed 4 June 2020.
38. Deutsche Welle (DW): Available at: https://www.dw.com/. Accessed 4 June 2020.
39. The Local: available at: https://www.thelocal.de//. Accessed 4 June 2020.
40. VILLACORTA R, TEEPLE A, LEE S, FAKHARZADEH S, LUCAS J, MCELLIGOTT S: A multinational assessment of work-related productivity loss and indirect costs from a survey of patients with psoriasis. *Br J Dermatol* 2020; 183: 548-58. https://doi.org/10.1111/bjd.18798
41. ROSENBAUM PR, RUBIN DB: The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983; 70: 41-55. https://doi.org/10.1093/biomet/70.1.41
42. AUSTIN PC: Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009; 28: 3083-107. https://doi.org/10.1002/sim.3697
43. ABADIE A, IMBENS G: Matching on the Estimated Propensity Score. *Econometrica* 2016; 84; 781-807. https://doi.org/10.3982/ECTA11293
44. StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.
45. DALL'ERA M: Systemic lupus erythematosus. *In*: IMBODEN JB, HELLMAN DB, STONE JH. (Eds). Current Rheumatology Diagnosis and Treatment. 3rd ed. New York, NY:McGraw-Hill; 2013.
46. CONTI F, CECCARELLI F, PERRICONE C *et al*.: Flare, persistently active disease, and serologically active clinically quiescent disease in systemic lupus erythematosus: a 2-year follow-up study. *PLoS One* 2012; 7: e45934. https://doi.org/10.1371/journal.pone.0045934
47. CHO J, LAHIRI M, TEOH LK, DHANASEKARAN P, CHEUNG PP, LATEEF A: Predicting flares in patients with stable systemic lupus erythematosus. *Semin Arthritis Rheum* 2019; 49: 91-7. https://doi.org/10.1016/j.semarthrit.2019.01.001
48. GOLIGHER EC, POUCHOT J, BRANT R *et al*.: Minimal clinically important difference for 7 measures of fatigue in patients with systemic lupus erythematosus. *J Rheumatol* 2008; 35: 635-42.
49. ELEFANTE E, TANI C, STAGNARO C *et al*.: Impact of fatigue on health-related quality of life and illness perception in a monocentric cohort of patients with systemic lupus erythematosus. *RMD Open* 2020; 6(1). https://doi.org/10.1136/rmdopen-2019-001133
50. GORDON C, ISENBERG D, LERSTRØM K *et al*.: The substantial burden of systemic lupus erythematosus on the productivity and careers of patients: a European patient-driven online survey. *Rheumatology* (Oxford) 2013; 52: 2292-301. https://doi.org/10.1093/rheumatology/ket300
51. ZEN M, SACCON F, GATTO M *et al*.: Prevalence and predictors of flare after immunosuppressant discontinuation in patients with systemic lupus erythematosus in remission. *Rheumatology* (Oxford) 2020; 59: 1591-8. https://doi.org/10.1093/rheumatology/kez422
52. HANAOKA H, IIDA H, KIYOKAWA T, TAKAKUWA Y, KAWAHATA K: Glucocorticoid, immunosuppressant, hydroxychloroquine monotherapy, or no therapy for maintenance treatment in systemic lupus erythematosus without major organ manifestations. *Clin Rheumatol* 2019; 38: 2785-91. https://doi.org/10.1007/s10067-019-04633-y
53. MATHIAS SD, BERRY P, PASCOE K *et al*.: Treatment satisfaction in systemic lupus erythematosus: development of a patient-reported outcome measure. *J Clin Rheumatol* 2017; 23: 94-101. https://doi.org/10.1097/rhu.0000000000000495
54. MANINGDING E, DALL'ERA M, TRUPIN L, MURPHY LB, YAZDANY J: Racial/Ethnic differences in prevalence of and time to onset of SLE manifestations: the California Lupus Surveillance Project (CLSP). *Arthtitis Care Res* (Hoboken) 2020; 72: 622-9. https://doi.org/10.1002/acr.23887