Lupus (2019) 0, 1–7
journals.sagepub.com/home/lup

LUPUS AROUND THE WORLD

Management of non-renal non-neurologic persistent lupus activity in real world patients from Argentina

M Scolnik[1,2], V Scaglioni[1,2], GJ Pons-Estel[3,4] and ER Soriano[1,2]
[1]Rheumatology Section, Hospital Italiano de Buenos Aires, Argentina; [2]Department of Medicine, Instituto Universitario Hospital Italiano de Buenos Aires, Argentina; [3]Internal Medicine Department, Centro Regional de Enfermedades Autoinmunes y Reumáticas, Rosario, Argentina; and [4]Rheumatology Service, Hospital Provincial de Rosario, Rosario, Argentina

Management of systemic lupus erythematosus patients is challenging because of disease heterogeneity. Although treatment of renal nephritis is more standardized, treating non-renal lupus activity remains controversial. Our objective was to identify non-renal, non-neurologic persistent active systemic lupus erythematosus patients in our cohort and described therapeutic behaviors in them. All systemic lupus erythematosus patients (American College of Rheumatology and/or Systemic Lupus Erythematosus International Collaborating Clinics criteria) seen at a university hospital between 2000 and 2017 were included and electronic medical records manually reviewed. Persistent lupus activity was defined as a patient with a Systemic Lupus Erythematosus Disease Activity Index score ≥ 6 (without renal and central nervous system manifestations) despite being on a stable treatment regimen for ≥ 30 days. Stable treatment could include prednisone alone (7.5–40 mg/d) or combined with antimalarial drugs and immunosuppressant therapies. A total of 257 lupus patients were included, 230 females (89.5%, 95% confidence interval 85.1–92.7), mean age at diagnosis 29.9 years (SD 16.4). After a median cohort follow-up of 5.7 years (interquartile range 2.4–10.2), 14 patients (5.4%, 95% confidence interval 3.2–9.0) showed persistent non-renal non neurologic lupus activity, with a median disease duration of 11.3 years (interquartile range 3.6–19.4). At that time, 12/14 (85.7 %, 95% confidence interval 52.6–97.0%) had low complement and 11/14 (78.6 %, 95% confidence interval 46.5–93.9%) had positive antiDNA antibodies. The main reasons for being refractory were mucocutaneous disease (50%, 95% confidence interval 23.5–76.5) and arthritis (42.9%, 95% confidence interval 18.5–71.2). Therapeutic choices after being refractory were: only increasing corticosteroid dose in one patient, starting rituximab in four, belimumab in eight, and in one mycophenolate and rituximab; with good response in all of them. In conclusion, 5.4% of systemic lupus erythematosus patients in our cohort were considered to have non-renal non neurologic persistent lupus activity, with mucocutaneous and arthritis the main manifestations. In total, 92.8% of these patients started a biologic treatment at this point (rituximab or belimumab). *Lupus* (2019) **0,** 1–7.

Key words: Systemic lupus erythematosus; treatment; persistent disease; belimumab; rituximab

Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease, with a reported prevalence in Argentina of 58.6 per 100,000 habitants (95% confidence interval (CI) 46.1–73.5),[1] capable of affecting almost every part of the human body. Design of clinical trials in SLE patients is challenging because recruiting SLE patients with homogenous characteristics is difficult and global outcome measures are not always accurate. Patients with lupus glomerulonephritis have been more extensively studied and many clinical trials have been performed resulting in more detailed treatment guidelines, whereas other SLE manifestations have not been so deeply analyzed in clinical trials and lupus guidelines.

In contrast, SLE neurologic manifestations are very often life threatening and treatments are generally aggressive, mainly including high steroids doses, cyclophosphamide, sometimes plasma exchange and/or intravenous immunoglobulin and, in the last few years, rituximab.[2,3]

Correspondence to: Marina Scolnik, Rheumatology Section, Hospital Italiano de Buenos Aires, Peron 4190, Buenos Aires, Argentina.
Email: marina.scolnik@hospitalitaliano.org.ar
Received 7 March 2019; accepted 12 June 2019

10.1177/0961203319861687

SLE patients with non-renal non-neurologic involvement receive different treatments, with less expert agreement achieved, no precise treatment guidelines available and great inter-rheumatologist treatment variations. At initial involvement, patients are usually treated according to the clinical manifestation in a similar way than other autoimmune specific organ diseases (e.g. arthritis, immune thrombocytopenic purpura, autoimmune hemolytic anemia, etc). When these initial therapies fail, there are no clear recommendations and treatments are more of an art than a science.[3–5]

Some clinical trials performed in the last few years have focused on SLE patients with active disease (Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[6] > 6 without significant central nervous system or renal compromise to assess patients' global response to treatments (such belimumab).[7,8]

Real-world prevalence of SLE patients with persistent active non-renal non-neurologic disease is unknown. Our objective was to identify this group of patients in our lupus cohort and describe therapeutic behaviors.

Methods

SLE patients

All SLE patients seen at the Rheumatology Section of Hospital Italiano de Buenos Aires, Argentina, after the year 2000 were included. SLE patients were identified using different methods: a) Rheumatology Section SLE database; b) electronic medical records with the SLE, lupus or cutaneous lupus in the oriented computer-based patient record system of the Hospital Italiano de Buenos Aires. Electronic medical records were manually reviewed and those patients fulfilling American College of Rheumatology (ACR) 1997[9] and/or Systemic Lupus International Collaborating Clinics (SLICC) 2012[10] criteria were included. Patient characteristics and treatments were retrospectively revised.

Non-renal, non-neurologic persistent lupus activity definition

For this study we defined non-renal non-neurologic persistent lupus activity as a patient with a SLEDAI 2K[11] score ≥ 6 (without any renal and/or central nervous system (CNS) manifestation) despite being on a stable treatment regimen for ≥ 30 days, which led the treating physician to a treatment change. Stable treatment could include prednisone alone (7.5–40 mg/d) or combined (0–40 mg/d) with antimalarial drugs and immunosuppressant therapies. Patients should not have had CNS or renal involvement at that time, because treatment decisions may have differed.

Statistical analysis

Descriptive statistics were performed. Data are presented in percentages and 95% CI for categorical variables, or media with standard deviation (SD) or median with interquartile ranges (IQR) when appropriate, for continuous variables. A multivariate logistic regression analysis was carried out to identify the factors associated with persistent lupus activity. STATA 14.0 software was used.

Ethical approval

The protocol was reviewed and approved by our local Ethical Committee (protocol number 3427).

Results

In total, 257 lupus patients were included and their medical records reviewed. Of these, 230 were female (89.5%, SD 85.1–92.7%), with a mean age at diagnosis of 29.9 years (SD 16.4) and followed for a median time of 5.7 years (IQR 2.4–10.2). Overall, 211 patients fulfilled ACR lupus criteria (82.1%, SD 76.9–86.3%) and 255 SLICC criteria (99.2%, SD 96.9–99.8%).

Clinical manifestations and treatments received during first year of disease onset and cumulative at the end of follow-up are shown in Table 1 and 2 respectively. Overall, 94.9% of patients were treated with antimalarials (95% CI 91.4–97.1%) and 67.5% (95% CI 61.7–72.8%) needed at least one immunosuppressant at some point (including methotrexate, azathioprine, cyclophosphamide, cyclosporine, rituximab and/or belimumab, with one patient receiving a TNF inhibitor).

While being under our hospital care, 14 patients (5.4%, 95% CI 3.2–9.0%) showed persistent non-renal non-neurologic lupus activity, with a SLEDAI score ≥ 6 despite being on a stable treatment for more than 30 days. At that time, patients had a median disease duration of 11.3 years (IQR 3.6–19.4), 85.7% (95% CI 52.6–97.0%) had low complement levels, and 78.6% (95% CI 46.5–93.9%) had positive antiDNA antibodies. Demographics, clinical involvement, and treatments are shown in Table 3 and in detail for each

Table 1 Lupus manifestations at disease onset and cumulative at the end of follow-up (all patients), median follow- up: 5.7 years (interquartile range (IQR) 2.4–10.2)

	At first year of SLE onset (n = *257*) N *(%, 95% CI)*	*Cumulative* (n = *257*) N *(%, 95% CI)*
Acute cutaneous lupus (SLICC definition)	140 (54.7, 48.5–60.7)	160 (62.3, 56.1–68.1)
Chronic cutaneous lupus (SLICC definition)	11 (4.3, 2.4–7.6)	15 (5.8, 3.5–9.5)
Oral/nasal ulcers	57 (22.3, 17.5–27.8)	68 (26.5, 21.4–32.2)
Alopecia	93 (36.3, 30.6–42.4)	122 (47.5, 41.4–53.6)
Arthralgia	188 (73.4, 67.6–78.5)	205 (79.8, 74.4–84.3)
Arthritis	133 (51.9, 45.8–58.1)	140 (54.5, 48.3–60.5)
Myositis	2 (0.8, 0.2–3.1)	3 (1.2, 0.4–3.6)
Pleural effusion	27 (10.6, 7.3–14.9)	33 (12.8, 9.2 –17.5)
Pericardial effusion	34 (13.3, 9.6–18.1)	45 (17.5, 13.3–22.7)
Hemolytic anemia	11 (4.3, 2.4–7.6)	13 (5.1, 2.9–8.5)
Leukopenia $< 3000/mm^3$	55 (21.5, 16.8–26.9)	73 (28.4, 23.2–34.3)
Thrombocytopenia $< 100{,}000/mm^3$	30 (11.7, 8.3–16.3)	43 (16.7, 12.6–21.8)
Renal involvement	110 (42.8, 36.8–48.9)	148 (57.6, 51.4–63.5)
Neurologic involvement	15 (5.9, 3.5–9.5)	24 (9.3, 6.3–13.6)
SLEDAI ≥ 6	171 (66.5, 60.5–72.1)	196 (76.3, 70.6–81.1)

CI: confidence interval; SLICC: Systemic Lupus International Collaborating Clinics/American College of Rheumatology; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

Table 2 Treatments received during follow-up (all patients), median follow-up: 5.7 years (interquartile range (IQR) 2.4–10.2)

	At first year of SLE (n = *257*) N *(%, 95% CI)*	*Cumulative* (n = *257*) N *(%, 95% CI)*
Corticosteroids low dose, < prednisone 7.5 mg/d, ever	234 (91.1, 86.9–93.9)	241 (93.8, 90.1–96.2)
Corticosteroids dose > 20 mg/d prednisone, ever	152 (59.1, 52.9–65.1)	189 (73.5, 67.8–78.6)
Antimalarials	210 (82.1, 76.8–86.3)	244 (94.9, 91.4–97.1)
Methotrexate	18 (7.1, 4.5–10.9)	37 (14.4, 10.6–19.3)
Azathioprine	36 (14.1, 10.3–18.9)	88 (34.2, 28.7–40.3)
Mycophenolate	45 (17.6, 13.4–22.8)	111 (43.2, 37.2–49.3)
Cyclophosphamide	57 (22.2, 17.5–27.7)	98 (38.1, 32.3–44.3)
Cyclosporine	2 (0.8, 0.2–3.1)	7 (2.7, 1.3–5.6)
Rituximab	3 (1.2, 0.4–3.6)	30 (11.7, 8.3–16.2)
Belimumab	0	7 (2.7, 1.3–5.6)
Other biologic drugs	0	1 (0.4, 0.1–2.7)
Any immunosuppressant	127 (45.8, 40.0–51.8)	187 (67.5, 61.7–72.8)

CI: confidence interval; SLE: systemic lupus erythematosus.

of the 14 patients in Table 4. Mucocutaneous (50%, 95% CI 23.5–76.5%) manifestations and arthritis (42.9%, 95% CI 18.5–71.2%) were the most frequent clinical persistent involvement.

Therapeutic options after reaching this persistent lupus activity (decided by the rheumatologist in charge, according to their own judgment) included increasing corticosteroid dose in 64.3% of patients (95% CI 34.4–86.1%), initiating belimumab in 57.1 % (95% CI 28.8–81.5%) or rituximab in 35.7 % (95% CI 12.7–64.9%) (Table 3). In only one patient (patient number 5, Table 4) the only treatment change was an increase in corticosteroid dose from 10 mg/d to 50 mg/d of prednisone, while continuing with hydroxychloroquine and azathioprine. Patient number 8 (Table 4) initiated mycophenolate along with rituximab.

Out of the 14 patients, 11 improved their SLEDAI score ≥ 4 points after treatment change (Table 4). After initiating belimumab the remaining three patients improved their SLEDAI from six points to four points continuing with a milder rash (patient number 4) or with serologic activity (patient number 12) and patient number 11 resolved her persistent pleural effusion and fever, although a cutaneous rash appeared (SLEDAI score change from seven to four points). (Table 4). None of the 14 patients died during our follow-up.

Table 3 Characteristics of lupus patients with persistent non-renal non-neurologic activity

	Refractory patients (n = 14)
Female, *n* (%, 95% CI)	13 (92.9, 60.9–99.1)
Median age at SLE diagnosis, years (IQR)	20.9 (19.5–25.2)
Median age at refractory disease, years (IQR)	34.5 (31.4–39.1)
Median disease duration at refractory time, years (IQR)	11.3 (3.6–19.4)
Median SLEDAI score at refractory time (IQR)	8.5 (8–10)
Clinical involvement at refractory time:	
Vasculitis, *n* (%, 95% CI)	1 (7.1, 0.8–43.3)
Mucocutaneous disease, *n* (%, 95% CI)	7 (50.0, 23.5–76.5)
Fever, (%, 95% CI)	2 (14.3, 2.9–47.4)
Arthritis, *n* (%, 95% CI)	6 (42.9, 18.5–71.2)
Myositis, *n* (%, 95% CI)	0
Pleural effusion, *n* (%, 95% CI)	1 (7.1, 0.8–43.3)
Pericardial effusion, *n* (%, 95% CI)	0
Hemolytic anemia, *n* (%, 95% CI)	0
Leukopenia < 3000, *n* (%, 95% CI)	2 (14.3, 2.9–47.4)
Thrombocytopenia < 100,000, *n* (%, 95% CI)	2 (14.3, 2.9–47.4)
Renal involvement, *n* (%, 95% CI)	0
Neurologic involvement, *n* (%, 95% CI)	0
Low complement levels, (%, 95% CI)	12 (85.7, 52.6–97.0)
Positive antiDNA antibodies, (%, 95% CI)	11 (78.6, 46.5–93.9)
New treatments received after being refractory:	
Corticosteroids, dose increased, any dose, *n* (%, 95% CI)	9 (64.3, 34.4–86.1)
Prednisone dose (or equivalent) > 20 mg/d, *n* (%, 95% CI)	6 (42.9, 18.5–71.2)
Mycophenolate, *n* (%, 95% CI)	1 (7.1, 0.8–43.3)
Rituximab, *n* (%, 95% CI)	5 (35.7, 12.7–64.9)
Belimumab, *n* (%, 95% CI)	8 (57.1, 28.8–81.5)

CI: confidence interval; IQR: interquartile range; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

Discussion

In our cohort, we found 5.4% of lupus patients with persistent non-renal non-neurologic disease activity despite being on stable treatment with corticosteroids and/or antimalarial and immunosuppressant drugs.

There is no consensus on a definition of refractory lupus. It is usually accepted when referring to a patient who has not responded to standard therapy or requires unacceptable doses of corticosteroids to maintain remission.[12] Of course, adherence to treatment and cumulative damage have to be considered and only persistent or new activity is taken into account. The Spanish Society of Rheumatology has proposed a definition of refractory lupus for each clinical domain.[12] These definitions were based on expert agreement.

Persistent active disease (PAD) has been analyzed in other cohorts, defined as a SLEDAI 2K ≥ 4 in two consecutive visits separated for >2 months (excluding serologic activity alone). In these cohorts, PAD included renal and CNS activity, patients could be on any medication and treatment changes were not reported.[13,14] PAD was found in patients of the Toronto Lupus cohort in 52.3% in 2004 and in 46.1% in 2005.[13] In the Italian cohort,[14] PAD was found in 9.4–13.5% of patients seen between 2009–2010.

General disease standard of care in lupus includes antimalarial drugs (with a general preference of hydroxychloroquine over chloroquine) and low-dose corticosteroids (<7.5 mg/prednisone/day) if needed.[5] Some society guidelines or consensus propose lupus management recommendations according to the specific organ involved,[5,15] whereas others such as the British Society Guidelines[3] suggest different treatment strategies according to the severity of lupus activity measured by composed indexes such as British Isles Lupus Assessment Group (BILAG)[16] and SLEDAI.[6]

Options for non-renal non-neurologic refractory patients appear in some guidelines.[3,5,12] Switching or adding other immunosuppressant drugs or starting a biologic one are some of the choices. Belimumab has shown disease improvement in clinical trials[7,8] and has been approved by different regulatory agencies around the world. In general, lupus patients with moderate to high disease activity despite being on standard treatments, without important renal or neurologic involvement and with serologic activity (low complement levels and/or anti DNA antibodies), may be candidates for belimumab.[3] Although rituximab failed to meet primary endpoints in clinical trials,[17,18] it is widely used in different countries in lupus patients with refractory renal, neurologic or any kind of persistent lupus activity. Evidence is based mostly on open-label or cohort studies, showing a greater rituximab efficacy in real-world patients than in controlled studies.[19,20] For example, in the United Kingdom, despite not being licensed, rituximab can be used in lupus patients with a SLEDAI score ≥ 6, with one BILAG A item or ≥ 2 BILAG Bs and failure of ≥ 2 immunosuppressants (including cyclophosphamide or mycophenolate) or requiring unacceptable high levels of steroids.[3] Of our 14 patients with persistent activity, eight (57.1%) initiated belimumab and five rituximab (35.7%), showing that biologics for lupus are a current therapeutic option with good responses.

Biologic treatments in Latin America are not available in all countries and the socioeconomic

Table 4 Lupus patients with persistent non-renal non-neurologic activity individual characteristics and treatments received at that time point

Patient	*Sex*	*Age at refractory time (y)*	*Disease duration (y)*	*Medication history (maximum dose)*	*SLEDAI at refractory time*	*Clinical manifestations*	*Low complement*	*Positive anti DNA antibodies*	*Stable previous treatment (>30 days)*	*Months with stable medication and SLEDAI≥6*	*Treatment modification*	*SLEDAI after 1–3 months*
1	Female	45.6	19.4	HCQ (400 mg) PRED (50 mg) CF (12 g cumulative) AZA (100 mg) MMF (2g)	16	Vasculitis Cutaneous rash Alopecia	Yes	Yes	HCQ 400 mg/d PRED 5 mg/d MMF 1.5 g/d	6	HCQ 400 mg/d PRED 8 mg/d MMF 1 g/d BELIMUMAB IV	4 (low complement, DNA antibodies+)
2	Female	39.1	19.6	HCQ (400 mg) CQ (200 mg) PRED (75 mg) METHYLPRED (1 g) CF (4.5 g cumulative) MTX (20 mg/w) AZA (100 mg) RTX (2 g) ETN (50 mg/w)	8	Cutaneous rash Alopecia	Yes	Yes	HCQ 400 mg/d PRED 7.5 mg/d	9	HCQ 400 mg/d PRED 7.5 mg/d BELIMUMAB IV	4 (low complement, cutaneous rash)
3	Male	21.1	1.5	HCQ (400 mg) PRED (20 mg) MTX (15 mg/w)	10	Cutaneous rash Mouth ulcers Alopecia	Yes	Yes	HCQ 400 mg/d PRED 10 mg/d MTX 15 mg/w	5	HCQ 400 mg/d PRED 15 mg/d BELIMUMAB IV	4 (low complement, DNA antibodies+)
4	Female	38.3	21.3	HCQ (400 mg) METHYLPRED (?) PRED (50 mg) CF (?) AZA (?) MTX 15 mg/w	6	Cutaneous rash Alopecia	Yes	No	HCQ 400 mg/d PRED 25 mg/d	4	HCQ 400 mg/d PRED 10 mg/d BELIMUMAB IV	4 (low complement, cutaneous rash)
5	Female	41.5	12.1	HCQ (400 mg) AZA (100 mg) PRED (50 mg) MMF (2 g)	12	Cutaneous rash Alopecia	Yes	Yes	HCQ 400 mg/d PRED 10 mg/d AZA 100 mg/d	2	HCQ 400 mg/d PRED 50 mg/d AZA 150 mg/d	4 (low complement, DNA antibodies+)
6	Female	38.9	18.7	HCQ (400 mg) PRED (50 mg) METYLPRED (250 mg) CF (3 g cumulative) AZA (100 mg)	10	Arthritis	Yes	Yes	HCQ 400 mg/d PRED 10 mg/d AZA 100 mg/d	5	HCQ 400 mg/d PRED 10 mg/d RITUXIMAB	4 (low complement, DNA antibodies+)
7	Female	31.4	8.0	HCQ (400 mg) PRED (75 mg) AZA (100 mg) MMF (2 g)	9	Arthritis Thrombocytopenia	Yes	Yes	HCQ 400 mg/d PRED 50 mg/d MMF 1 g/d	1	HCQ 400 mg/d PRED 50 mg/d RITUXIMAB	4 (low complement, DNA antibodies+)
8	Female	41.2	25.9	HCQ (400 mg) AZA (100 mg) PRED (75 mg) METYLPRED (1000 mg) CF (cumulative 16 g) MMF (1g)	10	Arthritis Cutaneous rash	Yes	Yes	HCQ 400 mg/d PRED 25 mg/d	4	HCQ 400 mg/d PRED 50 mg/d MMF 2 g/d BELIMUMAB IV	2 (DNA antibodies+)

(continued)

Table 4 Continued

Patient	*Sex*	*Age at refractory time (y)*	*Disease duration (y)*	*Medication history (maximum dose)*	*SLEDAI at refractory time*	*Clinical manifestations*	*Low complement*	*Positive anti DNA antibodies*	*Stable previous treatment (>30 days)*	*Months with stable medication and SLEDAI≥6*	*Treatment modification*	*SLEDAI after 1–3 months*
9	Female	23.7	3.6	HCQ (400 mg) MTX (15 mg/w)	7	Arthritis Leukopenia	Yes	No	HCQ 400 mg/d PRED 10 mg/d	6	HCQ 400 mg/d PRED 12 mg/d RITUXIMAB	2 (low complement)
10	Female	21.3	1.2	HCQ (400 mg) PRED (75 mg) AZA (100 mg) MMF (2 g) CF (5 g cumulative)	8	Cutaneous rash Mouth ulcers Alopecia	Yes	Yes	PRED 25 mg/d MMF 2 g/d	2	HCQ 400 mg/d PRED 40 mg/d RITUXIMAB	4 (low complement, DNA antibodies+)
11	Female	38.1	12.9	HCQ (400 mg) PRED (?)	7	Pleural effusion Fever	Yes	Yes	HCQ 400 mg/d PRED 20 mg/d	2	HCQ 400 mg/d PRED 20 BELIMUMAB IV	4 (low complement, cutaneous rash)
12	Female	32.8	8.6	HCQ (400 mg) PRED (?) AZA (100 mg) MTX (15 mg/w)	6	Arthritis	Yes	Yes	HCQ 400 mg/d PRED 10 MTX 15	3	HCQ 400 mg/d PRED 25 BELIMUMAB IV	4 (low complement, DNA antibodies+)
13	Female	34.8	0.6	HCQ (400 mg) PRED (100 mg) IVIG (2 g/kg)	7	Mouth ulcers Thrombocytopenia	Yes	Yes	PRED 50 mg/d	2	HCQ 400 mg/d PRED 12.5 mg/d RITUXIMAB	3 (low complement, leukopenia)
14	Female	32.2	10.5	HCQ (400 mg) PRED (50 mg) AZA (100 mg)	10	Alopecia Cutaneous rash Leukopenia Fever	Yes	Yes	HCQ 400 mg/d PRED 5 mg/d	3	HCQ 400 mg/d BELIMUMAB IV	4 (low complement, DNA antibodies+)

Y: years; HCQ: hydroxychloroquine; CQ: chloroquine; PRED: prednisone; AZA: azathioprine; MMF: mycophenolate mofetil; IV: intravenous; MTX: methotrexate; METHYLPRED: methylprednisolone; CF: cyclophosphamide; RTX: rituximab; ETN: etanercept; ?: unknown maximum dose; IVIG: intravenous immunoglobulin; DNA antibodies: antibodies to double-stranded DNA; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

situation may influence therapeutic choices.[5] Buenos Aires is the largest metropolis in Argentina and our hospital is private, providing healthcare to some prepaid health management organizations and social security insurance companies. Access to expensive treatments in this setting may be easier than in other countries and inside the public health system.

Limitations of the present study include the retrospective design and a lack of a local/national consensus on how to manage lupus patients with persistent disease, so therapeutic choices were up to each physician. On the other hand, SLEDAI[6,11] may not be the best way to assess lupus activity and other activity indexes such as BILAG[16] or SLE responder index (SRI)[21] were not available.

This study reflects real-world data on managing lupus with non-renal non-neurologic persistent activity and the frequency of this situation. Belimumab and rituximab are therapeutic options taken into account by rheumatologists in real-world settings.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was an Investigator Initiated Clinical Study supported by GlaxoSmithKline.

ORCID iD

M Scolnik https://orcid.org/0000-0002-0542-8001

References

1 Scolnik M, Marin J, Valeiras SM, *et al*. Incidence and prevalence of lupus in Buenos Aires, Argentina: An 11-year health management organisation-based study. *Lupus Sci Med* 2014; 1(1): e000021.
2 Bertsias GK, Ioannidis JPA, Aringer M, *et al*. EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: Report of a task force of the EULAR standing committee for clinical affairs. *Ann Rheum Dis* 2010; 69(12): 2074–2082.
3 Gordon C, Amissah-Arthur M-B, Gayed M, *et al*. The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults. *Rheumatology* 2018; 57(1): e1–45.
4 Bertsias G, Ioannidis JPA, Boletis J, *et al*. EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. *Ann Rheum Dis* 2008; 67(2): 195–205.
5 Pons-Estel BA, Bonfa E, Soriano ER, *et al*. First Latin American clinical practice guidelines for the treatment of systemic lupus erythematosus: Latin American Group for the Study of Lupus (GLADEL, *Grupo Latino Americano de Estudio del Lupus*)–Pan-American League of Associations of Rheumatology (PANLAR). *Ann Rheum Dis* 2018; 77(11): 1549–1557.
6 Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. *Arthritis Rheum* 1992; 35(6): 630–640.
7 Navarra SV, Guzmán RM, Gallacher AE, *et al*. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: A randomised, placebo-controlled, phase 3 trial. *Lancet* 2011; 377(9767): 721–731.
8 Furie R, Petri M, Zamani O, *et al*. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum* 2011; 63(12): 3918–3930.
9 Hochberg M. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40(9): 1725.
10 Petri M, Orbai A-M, Alarcón GS, *et al*. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012; 64(8): 2677–2686.
11 Gladman DD, Ibañez D, Urowitz MB. Systemic Lupus Erythematosus Disease Activity index 2000. *J Rheumatol* 2002; 29(2): 288–291.
12 Calvo-Alén J, Silva-Fernández L, Úcar-Angulo E, *et al*. Consenso de la Sociedad Española de Reumatología sobre el uso de terapias biológicas en el lupus eritematoso sistémico. *Reumatol Clínica* 2013; 9(5): 281–296.
13 Nikpour M, Urowitz MB, Ibañez D, Gladman DD. Frequency and determinants of flare and persistently active disease in systemic lupus erythematosus. *Arthritis Rheum* 2009; 61(9): 1152–1158.
14 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. Liossis S-N, editor. *PLoS One* 2012; 7(9): e45934.
15 Aringer M, Burkhardt H, Burmester GR, *et al*. Current state of evidence on ''off-label'' therapeutic options for systemic lupus erythematosus, including biological immunosuppressive, agents in, Germany, Austria and Switzerland: A consensus report. *Lupus* 2012; 21(4): 386–401.
16 Isenberg DA, Rahman A, Allen E, *et al*. BILAG 2004. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. *Rheumatology (Oxford)* 2005; 44(7): 902–906.
17 Merrill JT, Neuwelt CM, Wallace DJ, *et al*. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: The randomized, double-blind, Phase II/III systemic lupus erythematosus evaluation of rituximab trial. *Arthritis Rheum* 2010; 62(1): 222–233.
18 Scherlinger M, Carcaud C, Truchetet M-E, *et al*. Rituximab in moderate to severe non-renal systemic lupus erythematosus: A reanalysis of the EXPLORER study. *Ann Rheum Dis* 2019; Jan 4; annrheumdis-2018-214833.
19 Cobo-Ibáñez T, Loza-Santamaría E, Pego-Reigosa JM, *et al*. Efficacy and safety of rituximab in the treatment of non-renal systemic lupus erythematosus: A systematic review. *Semin Arthritis Rheum* 2014; 44(2): 175–185.
20 Duxbury B, Combescure C, Chizzolini C. Rituximab in systemic lupus erythematosus: an updated systematic review and meta-analysis. *Lupus* 2013; 22(14): 1489–1503.
21 Furie RA, Petri MA, Wallace DJ, *et al*. Novel evidence-based systemic lupus erythematosus responder index. *Arthritis Rheum* 2009; 61(9): 1143–1151.