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Follow-up and management of serologically active clinically quiescent cases in pediatric systemic lupus erythematosus

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Abstract

Objectives: Our aim is to identify the presence of serologically active clinically quiescent (SACQ) episodes in pediatric systemic lupus erythematosus (SLE) patients. We aim to identify serologic biomarkers associated with SACQ episodes and discuss risks and benefits of escalating treatments.
Material and methods: We evaluated 25 pediatric SLE patients, 13 of whom experienced SACQ episodes. Serologically active clinically quiescent was defined as two consecutive clinic visits without any clinical symptoms or clinical examination findings of a lupus flare with a clinical Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score of zero, but either elevated anti-dsDNA antibodies or low complement (C3 and/or C4) levels.
Results: Among the 13 patients who experienced a SACQ episode, there were a total of 24 episodes, with each patient experiencing 1–4 SACQ episodes. Erythrocyte sedimentation rate (ESR) was the most commonly elevated laboratory marker in a SACQ episode, followed by low hemoglobin levels, and then elevated anti-dsDNA antibodies. Of the 17 episodes treated during a SACQ episode, 15 (88%) did not progress to a clinical flare within six months, while two did. Furthermore, of the 7 patients who were not treated during their SACQ episode, 2 (29%) continued to be SACQ without flare, whereas 5 led to a clinical flare within six months.
Conclusions: Serologically active clinically quiescent episodes were identified in pediatric SLE patients, suggesting that the presence of SACQ is not limited to adults with SLE. Serologic markers such as increased ESR, hemoglobin, and elevated anti-dsDNA antibodies are preliminarily associated with pediatric SACQ episodes. Treating these SACQ episodes in pediatric SLE patients was less likely to lead to a clinical flare within six months when compared to not treating ($p < 0.05$). More research with a larger sample size is needed to define SACQ episodes, determine the prevalence in pediatric SLE patients, and establish SACQ treatment guidelines.

Key words: systemic lupus erythematosus, serologically active clinically quiescent, Systemic Lupus Erythematosus Disease Activity Index 2000.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by a variety of clinical manifestations and serologic changes, classically following an undulating course of activity and quiescence, often resulting in multisystem organ damage [1].

In 1979 Gladman et al. [2] identified a subset of adult SLE patients who presented with serologic abnormalities in the absence of clinical symptoms. This finding has been subsequently described in approximately 2–15% of SLE patients [3]. There is ongoing research regarding the efficacy of treatment for these serologically active and clinically quiescent (SACQ) patients [4–6].

This patient population requires a tailored approach to management because treatment protocols should depend on the existence of pathological consequences of the SACQ episodes.

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Treatment protocols for SLE are aimed at alleviating symptoms and controlling inflammation, with the overall goal of maintaining quality of life, while avoiding long term organ damage.

Treating patients without clinical symptoms or examination findings risks the morbidity of immunosuppressant and steroid treatment without the benefit of relieving symptoms or the knowledge that the treatment will provide long term benefits [5].

These considerations are especially pertinent in patients with pediatric-onset SLE. An estimated 10–20% of SLE patients are under the age of 18 [7]. Pediatric-onset SLE patients have a greater risk for renal, central nervous system (CNS), and hematologic manifestations, as well as more organ damage than adult patients [4, 7–10].

Pediatric patients are also susceptible to the negative effects of corticosteroids including but not limited to growth retardation, accelerated atherosclerosis, and severe infectious complications [11].

The presence of SACQ in pediatric-onset SLE has not been identified, even though pediatric SLE patients are at risk of both a more severe disease course and of greater pharmacological morbidities [4, 7, 8, 10].

Gensous et al. [12] concluded in their review, "Since the 1970s, no investigators have succeeded in identifying a biomarker with the potential to predict efficiently the occurrence of new flares, despite great clinical necessity".

The primary aim of this study is to determine the presence of SACQ in pediatric patients with SLE. The secondary aim is to highlight the outcome of escalating or not escalating SLE treatment in the case of SACQ, based on serologic markers such as hypo-complementemia, elevated erythrocyte sedimentation rate (ESR), elevated C-reactive protein (CRP), abnormal platelets, abnormal hemoglobin, and positive anti-dsDNA antibody levels.

Material and methods

This study protocol was approved by the University at Buffalo Institutional Review Board (IRB). The Institutional Review Board approved exemption from informed consent, as this is a retrospective chart review study. Patients were included in this study if they were followed up at John R. Oishei Children's Hospital in Buffalo, New York between January 2012 and June 2020 and met the revised 1997 American College of Rheumatology (ACR) criteria for systemic lupus erythematosus [13].

Patients were identified by diagnostic codes of systemic lupus erythematosus (ICD-10 code M32.9). Serologically active and clinically quiescent was defined as two consecutive clinic visits without clinical symptoms or examination findings indicative of a lupus flare with a clinical Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score of zero, but abnormal blood work, defined by increased anti-dsDNA antibody levels (normal 0–35 IU/ml) and/or low complement levels of C3 (normal range 80–175 mg/dl) or C4 (normal range 14–40 mg/dl).

Pediatric SLE patients in our study were typically seen in the clinic every 1–3 months. Twenty-five patients were included in our study: one male and twenty-four females between the ages of five and twenty years old at the time of diagnosis, with disease characteristics as described in Table I.

Thirteen of these patients had episodes that fit our definition of SACQ. We analyzed the medical charts retrospectively, using PowerChart. Data were entered into an electronic database and patient identifications were stored using an anonymous code. We recorded the patients' demographics, clinical presentation at time of diagnosis, initial treatment, and initial blood work results at time of diagnosis (Table I).

Additionally, we recorded medications before and after SACQ periods, along with the blood tests results, which included white blood cells count (WBC), hemoglobin, platelets count, C3 and C4 complement components, anti-dsDNA antibodies, red blood cells count (RBC) in urine, protein in urine, ESR, CRP, blood urea nitrogen (BUN), creatinine, and other positive antibodies when available. If a patient experienced a clinical flare of SLE following a SACQ episode, its duration in months was recorded.

We used Fisher's exact test to determine whether each of our blood work markers was associated with a SACQ episode. We also used Fisher's exact test to determine whether treatment was associated with fewer clinical flares in six months compared to no treatment. Statistical analyses were based on an alpha of 0.05 and conducted with SYSTAT 13 (SYSTAT Software, 2004).

Results

Of the 25 pediatric SLE patients evaluated, 13 (52%) experienced SACQ episodes over the course of the period studied and were included in the study. The mean age at diagnosis of SLE was 14 years. Of the 13 patients who experienced a SACQ episode, the number of episodes of SACQ per patient ranged from 1 to 4. Seven patients had one SACQ episode, three patients had two episodes, one patient had three episodes, and two patients had four episodes during the period studied. Among the 13 patients, there were a total of 24 SACQ episodes. The percentage frequency of abnormal laboratory values at the beginning of patients' SACQ episodes is displayed in Figure 1.

Table I. Demographic and disease characteristics of 25 patients with systemic lupus erythematosus

Parameters	*N* = 25
Gender, male/female	1/24
Age, years	5–20
Race	
Caucasian	10
African American	11
Asian	2
Declined	2
SLE duration in years at time of study	1–9
Symptoms on presentation	
Rash	9
Arthritis	10
Vasculitis	1
Oral ulcer	2
Seizure	3
Lymphadenopathy	4
Fatigue	3
Lupus nephritis	3
Weight loss	6
Fever	8
Arthralgia	8
Chest pain	2
Raynaud's phenomena	1
Serology on presentation	
Low WBC	8
Anemia	14
Low platelet	2
Low C3	17
Low C4	18
Positive dsDNA	17
Elevated ESR	15
Elevated CRP	4
Proteinuria	14
Positive ANA	24
Positive ENA RNP	13
Positive ENA smith	11
Positive ENA SSA	8
Positive ENA SSB	5
Positive histone antibodies	6
Positive antiphospholipid	5
Treatment in first 6 months of presentation	
Steroids	25
Hydroxychloroquine	25
Mycophenolate mofetil	10
Belimumab	2
Methotrexate	3
Azathioprine	2
Cyclophosphamide	1
Hydrocortisone cream	3
Anticonvulsant	3
Anticoagulant	1

ANA – antinuclear antibodies, CRP – C-reactive protein, ESR – erythrocyte sedimentation rate, SLE – systemic lupus erythematosus, WBC – white blood cells.

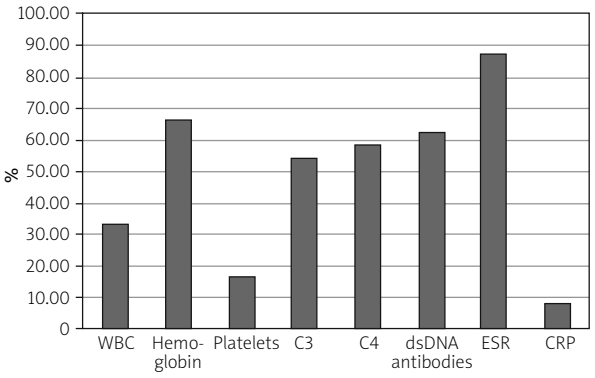

Fig. 1. Percentage frequency of abnormal laboratory values in serologically active and clinically quiescent episodes (*n* = 24).

The laboratory values most commonly found to be abnormal during the 24 SACQ episodes were ESR (87.5%), hemoglobin (66.6%), and anti-dsDNA antibodies (62.5%). None of the laboratory values studied were statistically significantly different between patients who progressed to a clinical flare and those who did not.

Of the 24 episodes of SACQ, 17 (71%) were treated based on physician's opinion and 7 (29%) were not treated. Of the 17 episodes treated during a SACQ episode, 15 did not progress to a clinical flare within six months, while two did.

Furthermore, of the 7 patients who were not treated during their SACQ episode, 5 experienced a clinical flare within six months, whereas 2 continued to be SACQ without flare (Table II).

Table II. Progression to clinical flare among serologically active and clinically quiescent (SACQ) episodes treated versus those not treated

Progression to clinical flare	SACQ and continued to be SACQ at least 6 months	SACQ leads to clinical symptoms within 6 months	Marginal row totals
With treatment	15	2	17
Without treatment	2	5	7
Total	17	7	24 (grand total)

Results indicated a lower percentage progression to clinical flare for serologically active and clinically quiescent (SACQ) episodes treated, with a prevalence of 12% (2/17), compared to 71% (5/7) progression to clinical flare when not treated ($p < 0.05$).

Treating the SACQ episodes was less likely to lead to a clinical flare within six months when compared to not treating a SACQ ($p < 0.05$). Table III shows a full description of SACQ episodes.

Discussion

Definition of serologically active and clinically quiescent

To our knowledge, this is the first study evaluating SACQ episodes in the pediatric SLE population; all studies we are aware of were conducted with adult-onset SLE patients [2, 3, 5, 14–18].

The primary aim of this study was to evaluate for the presence of SACQ episodes in pediatric-onset SLE patients, and to determine whether treatment of these episodes may be beneficial in preventing the onset of a clinical flare. During the period studied, 13/25 patients (52%) with pediatric-onset SLE experienced a SACQ episode. This is a significantly higher frequency than has been described in the literature evaluating the adult SLE population, with most describing a prevalence between 2.2 and 15% [14, 15, 17, 18].

This is likely due to various factors. First and foremost, there are variations in the definition of a SACQ episode. Many adult SLE studies have defined a SACQ episode as two or more consecutive years without clinical symptoms [3, 5, 14, 16].

Our definition required two consecutive clinic visits without clinical symptoms or examination findings indicative of a lupus flare, and in most cases this would equate to 4–6 months. As discussed previously, pediatric-onset SLE patients have a greater risk for renal, CNS, and hematologic manifestations, and most importantly organ damage. For this reason, pediatric SLE patients are monitored more frequently with both laboratory and clinical assessments.

A second variation in the definition is in the laboratory criteria. Ng et al. [18] defined SACQ as a mean global BILAG (British Isles Lupus Assessment Group) score less than 6 and anti-dsDNA antibody titers above the normal level on at least 2 occasions during a 6-month period.

In our study, SACQ was defined by elevated anti-dsDNA antibodies and/or low C3 or C4 levels. This definition was chosen based on both the literature [6] and the personal experience of the treating physicians that decreases in complement levels and increases in anti-dsDNA antibodies often herald the onset of a clinical flare.

Unfortunately, potentially due to the small sample size in our study, neither abnormal anti-dsDNA antibody levels nor C3 or C4 levels differentiated clinical flares. It is worth mentioning, however, that abnormal anti-dsDNA antibody levels were seen in 62.5% ($n = 15$) of SACQ episodes, 53% ($n = 8$) of which went on to clinical flare compared to 22% ($n = 2$) of normal anti-dsDNA antibody episodes which continued on to clinical flare.

A second difference in methodology between previous adult SLE studies and our study is that we included patients taking corticosteroids and/or immunosuppressive medications. These patients have been excluded in some previous adult studies because this could be a confounding factor in normalizing blood work [3, 5, 14, 16]. Lastly, our study consisted of a small sample size ($n = 25$), with only 13 (52%) out of the 25 patients experiencing a SACQ episode, limiting statistical power and extrapolation.

Development of serologically active and clinically quiescent into clinical flare

There has been research investigating the prevalence of clinical flares developing from SACQ episodes.

Walz LeBlanc et al. [15] observed that almost half of the 74 patients with SLE who had a SACQ period experienced a flare within a year, using the SLEDAI global activity score, with no predictive factors identified during or before the SACQ period.

Steiman et al. [14] reported that a similar proportion (58.9%) of patients who experienced a SACQ episode developed a clinical flare at a longer median of 158 weeks.

In a more long term study, Ng et al. [18] found that 9% ($n = 27$) of 290 SLE patients had SACQ episodes, with 17 (81%) SACQ episodes leading to a flare in the next five years. Median duration to the first flare was 15 months (range 2–46 months). They also suggested that anti-

Table III. Description of 13 patients with 24 serologically active and clinically quiescent (SACQ) episodes

No. of clinical description	Medication before SACQ	Medication after SACQ	WBC	HG	Plat	C3	C4	Anti-dsDNA	ESR	CRP	Other abnormal lab	End point	Treatment for SACQ	Clinical flare and treatment after flare
SLE1/E1	HCQ, MMF, oral steroids	Same	5.2	10.6	376	67	10.4	Neg	39	0.2	None	Doing well for 12 months then C4 became lower and dsDNA became positive	None	No clinical flare for at least 6 months
SLE1/E2	HCQ, MMF, methotrexate, oral steroids	Added steroids IV and increased oral steroids	4.1	11.7	278	54	1.7	316	43	0.2	None	Clinically and serologically quiescent for 7 months then became SACQ missing MM	IV steroids and increased oral steroids	No clinical flare for at least 6 months
SLE1/E3	HCQ, MMF, methotrexate, oral steroids	HCG, MMF, and increase oral steroids	5.7	11	296	46	4	351	26	0.2	Positive ENA, SSA and RNP	Clinically and serologically quiescent for 24 months then became SACQ after missing MM	Increased oral steroids	No clinical flare for at least 6 months
SLE1/E4	HCQ, MMF, methotrexate	Added IV steroids Rituximab	4.2	10.3	13	41	3	167	50	0.3	None	Clinically and serologically quiescent for 6 months so far	Added IV steroids Rituximab	No clinical flare for at least 6 months
SLE2/E1	HCQ, MMF	Add IV steroids	4	9.8	66	72	11	Neg	28	0.4	None	Clinically and serologically quiescent for 19 months then became SACQ	Add IV steroids	No clinical flare for at least 6 months
SLE2/E2	HCQ, MMF	Add IV steroids	4.6	10.3	155	63	12	Neg	23	0.6	None	Clinically and serologically quiescent for 10 months then transfer to adult	Add IV steroids	No clinical flare for at least 6 months
SLE3	HCQ, MMF	Increase MMF dose	5.3	12.8	341	97	10.3	186	17	1.7	None	Clinically and serologically quiescent for 38 months so far	Increase MMF dose	No clinical flare for at least 6 months
SLE4/E1	HCQ, MMF	Add IV steroids	2.6	11.5	205	48	15	461	23	1.1	None	Clinically and serologically quiescent for 13 months then became SACQ	Add IV steroids	No clinical flare for at least 6 months
SLE4/E2	HCQ, MMF	Add oral steroids	5.9	9.3	383	61	20	1000	85	19	None	Clinically and serologically quiescent for 11 so far	Add oral steroids	No clinical flare for at least 6 months
SLE5/E1	HCQ, MMF, tacrolimus, steroids oral	Increase steroids and tacrolimus	6.8	13.1	315	88	12	Neg	62	2	None	Clinically and serologically quiescent for 14 months then became SACQ after	Increase steroids and tacrolimus	No clinical flare for at least 6 months
SLE5/E2	HCQ, MMF, tacrolimus	Start rituximab	7.2	12.4	96	78	10	Neg	70	6	None	Clinically and serologically quiescent for 11 months then became SACQ	Add rituximab	No clinical flare for at least 6 months
SLE5/E3	HCQ, MMF	Add rituximab	2.7	11.3	279	71	24	Neg	99	0.4	None	Clinically and serologically quiescent for 13 months then became SACQ	Add rituximab	No clinical flare for at least 6 months

Table III. Cont.

No. of clinical description	Medication before SACQ	Medication after SACQ	WBC	HG	Plat	C3	C4	Anti-dsDNA	ESR	CRP	Other abnormal lab	End point	Treatment for SACQ	Clinical flare and treatment after flare
SLE5/E4	HCQ, MMF	Add rituximab	2.9	12.2	344	79	6	Neg	79	4	None	Clinically and serologically quiescent for 11 months then has clinical flare as was not able to continue on rituximab due to reaction	Add rituximab	No clinical flare for at least 6 months but flare after 11 months with rashes/rituximab
SLE6	MMF, HCQ	Same	2.8	10.2	233	114	13	111	20	2.7	IGG1205	Flare up with arthritis after 4 months	None	Arthritis/IV and oral steroids
SLE7	Belimumab, HCQ	Added oral and IV steroids	2.8	11.7	248	84	17	142	13	1.5	Histone, ENA Sm and RNP	Clinically and serologically quiescent for 15 months and then flared after self-discontinued all medications	Oral and IV steroids	No clinical flare for at least 6 months but flare after 15 months CNS lupus and IV lupus nephritis/ cyclophosphamide
SLE8/E1	MMF, HCQ, oral steroids	Same	5.8	13.4	291	71	20	Neg	15	0.6	None	Flare up with arthritis after 4 months	None	Arthritis/steroids joint injection and increase oral steroids
SLE8/E2	MMF, HCQ, oral steroids	Same	5.9	13.9	257	97	21	274	52	1.9	None	Flare up with arthritis and alopecia after 1 month	None	Arthritis and alopecia/ rituximab
SLE8/E3	MMF, HCQ, oral steroids	Same	5.5	13	263	90	19	101	46	2.6	None	Flare up with rash after 6 months	None	Rash/rituximab
SLE9	HCQ	Same	2.4	12.1	226	110	15	118	22	15	None	Same SACQ	None	No clinical flare for at least 6 months
SLE10	HCQ, MM, IVIG	Added steroids IV	2.6	11.4	272	55	7.8	Neg	53	1.1	None	Clinically and serologically quiescent for 22 months so far clinically	IV steroids	No clinical flare for at least 6 months
SLE11	HCQ, oral steroids	Increase oral steroids	19	9.4	373	118	18	231	122	3.7	Histone, ENA Sm and RNP	Flare up with arthritis after 1 month	Increase oral steroids	Arthritis/steroids patient is pregnant
SLE12	HCQ, MMF	Added steroids IV	4.7	11.8	198	104	17	260	8	0.4	None	Clinically and serologically quiescent for 10 months then flared with rash after missing MMF	IV steroids	No clinical flare for at least 6 months then flare after 10 months with rash/oral steroids and re-establish MMF
SLE13/E1	MMF, HCQ, oral steroids	Same	2.3	11.1	189	84	5.2	234	44	0.9	None	Flare up with rashes and arthritis after 3 months	None	Rash and arthritis/ belimumab
SLE13/E2	Belimumab, HCQ	IV and oral steroids	8.1	11.6	328	90	10	218	60	2.3	ENA SSA, SM and RNP	Flare up with rash after 4 months	IV and oral steroids	Rash/IV and oral steroids

Anti-dsDNA – anti-double stranded DNA antibody, normal 0–35 IU/ml, CNS lupus – central nervous system lupus, CRP – C-reactive protein, C3 – complement C3 (normal 80–175 mg/dl), C4 – complement C4 (normal 14–40 mg/dl), ENA RNP – extractable nuclear antigen anti-ribonucleoprotein, ENA Sm – extractable nuclear antigen anti-Smith antibody, ENA SSA – extractable nuclear antigen anti-SSA, ESR – erythrocyte sedimentation rate, HCQ – hydroxychloroquine, HG – hemoglobin, normal for girl aged < 18 years is 12–15 g/dl, girl >18 years old is 12–16 g/dl, we have one male with normal Hg for male < 18 years is 12.5–16.1 g/dl and > 18 is 14–18 g/dl, MMF – mycophenolate mofetil, Plat – platelet (normal 150–450 × 10^9/l), SACQ – serologically active and clinically quiescent, E – indicates episode of SACQ with number of episodes following, WBC – white blood cells, normal 4–10.5 × 10^9/l with leukopenia < 3 × 10^9/l, IV – intravenous.

nucleosome antibodies (anti-NCS) may be a better predictor than anti-dsDNA antibodies for future flares.

Steiman et al. [5] observed that patients with a prolonged SACQ period accrued less damage over a decade compared to matched (SLE) controls, supporting a conservative treatment approach.

This literature has supported the general consensus that active serology without clinical manifestations should not guide treatment decisions, and that these patients are best managed conservatively with close follow-up.

However, this is not always an approach that physicians are comfortable with. For example, one patient in our study presented with severe manifestations at the time of diagnosis, including seizures, thrombosis in multiple organs, and an eleven year history of lymphadenopathy; this was previously published as a case report [19].

Following treatment he went into remission both clinically and serologically. In a follow-up visit, he was positive for anti-dsDNA antibodies after having previously tested negative and had elevated ESR after it was previously normal with no clinical symptoms, prompting the physician to advise treatment.

Despite this recommendation, the patient chose not to be treated, and six months later presented to the emergency room with a very severe clinical flare. This is an example of a case where treating a SACQ period may prevent a clinical flare.

Treatment considerations

One of the goals of our study was to determine whether treating a SACQ episode is associated with a better clinical outcome. According to our data (Table II), 71% of SACQ flares that were not treated led to clinical flares within 6 months compared to only 12% of SACQ flares that were treated.

Due to multiple scoring systems for monitoring SLE and following flares, physician's opinion is often considered the 'gold standard' for the evaluation of disease activity with bias based on personal experience [20].

In our study, physician's opinion was used to decide whether or not to escalate treatment of the SACQ episode based on the physician's knowledge of each patient. For example, in our study we have a case of a patient with a SACQ episode with significantly low platelets of 13,000, low C3, low C4, and positive anti-dsDNA antibodies without any clinical sign of bleeding who underwent treatment for low platelets given the balance of benefit and risk of treatment. This patient went into remission serologically and continued to be in remission clinically.

If serological activity serves as a marker of future clinical manifestations, and if underlying damage were to persist even in the absence of symptoms, it would be appropriate to institute a treatment protocol for abnormal serology. However, if SACQ flares neither cause harm nor indicate future harm, the patient risks the morbidity of immunosuppressant or steroid treatment without gaining the benefit of pharmacological intervention.

Treatment of a SACQ episode usually consists of adding either corticosteroids or an immunosuppressant medication. Pediatric-onset SLE patients have a longer disease course and are at greater risk of morbidity from medications. Corticosteroid use can lead to acne, weight gain, cushingoid appearance, growth retardation, accelerated atherosclerosis, and severe infectious complications [11].

Physicians have to weigh the risks and benefits of treatment carefully. Adolescent patients in particular may struggle with medication compliance as they grapple with the severity and chronicity of their diagnosis and the side effects of the medications. In this population, non-adherence to medication regimens is of particular concern and could be associated with SACQ episodes.

Several patients in our study had low or non-detectable medication levels when tested. It is important to establish evidence-based approaches for SACQ episodes so pediatric patients do not experience negative consequences of unnecessary treatment or systemic damage that could have been avoided by treatment.

Conclusions

Decisions surrounding the benefits and risks of treating SACQ SLE prove even more challenging in the pediatric population due to more severe lupus manifestations, longer disease course, unknown risk of end organ damage in SACQ disease, and unknown data about risk of flares.

The goals of therapy for patients with SLE are to ensure long-term survival, achieve the lowest possible disease activity, prevent organ damage, minimize drug toxicity, improve quality of life, and educate patients and their families about their role in disease management.

The management of disease flares in children with SLE is highly individualized. Further research with prospective study is warranted to determine whether pediatric patients with SACQ episodes should be treated and how these decisions then affect the health of these patients in the long term.

The authors declare no conflict of interest.

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