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Clinical and serological characteristics of early systemic lupus erythematosus

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Abstract

Background: Early diagnosis in patients with systemic lupus erythematosus (SLE), which is based on the knowledge of the variability of the initial disease manifestation, followed by prompt initiation of basic therapy is essential for a favorable prognosis in these patients. Thus, the determination of early manifestations of the disease in patients with lupus was the main objective of this study.
Material and methods: This present descriptive study included 68 patients with early SLE – the disease duration being of up to 2 years after the diagnosis. The evaluation of the characteristics of the disease was performed by a questionnaire developed by this study, which included the clinical and paraclinical examination. Statistical data processing was performed via Excel program.
Results: The analysis of the results on early manifestations of the disease revealed the high frequency of joint involvement in 64.7%, photosensitivity and malar rash – in 58.82% and 32.35%, respectively, and oral ulcers and alopecia were found in about 1/4 cases. The signs detected, but omitted from the criteria with increased occurrence were represented by fatigue in 42.64% of cases, fever – 29.41%, myalgia and Raynaud's syndrome in 20.58% of patients. It should be noted that the first lupus-associated manifestations were noticed 1-4 years prior to diagnosis.
Conclusions: Top early manifestations in patients enrolled in the current study included arthralgia, photosensitivity and fatigue. These symptoms were followed by malar rash and fever.
Key words: early systemic lupus erythematosus.

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a wide spectrum of clinical and immunological abnormalities of unknown etiology, which develops on the base of imperfect genetically determined immunoregulatory processes, associated with the overproduction of autoantibodies. Genetic, environmental and sociodemographic factors play important roles in the pathogenesis and expression of this disease. This multiplicity of etiological factors could explain the variability of disease manifestations observed, not only between individuals, but also between ethnic groups [1, 2]. SLE is a pathology that affects people of different ages, races, origins, gender; mostly women of childbearing age are affected, in 83-97% of cases. The systematic literature review (Rees, 2017) of the global incidence of SLE reported the highest estimated incidence and prevalence of SLE which were found in North America (23.2/100 000 person-year and 241/100 000 people, respectively). The lowest incidence of SLE was reported in Africa and Ukraine (0.3/100 000 person-year), and the lowest prevalence was found in Northern Australia (zero cases in a sample of 847 people) [3].

Over the last few decades, SLE has changed its expression, which was reflected in the revision of the disease classification criteria. The first SLE classification criteria were developed by the American College of Rheumatology in 1971 by the Cohen A.S. Working Group, and were subsequently revised in 1982 (E. Tan et al.). In the light of the new findings , that is the presence and association of antiphospholipid antibodies in patients with SLE, the 1982 criteria were revised and new criteria were approved in 1997 (Hochberg M.C.). The latest criteria from 2012 – SLICC (Systemic Lupus International Collaborating Clinic) have been extended due to skin manifestations and strengthening of immunological indices by the complement fractions C3, C4 [4].

Systemic lupus erythematosus, however, remains an ac-

tual research domain over the last years, especially the early stage of the disease. Over the last decade, SLE has changed due to improved classification criteria and, last but not least, due to the early use and administration of aggressive treatment [5]. The clinical onset depends on several risk factors, including gender, age, ethnicity, geographic area, etc. Specific and non-specific clinical events, which occur during the inception and evolution of SLE, have a high variability. Thus, the vector of the research in the field is being directed for a few years at studying the clinical and immunological manifestations of onset of SLE, as well as in the first years of the disease [6-9]. This trend can be explained by the attempt of researchers to further improve the criteria for classifying the disease, increasing the sensitivity and specificity of these criteria, to reduce the time of diagnosis of the disease from the onset of the first symptom associated with lupus erythematozus to clinical diagnosis.

The evolution of SLE is characterized by the complexity and uncertainty of the disease diagnosis, which can lead to considerable delays between the initial manifestations of the disease, establishing a diagnosis and initiating appropriate medical treatment. Delayed or lack of treatment may increase the likelihood of organic damage due to high disease activity. Thus, in earlier diagnosed patients, the inflammatory disease can be treated earlier and organic damage could be minimized [10].

Thus, the necessary time for diagnosis of the disease expresses the first principle in the proper management of the disease, while the reduction of the diagnosis period reveals the importance of early therapeutic intervention.

Based on the aforementioned, this research study was oriented towards determining the manifestations of early SLE, which is the most important factor for a prompt establishment of the disease diagnosis. The purpose of the study was to evaluate early manifestations of the disease in patients with SLE within the study group.

Material and methods

A cross-sectional study was conducted at the Department of Internal Medicine within *Nicolae Testemitanu* State University of Medicine and Pharmacy of the Republic of Moldova, and at the Rheumatology Department of the Institute of Cardiology. The patients were enrolled from June 2016 to May 2019, according to the accepted approval of the Research Ethics Committee (No 66 of 16.06.2016). The research included 68 patients who were selected according to SLICC classification criteria for systemic lupus erythematosus, validated in 2012. The SLICC 2012 classification criteria consist of 11 points, which form two compartments: clinical and immunological. The diagnosis is established if at least four criteria are included, one clinical and one immunological, except for renal damage confirmed by renal biopsy associated with an immunological criterion. The research included subjects over 18 years old, who signed an informed consent for study participation. Exclusion criteria included other confirmed rheumatologic diseases as well as patient's refusal. The clinical and demographic data, as well as information about disease characteristics were collected according to a file prepared within the present study. The questionnaire included information on clinical and demographic data – gender, place of residence, marital status, age at onset and duration of the disease. The special investigation was performed in order to highlight the symptoms and signs at the onset of the disease, which represented the criteria for the established diagnosis. The model used within the present study was based on literature analysis, and presented as early signs of lupus, which was completed together with the subject. Moreover, every patient was asked about the time of symptom onset, before and after the diagnosis of SLE was established.

The obtained results were analyzed via the Microsoft Office Excel program. The structure and dynamics of the researched phenomena were examined using statistical methods with the assessment of arithmetic means (M), standard deviations (SD) and confidence interval (CI). The statistical comparison of the data and the determination of the significance test allowed the assessment of the differences between the mean and percentage values. The differences between the mean values of the studied parameters were estimated using the t-Student criterion.

Results

A performed cross-sectional study included 68 consecutive patients with early SLE, admitted to the Rheumatology Department at the Institute of Cardiology, the duration of the disease lasted up to 2 years after being diagnosed.The demographic data of the study lot is presented in the table 1.

Table 1

Demographic indices in the investigated sample (No = 68)

Parameters	Patients, No	%
Gender:		
Women	65	95.59
Men	3	4.41
Place of residence:		
Rural	36	52.94
Urban	32	47.06
Marital status:		
Married	36	52.94
Divorced	14	20.59
Widower	4	5.88
Bachelor	14	20.59

The data presented in the table 1 revealed the predominance of women (95.59%) in the study group, with a female to male ratio of 22:1. According to the place of residence, patients from rural areas evidenced their light preponderance in the space. After the segregation of the patients' marital status we attested that at the time of research 36 (52.94%) subjects lived with families being married, 20.59% of cases were divorced or not married yet, and 5.88% of the subjects included in the study were widows/widowers.

Further reseasch assessed the age characteristics at the time of research and at the onset of the disease in patients included in the study, as well as the mean duration of the disease and the time from the first symptoms to diagnosis.

Table 2

Characteristics of variables in the research group

Parameters	Mean value±SD	Min V Max V
Mean age at the time of the research, years	39.6±15.0	20-73
Mean age at the time of the disease onset, years	38.47±14.88	20-67
Mean duration of the disease, months	12.42±8.70	0.5-24
Time from the disease onset to the SLE diagnosis confirmation, months	7.08±8.22	1-47
SLICC cumulative criteria number, abs.nr.	7.32±2.06	4-12

The data presented in the table 2, concluded that patients with early SLE had a mean age of 39.6 years, ranging between 20 and 73 years, while the mean age at the disease onset was 38.47 years. Concerning the duration of the disease, it varied from 1 to 24 months, as the definition of the early SLE, the mean duration was 12.42 months. The time from the first symptoms, claimed by the patient, until the confirmation of the SLE diagnosis varied from 1 to 47 months, with the mean time of the disease diagnosis of 7 months. The cumulative number of SLICC based on 2012 classification criteria at study entry was in average 7.3, with the highest number of 12 criteria.

In order to analyze and describe the study group, the time from the onset of the first symptoms to the referral to the doctor and later to diagnosis confirmation of systemic lupus erythematosus was identified.

Table 3

Quantification of the disease diagnosis term

Parameters	Mean value±SD	Min V Max V
Time from the disease onset to referral to healthcare (months)	4.81±6.57	0.25-37
Time from referral to healthcare to diagnosis confirmation (months)	2.27±2.1	0.75-10

Patients referred to the doctor on average at 4.81 months, with one or more symptoms that were later related to systemic lupus erythematosus (tab. 3). The shortest time was one week, the earliest manifestations being fever and edema. Patients with clinical signs, such as malar rash, arthritis and serositis referred to the doctor one month after the symptoms appeared. In addition to these manifestations, many patients experienced a marked fatigue at the time of disease onset, which they thought was not a reason for referring to healthcare. Patients who had photosensitivity, malar rash and joint pain as first manifestations referred to medical healthcare starting from 0.25 to 37 months. Thus, regarding the time of diagnosis confirmation from the first medical referral, the mean time of diagnosis established was 2.27 months, the shortest term being 3 weeks.

The complexity of the autoimmune process and the difficulty of diagnosing early SLE, due to the insufficiency of diagnostic criteria, can lead to considerable delays between the onset of the disease and the time of diagnosis. In fact, patients from the study group developed specific manifestations of lupus at the onset of the disease, stated in the disease classification criteria, as well as pathological changes omitted from the classification criteria, which however deserve special attention in case of early diagnosis of the disease. Further, the study identified the early signs of the disease by calculating their frequency in the study subjects (tab. 4).

Table 4

Clinical signs in patients before referral to primary care

SLE signs	Patients No=68		
	No	%	95% CI
Malar rash	22	32.35	0.22-0.44
Fotosensitivity	40	58.82	0.46-0.69
Maculopapular rash	4	5.88	0.02-0.14
Discoid rash	2	2.94	0.008-0.01
Oral/nasal ulcers	18	26.47	0.17-0.38
Difuse alopecia (non-cicatriceal)	18	26.47	0.17-0.38
Arthritis/arthralgia	44	64.70	0.52-0.75
Serositis: Pleuritis Pericarditis	6 2	8.82 2.94	0.04-0.17 0.008-0.01
Lupus nephritis (nephrotic/nephritic syndrom)	4	5.88	0.02-0.14
CNS involvement: Polineuropathy	4	5.88	0.02-0.14
Headache	8	11.76	0.06-0.21
Depression	10	14.70	0.008-0.25
Hemolitic anemia	1	1.47	0.02-0.07
Fever	20	29.41	0.19-0.41
Fatigue	29	42.64	0.31-0.54
Weight loss	10	14.70	0.08-0.25
Limphadenopathy	9	13.23	0.7-0.23
Myalgia	14	20.58	0.12-0.31
Livedo reticularis	10	14.70	0.08-0.25
Sjogren syndrom	8	11.76	0.06-0.21
Raynaud syndrom	14	20.58	0.12-0.31
Vascular thrombosis	2	2.94	0.008-0.1
Spontaneous pregrancy loss, n-65	3	4.62	0.001-0.12

The material presented in table 4 resume the early signs that can be associated with lupus. Therefore, the clinical picture from the onset of the disease until the doctor's assessment was determined in 64.70% of cases related to joint involvement according to the classification criteria. It should

be noted that joint pain without synovitis or morning stiffness, was most commonly reported, accounting for 80.88% of patients.

The skin involvement manifested by photosensitivity and malar rash was registered in 58.82% and 32.35% of cases, respectively; followed by oral and / or nasal ulcers and diffuse non-scarring alopecia in 26.47% of cases. Maculopapular and discoidal rash were rare skin manifestations in the early period and were reported in 5.88% and 2.94% of patients. The characteristic SLE signs, however not occurring at the onset of the disease were serous pleurisy and pericarditis (8.82% and 2.94%, respectively). Regarding renal impairment, it was manifested by nephrotic or nephritic syndrome and was present in 5.88% of cases. The involvement of the nervous system, which is a part of the SLICC classification criteria, was characterized by polyneuropathy, in 5.88% of cases. Hemolytic anemia, which is an early manifestation of lupus, has been rarely reported, only in one patient viz. 1.74% of cases.

Carefully analysis identified signs related to systemic lupus erythematosus in the early stages of the disease, though not included in the 2012 SLICC classification criteria. Fatigue, one of the most exhausting symptoms in patients with SLE was reported in 29 (42.64%) subjects from our study lot. Another important constitutional sign was fever in the absence of infection, estimated in 20 (29.41%) cases. Weight loss of more than 5-10% of body weight in the last 6 months or a decrease of more than 5 kg in the last month, in the absence of other causes, as an early symptom of the disease, was reported in 14.70% of cases. Another early manifestation-myalgia, was reported as pain or muscle weakness in the absence of obvious causes in 14 (20.58%) patients. The presence of lymphadenopathy was characterized by the increase in size of more than 5 cm of the lymph nodes in the cervical, axillary or inguinal areas, in the absence of infectious or malignant process, being detected in 9 (13.23%) cases. Neurological manifestations, such as depression and headache, which are not included in classification criteria of the disease, were reported in 10 (14.70%) and eight (11.76%) subjects, respectively. The involvement of peripheral vessels at the onset, manifested by Raynaud's Syndrome and / or reticular livedo, was found in 14 – 20.58% and 10 – 14.70% of patients, respectively. Venous thrombosis was an early manifestation of the disease in 2.94% of cases. Sjogren's syndrome, one of the early signs of the disease, was present in 8 (11.76%) patients as the first symptom of the disease. Spontaneous abortion, which is an important manifestation at the onset of the disease among young patients, occurred in 3 patients out of 65 (4.62%).

Following the idea of early signs, this present study separated the top most common manifestations of systemic lupus erythematosus (fig. 1).

The first signs attributed to lupus, at the time of referral corresponded to the 2012 SLICC classification criteria, as well as included the constitutional ones, which were not provided by these criteria. In fact, as shown in figure above, the top three early manifestations were arthralgia, photosensitivity and fatigue, while the top five variables were followed by malar rash and fever.

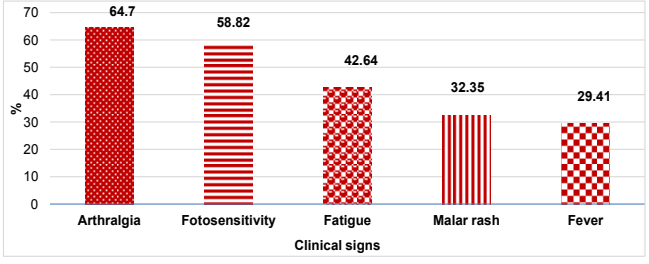

Fig. 1. Top early manifestations of SLE

Hypothetically, the study was oriented towards the clinical signs preceding the diagnosis of SLE and their chronological stratification. The earliest SLE-associated clinical manifestations were recorded 1-3 and even 4-5 years before the diagnosis of the disease. From the first year until the established diagnosis, 68 patients presented 188 criteria, each patient had 2.64 clinical signs, 2 years before patients had 104 (1.52), 3 years before – 88 (1.29) signs and 4-5 years before the diagnosis was established 39 (0.57) criteria were recorded for patients with early SLE. A year prior to establishing the diagnosis was characterized by presence of at least 3-4 signs of lupus in the same patient, which led to the motivation of their immunological research. Thus, transient arthralgia, seasonal photosensitivity and episodic fever were the 4-5 year preceding signs of the diagnosis; at the same time, 3 years before, malarial rash, weight loss and leukopenia up to 4.0 x 10^9 occurred. Two years before the diagnosis, the patients' signs were characterized by installation of serositis, oral ulcers and thrombocytopenia, increased ESR, anemia and false positive MRS. The year preceding the diagnosis was characterized by installation of several signs, including the laboratory ones.

Moreover, the supplementation of clinical variables with laboratory research could have accelerated the establishment of the diagnosis of lupus, which could have been established at least 2 years before, based on clinical picture and in compliance with four diagnostic criteria.

Furthermore, the study examined the laboratory indices by analyzing the hematological parameters at the time of the research in the context of the disease classification criteria. Thus, the most frequent hematological manifestation in early disease was leucopenia in 29.41% of cases, followed by anemia in 20.59% of subjects. Thrombocytopenia and lymphopenia were found in 19.12% and 16.18% of cases, respectively.

The immunological criteria analysis distinguished that the most common were the antinuclear antibodies (ANA) (92.65% of cases) and anti-dsDNA (91.17%). Another immunological criterion in early lupus patients was the increased incidence of low titers of complement fractions C3 and C4, identified in 58.82%. The presence of antiphospholipid antibodies was characterized by a higher frequency of lupus anticoagulant – 17.64%, followed by anti-CL antibodies and anti-β2GP1 antibodies, found in only 5.88% and

2.94% of cases, respectively. As regarding the anti-Smith antibodies and the Coombs test, these were present in 11.76% and 14.70% of patients, respectively.

Consequently, the most common paraclinical manifestations, including the immunological ones, in the early period of the disease were the anti-dsDNA (91.17%), ANA (79.41%), low titer of complement fractions (C3, C4) (58.82%), as well as leukopenia (29.41%).

Discussion

The present study, described the frequency and characteristics of the major SLE clinical manifestations and the time of the disease diagnosis in patients from the Republic of Moldova. The important fact is that the time between the onset of symptoms and established diagnosis in last decades has been shortened [2, 5, 11], and yet suggests that it is not short enough and more efforts should be made to establish the diagnosis of SLE even faster [12]. For patients diagnosed with SLE before 1980, the mean time between the onset and established diagnosis was 59 months, which subsequently decreased to 28 months for patients diagnosed between 1980 and 1989, and to 20 months for patients diagnosed between 1990 and 2010 [11, 13]. ANA testing credited differences in the diagnosis delay before 1980th and after 1980th. Some authors suggest that the average time to disease diagnoses after the 2000s has been reduced to 9 months [14]. The present study data showed that the average time for disease diagnosis was 7.08 months. These results could be explained by improving the diagnosis, by providing a wider use of immunological criteria, which are more extensive and accessible to perform, as well as medical assistance provided by the highly qualified doctors and dissemination of information through reports presented at conferences and working groups or multidisciplinary and continuing medical education. The main cause of the shortest diagnosis, lasting up till one month prior to primary healthcare was the addressability of the patient presenting such symptoms like fever, edema, malar rash and arthritis. The longest period requiring medical referral from the symptom onset lasted 37 months, and the patients experienced their first manifestations as photosensitivity, malarial rash or non-swollen joint pain. Thus, as regarding the time of diagnosis confirmation from the time referral to primary care, the mean time of diagnosis established was at 2.27 months, the shortest term being 3 weeks, which was confirmed by paraclinical and immunological tests that require time to perform. Moreover, based on the data obtained, the period of diagnosis of the disease in recent years has improved due to the high addressability of patients in the first 3 months after the disease. The review analysis of the literature from the last decades reported that the time to establish the diagnosis varies depending on the cohort performed, the countries involved in the research and the methods of patients' selection. At the same time, the results of research in the field do not present similar data regarding the time of diagnosis of the disease, thus, the topic of the early diagnosis of the disease remains in force [6-9].

The importance of recognizing the initial manifestations of the disease is indisputable and is explained by the researchers' attempt to further improve the disease classification criteria, with increasing their sensitivity and specificity, in order to reduce the time of diagnosis confirmation from the onset of the first SLE-related symptom to complete clinical diagnosis. However, the disease diagnosis is currently difficult to establish due to both symptom variety and nature of acute to insidious symptom onset. Moreover, the signs of the disease may be non-specific and characteristic of several medical conditions, which may lead to a delayed diagnosis [5-7, 14].

In order to compare the data the present study examined some of the important researches on early SLE. Data published by Pons Estel B.A. et al. (2004) presented the study findings of the Latin American Lupus Study Group research (GLADEL), which assessed the manifestations at the onset of the disease in the research groups according to race: Whites, Mestizo and African-Latin Americans [15]. Thus, according to the study findings, the top manifestations at onset in the total group of patients with joint involvement were recorded in 67.3% of cases, fever – 28.6%, photosensitivity – 24.5%, malarial rash – in 23.6 % and alopecia – in 20.3% of cases, and total skin disorders – in 46.3% of cases. It should be mentioned that the top five manifestations are followed by weight loss, nasal / oral ulcers, Raynaud's syndrome and hematological manifestations, which were present in more than 10% of cases. Due to the difference in race of the total research group, the study aimed to compare the frequency of onset manifestations with the cumulative signs found within the group of White people. Therefore, the most common symptoms were arthralgia and / or arthritis – 93.5%, skin manifestations – 89.5% and fever – 60.2%, which is similar to the data from this study, while hematological manifestations – 68.2%, alopecia – 55.0% and renal impairment – 43.6% were detected more frequently in this cohort. To note, the frequency of the top manifestations in that cohort described was much higher than the data presented in our study.

The most recent data on early lupus research were published in 2018 by M. Mosca [6]. In this study, researchers evaluated the manifestations of the disease at the time of diagnosis compared with the manifestations of the diseases that mimic lupus (Sjogren's syndrome, antiphospholipid syndrome primary, mixed connective tissue disease, systemic sclerosis, rheumatoid arthritis, thyroiditis and autoimmune hepatitis). Thus, the most common clinical manifestations, according to the researchers and appropriate to our data were arthritis (57.6%) and alopecia (30.6%), while photosensitivity (31.6%) and malar rash (49.6%), which were also in the top, in this research cohort showed a higher frequency. The important signs of the disease highlighted by this cohort study and by M. Mosca were those not included in the classification 2012 SLICC criteria. The frequency of fever (34.5%) and Raynaud's syndrome (22.1%) in these studies was compliant, whereas the fatigue (28.3%), livedo

reticularis (3.1%) and Sjogren's syndrome (3.9%) prevailed within this study. Regarding fatigue, which was one of the most important signs of this research paper, it was included in the list of the early lupus symptoms only in the study conducted by M. Mosca, while in other important studies it was omitted [6-9, 15-17].

The study of the laboratory abnormalities, namely hematological manifestations showed the highest frequency in the early period of leukopenia, which ranged from 5.1% in the GLADEL study to 54% in the Europe Inception cohort, but also for lymphopenia, noted in these studies in 5.9% and 45%, respectively, our data being intermediate, consisting 29.41% and 16.18%, respectively. Regarding thrombocytopenia, it was found in only 5.2% of cases in GLADEL and 21% of cases from Europe Inception studies, respectively, which is more appropriate to our results [9, 15]. Thus, as it could be seen the frequency of hematological changes in the early period of lupus varies, however, the presence of leukopenia and lymphopenia requires greater attention. Immunological criteria data highlighted a very high frequency of ANA found in most of studies, similar to our study data. It should be noted that the LUMINA study reported only one third of the patients with positive ANA [2]. Partial examination of each immunological marker revealed the presence of Anti-DNA in 71.7% of cases in the study conducted by Mosca and 78% of cases each in the studies conducted by Rees and Sebastiani, while this criterion was more frequenty encountered in our study (91%) [6, 7, 9]. The frequency of antiphospholipid antibodies did not vary significantly and was found in 18.1% and 22% of patients in the Early SLE and Europe Inception cohort [7, 9], which corresponds to our data. Another immunological marker, which is part of the 1992 ACR criteria, Ac anti-Smith, was determined in 10% of cases in the Euro-Lupus cohort [16], comparable with our data, thus, a higher frequency was noted in the Early SLE and Europe Inception studies, 30.2% and 54% respectively [6, 9]. Complement analysis as an immunological criterion for diagnosing the disease was introduced only in 2012, thus the previous studies did not determine it. Only the Early SLE study determined the frequency of this marker in patients with early lupus and established its presence in 73.4% of cases while 58.8% of our patients fulfilled this criterion [6].

Thus, this present research work might assume that the frequency of clinical and paraclinical manifestations in the early period of the disease largely varies depending on the study performed, the inclusion criteria and the study conducting approach. Disease-specific manifestations, such as arthritis / arthralgia, malar rash, photosensitivity and lupus nephritis, as well as nonspecific ones – fever, fatigue and Raynaud's phenomenon, as well as hematological and immunological changes show a higher frequency in early disease among patients with systemic lupus erythematosus and requires a more detailed assessment.

Conclusions

This present study results indicate that top early manifestations in SLE patients included in the study were the arthralgia/arthritis, photosensitivity and fatigue, followed by malar rash and fever. The mean time of the diagnosis confirmation from the first symptom onset that can be referred to lupus was 7.08 months.

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MG drafted the first manuscript, VS and VSB acquired and interpreted the data, MG, LMN and MM designed the trial, MM and GC revised the manuscript critically. All the authors revised and approved the final version of the manuscript.

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Conflict of Interests
The authors have no conflict of interests to declare.