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Evaluation of Lupus Low Disease Activity: Characteristics, Predictors, and Association with Disease Damage: A Retrospective Cohort from Two Tertiary Centers in Egypt

BASMA M. MEDHAT, M.D.*; MERVAT E. BEHIRY, M.D.** and NAGLAA AFIFI, M.D.**

The Department of Rheumatology & Rehabilitation and Internal Medicine Department**, Faculty of Medicine, Cairo University, Cairo, Egypt*

Abstract

Background: Remission in systemic lupus erythematosus (SLE) is seldom achieved; making Lupus Low Disease Activity (LLDA) an alternative yet promising target.

Aim of Study: The aim of this study was to evaluate the prevalence of remission and LLDA achieved, and the characteristics and predictors of LLDA, and its potential association with disease damage.

Patients and Methods: The medical records of 243 patients fulfilling the 2012 Systemic Lupus Collaborating Clinics (SLICC) classification criteria for SLE and managed at Cairo and Ainshams Universities from January to December 2019 were viewed. Remission was categorized to: (i) Complete remission off glucocorticoid (GC) and Systemic Lupus Erythematosus Disease Activity Index-2K (SLEDAI-2K) = zero (antimalarial only); (ii) Clinical remission off GC with serologic activity (SKLEDAI-2K ≤4); (iii) Clinical remission on GC ≤5mg/day (SLEDAI-2K score ≤ 4 and serologic activity). LLDA was defined as SLEDAI-2K ≤4 in the absence of major organ involvement, GC dosage ≤7.5mg/day. Disease damage was assessed through the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI).

Results: Seventy two (29.6%) patients achieved LLDA at the last visit; whereas 142 (58.4%) patients had a SLEDAI-2K score >4 and/or received a GC dosage of >7.5mg. One (0.4%) and 28 (11.5%) patients achieved clinical remission off and on GC, respectively. None of the patients achieved complete clinical and serologic complete remission. Patients achieving LLDA had an older age of onset compared to those with higher disease activity (p=0.003), and a lower prevalence of fever (p=0.009), weight loss (p=0.07), cutaneous vasculitis (p=0.002), serositis (p=0.006), nephritis (p=0.02), a lower median SDI score, and lower prevalence of developing severe damage (SDI ≥3) (p=0.04). Predictors of LLDA were an older age of onset [p=0.006 (OR=1.05; 95% CI=1.01-1.09)] and weight loss [p=0.009 (OR=5; 95% CI=1.9-16.5)]; whereas patients with LLDA were less likely to have cutaneous vasculitis [p=0.01 (OR=0.2; 95% CI=0.06-0.7)] or pleurisy and/or pleural effusion [p=0.001 (OR=0.2; 95% CI=0.1-0.5)].

Conclusion: Achieving remission was substantially low. Lupus Low Disease Activity (29.6%) was associated with a higher age of onset, several distinct clinical characteristics, and lower damage.

Key Words: *Systemic lupus erythematosus – Lupus low disease activity - Disease activity – Disease damage.*

Correspondence to: Dr. Basma M. Medhat,
E-Mail: basmamedhat@kasrlainy.edu.eg

Introduction

SEVERAL interrelated factors contribute to the outcome of systemic lupus erythematosus, including disease activity. Furthermore, accrual damage has been associated with high disease activity; hence making remission or low disease activity alluring targets [1].

Interestingly, distinct definitions of remission [2] and Lupus Low Disease Activity (LLDA) [4] have been proposed. Moreover, a 'Treat to Target' approach has been delineated [3]; yet, abiding by it and attempting to achieve the aforementioned targets is quite challenging owing to several factors, including the variation in the disease characteristics, and race and ethnicity [5]; however, studies utilizing the proposed definitions of remission and LLDA as primary end points in the Middle East are lacking to the best of our knowledge.

We aimed in this study to portray the characteristics of patients with LLDA and potential factors influencing disease activity and damage.

Patients and Methods

The medical records of 243 patients fulfilling the 2012 Systemic Lupus Collaborating Clinics (SLICC) classification criteria for SLE [6] managed at the Rheumatology and Rehabilitation and Internal Medicine Departments of Cairo and Ain Shams Universities from January to December 2019 were viewed. The study was approved by the Local

Ethics Committee, according to the provisions of the World Medical Association Declaration of Helsinki.

Baseline characteristics:

Demographic data recorded included gender, the age at the last recorded visit and at the onset, where the disease onset was determined at the onset of the initial manifestation(s). Cumulative clinical characteristics were documented; with secondary antiphospholipid syndrome being diagnosed according to the modified Sapporo criteria [7]. Serologic markers recorded included antinuclear antibody (ANA), anti-double stranded deoxyribonucleicacid (anti ds-DNA), and complement 3 and 4 were recorded as consumed or normal.

Disease activity and damage:

Disease activity at onset and last visit was investigated utilizing the Systemic Lupus Erythematosus Disease Activity Index-2K (SLEDAI-2K) [8]; whereas disease damage was assessed through the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) [9], and was recorded as continuous numerical score and dichotomously to assess the prevalence of development of any (SDI $\geq$ 1) and severe damage (SDI $\geq$ 3) [10].

Definition of remission:

Remission was determined according to the 'Definition of Remission in SLE project' (DORIS) [2] and Zen et al's proposed definitions [11]; with the latter study further coupling the definition of remission with the nature of treatment implemented: (i) Complete remission which is a SLEDAI-2K score of zero in the absence of GC intake and the possibility of antimalarial administration only as an immunomodulatory; (ii) Clinical remission in absence of GC implementation: Defined as SKLEDAI-2K score of $\leq$ 4, with the presence of serologic activity in the form of hypocomplementinemia and/or positive anti-ds DNA; yet with patients being off GC and antimalarials and other immunosuppresives are administered; (iii) Clinical remission: A SLEDAI-2K score of $\leq$ 4 and serologic activity in the form of hypocomplementinemia and/or positive anti-ds DNA, and patients are receiving GC in a dose equivalent to prednisolone 5mg/day.

Definition of lupus low disease activity state:

Lupus Low Disease Activity state was defined as a SLEDAI-2K $\leq$ 4 in the absence of major organ involvement (fever, hemolytic anemia, central nervous system, renal involvement, cardiopulmonary, and vasculitis), GC dosage $\leq$ 7.5mg/day, no evidence of new activity compared to the prior visit, well tolerated of immunosuppressive or biologic agents, and a physician global assessment of $\leq$ 1 (on a scale of 0-3) [4].

Statistical method:

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data was summarized using median and interquartile range in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test. For comparing categorical data, Chi square (ξ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. Logistic regression was done to detect independent predictors of LLDA. p-values less than 0.05 were considered as statistically significant.

Results

Baseline characteristics:

This retrospective study included 243 patients, including 33 (13.6%) males and 210 (86.4%) females. The mean age at the last visit and at onset was 31.4 (9.4) and 24.5 (8.5) years, respectively; with the median disease duration being 72 (Interquartile Range (IQR): 44-120)]. Mucocutaneous manifestations were the most prevalent being present in 192 (79%) patients, followed by arthritis which was present in 170 (70%) patients. Other cumulative clinical and serologic characteristics are shown in Table (1).

Table (1): Baseline cumulative clinical and serologic characteristics of the cohort*.

Cumulative clinical characteristics	N=243
Constitutional	110 (45.3)
Mucocutaneous	192 (79)
Arthritis	170 (70)
Serositis	86 (35.4)
Hematologic	147 (60.5)
Nephritis	139 (57.2)
Neuropsychiatric	80 (32.9)
APS	42 (17.3)
Serologic characteristics:	
ANA	239 (98.4)
Anti-ds DNA	150 (61.7)
Hypocomplementinemia	159 (65.4)
aPL	81 (33.3)
Comorbidities	121 (49.8)

*Unless indicated, data is presented in number and percentage.
Abbreviations:
APS : Antiphospholipid syndrome.
ANA: Anti-nuclear antibody.
Anti-ds DNA: Anti-double stranded deoxyribonucleic acid antibody.
aPL : Antiphospholipid antibodies.

Disease activity and damage:

The definition of LLDA was met in about third of our patients [72/243 (29.6%)]. On the other hand, the majority of our cohort [142/243 (58.4%)] had a SLEDAI-2K score > 4 and/or received a GC dosage of >7.5mg was; while 1 (0.4%) and 28 (11.5%) patients achieved clinical remission off and on GC, respectively. None of the patients achieved complete clinical and serologic complete remission (Table 2).

Table (2): Disease activity and damage of the cohort (243 patients).

Disease activity:	
SLEDAI-2K	Median (IQR)
At onset	12 (8-22)
At the last visit	4 (1-8)
State of remission achieved:	N (%)
Complete with serologic activity (Off GC)	1 (0.4)
Partial remission (on GC)	28 (11.5)
LLDA with GC dose ≤7.5mg/day	72 (29.6)
SLEDAI-2K >4 and/or GC dose >7.5mg/day	142 (58.4)
Disease damage:	
SDI score at last visit [Median (IQR)]	1 (0-3)
Damage attained:	N (%)
Any damage (SDI ≥1)	178 (73.3)
Severe damage (SDI ≥3)	73 (30)

*Unless indicated, data is presented in number and percentage.

Abbreviations:
IQR : Interquartile range.
- Systemic Lupus Erythematosus Disease Activity Index-2K (SLEDAI-2K).
GC : Glucocorticoids.
LLDA: Lupus Low Disease Activity.
SDI : Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index

Characteristics of patients with LLDA:

Of the patients with LLDA [72/243 (29.6%) patients], 8/72 (11.1%) were males. The mean age at the last visit of this group of patients was 33.7 (10.3) years, whereas the mean age at onset was 26.6 (±9.4) years. The mean disease duration was 86 (±48) months. Cumulative clinical, serologic characteristics of patients with LLDA and the association of LLDA with disease damage are shown in Table (3).

Differences between patients with LLDA and SLEDAI-2K > 4:

The low prevalence of patients achieving remission hampered the analysis of these subgroups. On the other hand, upon assessing patients with LLDA, there were several differences between them and those who had at last visit a SLEDAI-2K >4 and/or were receiving a GC dose of >7.5mg/day at the last visit. Of the demographic features recorded, patients characterized by having a low activity state had an older age of onset (p=0.003); yet there was no gender differences between the two groups (p=0.5) and no association with the disease duration (p=0.4) (Table 4).

Table (3): Baseline cumulative clinical, and serologic characteristics of patients achieving Lupus Low Disease Activity at the last visit*.

Cumulative clinical characteristics	N=72
Constitutional	28 (38.9)
Mucocutaneous	53 (73.9)
Arthritis	51 (70.8)
Serositis	18 (25)
Hematologic	44 (61.1)
Nephritis	36 (50)
Neuropsychiatric	18 (25)
APS	15 (20.8)
Serologic characteristics:	
ANA 71	71 (98.6)
Anti-ds DNA	41 (56.9)
Hypocomplementinemia	43 (59.7)
aPL	23 (31.9)
Comorbidities	29 (40.3)

*Unless indicated, data is presented in number and percentage.

Abbreviations:
APS : Antiphospholipid syndrome.
ANA: Anti-nuclear antibody.
Anti-ds DNA: Anti-double stranded deoxyribonucleic acid antibody.
aPL : Antiphospholipid antibodies.

Table (4): Demographic differences between patients with achieving LLDA and those with a SLEDAI-2K >4 and/or receiving GC >7.5mg/day¶.

	LLDA N=72	SLEDAI-2K >4 or GC dose >7.5 N=142	p-value*
Demographic characteristics:			
Age (years) [Median (IQR)]:			
Age at onset	25 (19-33)	20 (17-27)	0.003
Age at last visit	32 (26.5-39)	28 (23-35)	0.006
Gender:			
Males	8 (11.1)	20 (14.1)	
Females	64 (88.9)	122 (85.9)	0.5
Disease duration (months) [Median (IQR)]	84 (48-120)	72 (48-120)	0.4

¶Unless indicated, data is presented in number and percentage.
*Significant p-value <0.05.

Abbreviations:
LLDA: Lupus Low Disease Activity.
GC : Glucocorticoids.
IQR : Interquartile range.

Among the cumulative clinical characteristics investigated, patients with LLDA had a lower prevalence of fever (p=0.009) and weight loss

(p=0.07). Moreover, they showed a lower prevalence of cutaneous vasculitis (p=0.002), serositis (p=0.006), and nephritis (p=0.02). On the other hand, there was no difference between the two groups in any of the studied serologic markers. It is of note that patients having a lower SLEDAI-2K at onset were more inclined to achieve LLDA (p<0.001) (Table 5).

Table (5): Comparison between patients achieving LLDA and those with a SLEDAI-2K >4 and/or receiving GC >7.5mg/day¶.

	LLDA N=72	SLEDAI-2K >4 or GC dose >7.5 N=142	p-value*
Cumulative clinical characteristics:			
Constitutional	28 (38.9)	75 (52.8)	0.05
Fever	24 (33.3)	74 (52.1)	0.009
Lymphadenopathy	3 (4.2)	0	0.03
Significant unintended weight loss	9 (12.5)	8 (5.6)	0.07
Mucocutanoeus	54 (73.6)	118 (83.1)	0.1
Cutaneous vasculitis	3 (4.2)	29 (20.4)	0.002
Malar rash	44 (61.1)	100 (70.4)	0.1
Photosensitvity	22 (30.6)	61 (43)	0.1
Discoid rash	3 (4.2)	11 (7.7)	0.3
Oral ulcers	18 (25)	51 (35.9)	0.1
Alopecia	31 (43.1)	63 (44.4)	0.8
Arthritis	51 (70.8)	104 (73.2)	0.7
Serositis	18 (25)	63 (44.4)	0.006
Pleurisy and/or pleural effusion	14 (19.4)	56 (39.4)	0.003
Pericarditis and/or pericardial effusion	8 (11.1)	17 (12)	0.8
Nephritis	36 (50)	93 (65.5)	0.02
Neuropsychiatric	18 (25)	54 (38)	0.05
Psychosis	4 (5.6)	19 (13.4)	0.08
Seizures	4 (5.6)	9 (6.3)	1
Peripheral and/or cranial neuropathy	3 (4.2)	8 (5.6)	0.7
Hematologic	44 (61.1)	84 (59.2)	0.7
Hemolytic anemia	8 (11.1)	23 (16.2)	0.3
Thrombocytopenia	9 (12.5)	31 (21.8)	0.09
Leukopenia	41 (56.9)	73 (51.4)	0.4
Secondary antiphospholipid syndrome	15 (20.8)	24 (16.9)	0.4
Associated comorbidities	29 (40.3)	80 (56.3)	0.02
Serologic:			
ANA	71 (98.6)	139 (97.9)	1
Anti-ds DNA	41 (56.9)	90 (63.4)	0.3
Hypocomplementinemia	43 (59.7)	98 (69)	0.1
aPL	23 (31.9)	52 (36.6)	0.4
SLEDAI at onset [Median (IQR)]	10 (8-16)	16 (10-25)	<0.001
Disease damage:			
SDI score [Median (IQR)]	1 (0-2)	2 (1-3)	0.008
Presence of any damage (SDI ›_1)	49 (68.1)	111 (78.2)	0.1
Presence of severe damage (SDI ›_3)	17 (23.6)	53 (37.3)	0.04

¶Unless indicated, data is presented in number and percentage. *Significant p-value <0.05.

Abbreviations:
LLDA : Lupus Low Disease Activity.
GC : Glucocorticoids.
IQR : Interquartile range.
APS : Antiphospholipid syndrome.
ANA : Anti-nuclear antibody.
Anti-ds DNA: Anti-double stranded deoxyribonucleic acid antibody.
aPL : Antiphospholipid antibodies.
SDI : Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index

Association of disease activity with accrual damage:

The median SDI score was higher among patients with higher disease activity (p=0.008). Although there was no difference in the prevalence of attaining any damage (SDI ›_1) between the two groups (p=0.1), the prevalence of developing severe damage (SDI ›_3) was higher among patients with a higher SLEDAI-2K (p=0.04).

Predictors of LLDA:

Upon multivariate logistic regression analysis, patients with LLDA were more inclined to have an older age of onset [p=0.006 (OR=1.05; 95% CI=1.01-1.09)] and manifest with weight loss [p=0.009 (OR=5; 95% CI=1.9-16.5)]. On the other hand, they were less likely to develop cutaneous vasculitis [p=0.01 (OR=0.2; 95% CI=0.06-0.7)] or pleurisy and/or pleural effusion [p=0.001 (OR=0.2; 95% CI=0.1-0.5)].

Discussion

The management of SLE is challenging owing to several factors; including the racial, ethnic, and individual variations characterizing the disease nature **[12]**. Hence, the emerging concept of 'Treat to Target', although described in SLE **[3]**, is seldom achieved, unlike other rheumatic diseases such as rheumatoid arthritis **[13]**.

Moreover, the variation in the proposed definitions of SLE activity and remission across various studies could be considered as one of the main factors adding to the disparity in the prevalence of remission and disease activity states achieved **[2,11,14-19]**. In our study, remission was determined according to that defined by the DORIS project **[2]** and Zen et al. **[11]**, and LLDA was defined according to that described by Franklyn et al. **[4]**; with the prevalence of LLDA at the last visit being about 30% and that of clinical remission off and on GC being 0.4% and 28 11.5%, respectively. On the other hand, none of the patients achieved complete serologic and clinical remission. In a previous study from the Netherlands **[20]**, the prevalence of achieving LLDA was 76%; yet this prevalence represented the occurrence of LLDA at least once throughout the course of the disease; whereas the prevalence of LLDA in a previous multiethnic cohort was 44% **[12]**. Interestingly, a previous report demonstrated a higher prevalence of remission achieved on (20.1%) and off GC (12.9%) **[21]** as compared to that detected in our study. The variation in the prevalence of remission and LLDA reported could be attributed to several factors including the implemented definition of low activity and remission, timing of assessment, and study design.

Interestingly, patients achieving LLDA (29.6%) showed several differences to those whom failed to achieve either LLDA or remission (58.4%). Among the demographic features investigated, patients with LLDA were more inclined to have an older age of onset (p=0.003). Contrary to our finding, a previous study showed no association of LLDA with the age of onset was; yet, similar to our study, the authors did not detect gender differences or an association with the duration of the disease **[21]**.

Of the cumulative clinical characteristics included, patients with LLDA demonstrated a lower prevalence of fever (p=0.009), weight loss (p=0.07), cutaneous vasculitis (p=0.002), serositis (p=0.006), and nephritis (p=0.02). Similar to our findings, the presence of renal involvement at baseline and one year follow-up was lower among patients with LLDA in a previous study **[21]**; yet, unlike our study, the authors detected a higher prevalence of serositis among their patients with LLDA and a lower prevalence of hematologic involvement, which was comparable between both groups in our study (p=0.7).

It is of interest that patients having a lower SLEDAI-2K at onset were more inclined to achieve a low activity state by the last visit (p<0.001). This finding is similar to previous reports **[20-22]**.

The importance of assessing activity in SLE and thriving to achieve it lowest possible state rises from its potential impact on disease damage, as demonstrated in several previous studies **[20-26]**. Similarly, the median SDI score at the last visit was lower among patients with LLDA (p=0.008); whom developed severe damage less frequently than those demonstrating a higher disease activity (p=0.04).

Predictors of LLDA in our study were an older age of onset [p=0.006 (OR=1.05; 95% CI=1.01-1.09)] and manifesting with weight loss [p=0.009 (OR=5; 95% CI=1.9-16.5)]. On the other hand, patients with LLDA were less likely to have cutaneous vasculitis [p=0.01 (OR=0.2; 95% CI=0.06-0.7)] and pleurisy and/or pleural effusion [p=0.001 (OR=0.2; 95% CI=0.1-0.5)]. Interestingly, a previous study **[12]** assessing the predictors of LLDA demonstrated that LLDA was associated with an older age of onset, hence similar to our study; yet the authors further detected an association with the disease duration being longer among patients achieving LLDA; whereas there was no association

with the disease duration in our study. Moreover, in the authors detected that patients with nephritis and discoid rash were less likely to achieve LLDA; whereas the presence of arthritis was associated with achieving LLDA; hence detecting different predictors than those in our study. This disparity could be explained by several factors including race and ethnicity, time of assessment, and patients' inclusion criteria.

Our study's main limitation lies in its retrospective nature that has led to the absence of some data. Yet, it has several strengths; including the participation of two tertiary centers in Egypt and that it has assessed the prevalence of remission and LLDA utilizing distinct definitions; an assessment that to the best of our knowledge has not been investigated in Egypt previously.

To conclude, LLDA was achieved in 29.6% patients, and was associated with an older age of onset, lower disease activity at baseline, several distinct clinical characteristics. Moreover, disease damage was lower among patients with LLDA.

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دراسة معدل الوصول إلى النشاط البسيط لمرض الذئبة الحمراء والعوامل والخصائص المصاحبة له وعلاقته بمعدل الضرر الناجم عن المرض دراسة استعادية من مركزين

من أهداف علاج مرض الذئبة الحمراء الوصول بالمرض لحالة من الخمول أو حالة من نشاط بسيط للمرض. هدف هذا البحث هو دراسة معدل الوصول لحالة نشاط بسيط بمرض الذئبة الحمراء والعوامل والخصائص المصاحبة لهذه الظاهرة وعلاقته بمدى الضرر الناتج عن المرضى.

لقد تم مراجعة ملفات 243 مريض ذئبة حمراء تم علاجهم بمستشفيات جامعة القاهرة وعين شمس من يناير إلى ديسمبر ٢٠١٩. وقد تم تعريف المرضى الذين لا يتناولون عقار الكورتيزون وليس لديهم أى ارتفاع فى مقياس نشاط الذئبة الحمراء على أنهم لديهم خمول بالمرض. وتم تعريف المرضى الذين يتناولون كورتيزون بجرعة لا تتجاوز 7.5 مجم يومياً أو / ولديهم ارتفاع فى مقياس نشاط الذئبة الحمراء لا يتجاوز 4، تم تعريفهم على أنهم لديهم نشاط بسيط بالمرض. وقد تم قياس معدل الضرر الناتج عن المرض من خلال المؤشر الخاص به.

وقد تبين أن (58.4%) 142 مريضاً كان لديهم نشاط عالى بالمرض حيث أنهم كانوا يتناولون جرعات كورتيزون تتجاوز الـ 7.5 مجم فى اليوم أو / وكان مقياس نشاط الذئبة الحمراء لديهم يتجاوز 4. فى حين أن (29.6%) 72 مريضاً كان لديهم نشاط بسيط بالمرض كما هو معرف أعلاه. ولم يصل أى مريض لحالة من الخمول التام للمرض.

ومن خصائص المرضى الذين كان لديهم نشاط بسيط بالمرض أنهم كانوا أكبر سناً (p=0.003) من اللذين كانوا لديهم مقياس نشاط أعلى للمرض، وكانوا أيضاً يعانون من ارتفاع فى درجة الحرارة (p=0.009) وإلتهاب الأوعية الدموية بالجلد (p=0.002) وإلتهاب بالاغشية البلورية (p=0.006) وإلتهاب بالكلى (p=0.02) بنسبة أقل. وكان معدل قياس الضرر الناتج عن المرض أقل فى المرضى الذين تميزوا بنشاط بسيط بالمرض عكس الذين كانوا يعانون بمعدلات أعلى لنشاط المرض (p=0.04).

ومن العوامل التى تم تحليلها إحصائياً التى يمكن أن تنبأ بالوصول لنشاط بسيط للمرض، هى أكبر السن [(95% CI=1.01-1.09 ;OR=1.05) p=0.006], ونقص الوزن الناجم عن المرض [(95% CI=1.9-16.5 ;OR=5) p=0.009] فى حين أن وجود إلتهاب بالأوعية الدموية بالجلد [(95% CI=0.06-0.7 ;OR=0.2) p=0.01] وإلتهاب بالغشاء البلورى [(95% CI=0.1-0.5 ;OR=0.2) p=0.001] من العوامل الغير مصاحبة لحالة النشاط البسيط للمرض.