European Review for Medical and Pharmacological Sciences 2023; 27: 949-959

Remission and low disease activity in Polish patients with systemic lupus erythematosus – real-life, five-year follow-up outcomes

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Abstract. – OBJECTIVE: Remission in systemic lupus erythematosus (SLE) or Lupus Low Disease Activity State (LLDAS) are associated with less organ damage and thus create new perspectives for effective damage-limiting treatment. The aim of this study was to assess the occurrence of remission defined by The Definition of Remission In SLE (DORIS) and of LLDAS as well as their predictors in the Polish SLE cohort.

PATIENTS AND METHODS: In this retrospective study data were collected on patients with SLE that achieved at least one year of DORIS remission or LLDAS and were followed up for 5 years. Clinical and demographic data were gathered; DORIS and LLDAS predictors were determined by univariate regression analysis.

RESULTS: The full analysis set included 80 patients at baseline and 70 at follow-up. Over half of patients with SLE (39; 55.7%) fulfilled the DORIS remission criteria. In this group, 53.8% (21) of patients were in remission on-treatment and 46.1% (18) in remission off-treatment. LLDAS was fulfilled by a cohort of 43 (61.4%) patients with SLE. Among patients that achieved DORIS or LLDAS at follow-up, 77% were not treated with glucocorticoids (GCs). The most important predictors for DORIS and LLDAS off-treatment were mean SLEDAI-2K score with cut-off of ≤8.0, treatment with mycophenolate mofetil or antimalarials, and the age at disease onset above 43 years.

CONCLUSIONS: Remission and LLDAS are achievable goals in treating SLE as over half of study patients fulfilled the DORIS remission and LLDAS criteria. The identified predictors for DORIS and LLDAS indicate the importance of effective therapy leading to reduction of GC use.

Key Words:
DORIS, Lupus low disease activity state, Remission, SLEDAI, Systemic lupus erythematosus.

Introduction

The treat-to-target strategy in rheumatology has become an achievable goal in systemic lupus erythematosus (SLE), and the evolution of SLE treatment strategies has been evidenced by the significant decrease in mortality of patients with SLE over the last decade[1]. The mortality in SLE is associated with chronic glucocorticoids (GSs) treatment which increases major organ damage and the risk of cardiovascular events[2,3]. Remission and lupus low disease activity state (LLDAS) are associated with less organ damage, and therefore create new perspectives for effective damage- and mortality-limiting treatment.

The remission should be the goal and the first potential treatment target in SLE. The universal definition of remission is still missing; however, the 2021 DORIS (The Definition of Remission In SLE) International task force recommended SLE remission as a definition for clinical care and education[4].

According to DORIS, remission is a complex of factors measured by clinical SLE Disease Activity Index 2000 (cSLEDAI-2K) and Physical Global Assessment (PGA) to reflect patients' perspective, as well as the dose of prednisone (PDN) as a factor contributing to long-term damage risk[4,5]. The DORIS task force defines remission as cSLEDAI=0, PGA<0.5 and PDN≤5mg daily.

The LLDAS is an alternative and more easily achievable goal of the treat-to-target strategy[1,6,7]. Its definition includes SLEDAI-2K ≤4 with no activity in major organ systems, no hemolytic anemia or gastrointestinal activity, PGA≤1, PDN ≤7.5 mg per day and well-tolerated standard maintenance doses of immunosuppressive and/or biologics agents. This definition is a compromise between effective treatment possibilities and lower doses of GCs. Further-

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more, LLDAS has been demonstrated as an outcome measure in clinical trials discriminating belimumab or anifrolumab from placebo[8,9]. The most important features of remission and LLDAS are their consolidation and long-term sustainability.

Knowing the importance of remission and/or low disease activity achievement, the primary aim of this 5-year real-life follow-up study was to analyze the Polish SLE cohort in terms of DORIS remission and LLDAS as well as their predictors. The organ damage and mortality rate were also assessed to better characterize our cohort.

Patients and Methods

Diagnostic Criteria

Systemic lupus erythematosus patients fulfilled either ≥4 revised American College of Rheumatology (ACR) classification criteria for SLE or 2012 SLICC (Systemic Lupus International Collaborating Clinics) classification criteria (depending on the time of diagnosis)[10,11].

Positive antinuclear antibodies (ANAs) were determined at a titer of 1:80 or greater, according to the ACR and European League Against Rheumatism (EULAR)[12].

Lupus nephritis was confirmed by kidney involvement and laboratory results like proteinuria, active urinary sediment and/or kidney biopsy with a specified histopathological pattern. Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) was defined according to the 1999 ACR nomenclature[13].

Methodology

Data were collected retrospectively from patients with SLE, with outcome assessment after 5 consecutive years of follow-up (between 2015 and 2021) in the ambulatory care Department of Rheumatology and Osteoporosis, Józef Struś Specialist Municipal Hospital, Poznań, Poland. Enrolled patients had minimum 2 ambulatory visits per year. Following clinical data were gathered at baseline and after 5-year follow-up period using a questionnaire:

- demographic data (age, sex)
- medical history
- disease activity components: SLEDAI-2K[14,15], cSLEDAI (SLEDAI-2K without anti-dsDNA antibodies and C3/C4 complement components), PGA[16], DORIS[5], LLDAS[6]
- organ damage measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SDI)[17]
- clinical judgment of SLE domains (constitutional, mucocutaneous, serosal, musculoskeletal, hematologic, neuropsychiatric, renal)
- laboratory results: (i) titer and profile of anti-nuclear antibodies (ANA); (ii) anti-dsDNA antibodies and anti-phospholipid antibodies (APLA); (iii) concentration of complement components 3 (C3) and 4 (C4)
- hematologic measurements (morphology, biochemistry, urinalysis, daily proteinuria)
- medication taken (GCs in low dose [PDN ≤7.5 mg/day], GCs in moderate/high dose [PDN >7.5 mg/day], antimalarials, immunosuppressive therapy, biologics).

Immunoassays

IgG ANA was assessed on the HEp-2 cell line by the IIFA technique. Anti-dsDNA antibodies were assessed with monospecific sandwich ELISA tests. The elevated level of anti-dsDNA was defined as 2x upper limit of normal (ULN). Antiphospholipid antibodies (APLA) positivity was defined as: positive lupus anticoagulant (dilute Russell's viper venom time – dRVVT in a screening test and correction/neutralization as confirming test) or anti-β2-glycoprotein-1 in IgG or IgM class exceeding ULN in ELISA) or anti-cardiolipin in IgG or IgM class autoantibodies exceeding ULN in ELISA.

Outcome Measures

Systemic lupus erythematosus disease activity was assessed according to the definitions proposed by the DORIS International task force[5] and LLDAS[6]. Patients that achieved at least one year of DORIS remission or LLDAS were followed up. DORIS remission was defined as a state without any symptoms and signs of SLE assessed by cSLEDAI=0; PGA<0.5, and PDN ≤5mg per day or equivalent. cSLEDAI is defined as SLEDAI 2-K without serology results. PGA is a tool that contributes to the definition of the patient's assessment of the disease.

Clinical remission "on-treatment" was defined as an achievable state with GCs and/or immunosuppressant and/or biologic agent maintenance therapy with stable doses. Clinical remission "off-treatment" was defined as a good SLE condition without any drugs except antimalarials which were allowed in every case. LLDAS was defined as a state with SLEDAI-2K ≤4 with restrictions as to major organ involvement (renal, neuropsychiatric, vasculitis), no flare, PGA≤1, PDN ≤7.5 mg per day or equivalent and standard maintenance

doses of immunosuppressive and/or biologics agents. For better characteristics of the SLE cohort during the 5 years follow-up, Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SDI) and mortality data were included[17]. SDI was calculated at the beginning of assessment and after 5 years of clinical observation.

Based on previous analyzes[18,19], the following possible factors were taken into account as predictors of remission or LLDAS: age at disease onset, disease duration, SLEDAI-2K score at baseline, SDI score at baseline, mean SLEDAI-2K score (calculated as the mean from SLEDAI-2K scores at baseline and at follow-up) lupus nephritis, NPSLE, vasculitis, APS (antiphospholipid syndrome), antimalarials use and immunosuppressive therapy with mycophenolate mofetil or cyclophosphamide (ever).

Ethics and Data Availability

This study was approved by the Bioethical Committee of the Poznań University of Medical Sciences (no. 107/21). Patient consent was waived due to the retrospective design of the study. Restrictions apply to the availability of these data. Data were obtained from J. Struś Municipal Hospital in Poznań, Poland, and are available from the corresponding author with the permission of the hospital authorities.

Statistical Analysis

The statistical analysis was performed using Statistica v.13.3 and MedCalc v.19.8. Data in the Tables I-III were presented as frequencies (%) for categorical variables or medians with interquartile ranges (IQR; Q1-Q3) for continuous variables. For the univariate regression analysis, we used the Chi-square test with Yates correction, and Fisher's exact test to compare categorical data, depending on expected frequencies (>10, 5-10, and <5, respectively). The ROC curves of chosen variables were tested to obtain cut-off points of selected variables. Subsequently, odds ratios (OR) were calculated. *p*-value equal to or less than 0.05 was considered statistically significant.

Results

Baseline and Follow-Up Assessments

A group of 168 patients was recruited, but the full analysis was conducted on 80 patients (baseline group) with complete data from 5-year follow-up period. Eighty-eight patients were excluded from the analysis because of incomplete data (they did not fulfill the criterion of minimum 2 ambulatory visits per year).

The mortality rate in the baseline group was 12.5% (10 patients). Comparing to the follow-up group, the group of patients who deceased showed higher baseline SLE activity score measured by SLEDAI-2K (median [IQR; Q1-Q3]: 26 [8.5; 19-27.5] *vs.* 12 [13.5; 8-21.5], p=0.01, Mann U-Whitney test) and damage index measured by SDI (1 [0; 1-1] *vs.* 0 [1; 0-1], p=0.004, Mann U-Whitney Test). The follow-up group, consisting of 70 patients, was assessed for SLE disease activity on at least two outpatient visits per year during a 5-year follow-up.

Details concerning demographics, clinical characteristics and medical treatment of baseline and follow-up groups are presented in Table I.

The immunological profiles at baseline and after the 5-year follow-up period were similar and typical for SLE, with about half of the patients presenting elevated anti-dsDNA, anti-SSA antibodies, and low levels of C3/C4. Nonetheless, the proportion of patients with elevated anti-dsDNA and/or low C3/C4 levels decreased after the 5-year follow-up (65.0% *vs.* 51.4%). Anti-phospholipid syndrome was confirmed in about 11.0% of patients with SLE at baseline and follow-up. The SLE activity assessed by the SLEDAI-2K score was moderate to severe (median [IQR; Q1-Q3]: 12.0[18.0; 8.0-26.0] points) at baseline and low/moderate (3.0[8.0; 0.0-8.0] points) at follow-up. The group of 29 patients (41.4%) presented with organ damage at baseline. During the 5-year follow-up period, 16 more patients (22.0%) developed damage in at least one organ (had at least one item of the SDI score).

Similar to the baseline group, most of the patients at follow-up had mucocutaneous (81.2% *vs.* 80.0%) and musculoskeletal (62.5% *vs.* 60.0%) involvement. More than 30.0% of patients had a history of renal involvement, and about 40.0% experienced neuropsychiatric manifestations.

After 5 years of treatment, fewer patients required treatment with IS (81.2% *vs.* 65.7%) (importantly, none of the patients from the follow-up group required the most aggressive cyclophosphamide therapy) and with GCs (60.0% *vs.* 50.0%). Most patients from both groups were on antimalarials (over 80.0%). Clinical and immunological SLE activity was the reason for implementing biologics in 20.0% of the follow-up patients.

Table I. Demographic and clinical characteristics of the study group at baseline and after a 5-year follow-up period.

Characteristic†	Baseline (N=80)	Follow-up (N=70)
Sex (female/male)	75 (93.7%)/ 5 (6.3%)	66 (94.3%)/ 4 (5.7%)
Age, years	38.0 (21.2; 29.0-50.2)	42.5 (18.5; 33.2-51.7)
Disease duration, years	5.0 (7.0; 3.0-10.0)	10.0 (7.0; 8.0-15.0)
Disease duration ≤2 years	12 (15.0%)	0 (0.0%)
SLEDAI-2K, points	12.0 (18.0; 8.0-26.0)	3.0 (8.0; 0.0-8.0)
SDI, points	0.0 (1.0; 0.0-1.0)	0.0 (1.0; 0.0-1.0)
Lupus manifestations		
Constitutional	7 (8.7%)	6 (8.6%)
Mucocutaneus	65 (81.2%)	56 (80.0%)
Musculoskeletal	50 (62.5%)	42 (60.0%)
Serosal	8 (10.0%)	5 (7.1%)
Renal	30 (37.5%)	23 (32.9%)
Neuropsychiatric	33 (41.2%)	27 (38.6%)
Vasculitis	7 (8.7%)	5 (7.1%)
Hematological	25 (31.2%)	23 (32.9%)
Immunological profile		
Elevated anti-dsDNA	47 (58.7%)	39 (55.7%)
Low C3/C4 complement	41 (51.2%)	36 (51.4%)
Elevated anti-dsDNA and/or low C3/C4 complement	52 (65.0%)	36 (51.4%)
Anti-SSA	41 (51.2%)	33 (47.1%)
Anti-SSB	15 (18.7%)	11 (15.7%)
Anti-RNP	14 (17.5%)	11 (15.7%)
Anti-Sm	15 (18.7%)	11 (15.7%)
Antiphospholipid antibodies	10 (12.5%)	9 (12.9%)
APS	9 (11.2%)	8 (11.4%)
Treatment	65 (92.9%)	51 (72.9%)
Antimalarials CQ/HCQ	61 (87.1%)	51 (72.9%)
Immunosuppressants	65 (81.2%)	46 (65.7%)
Cyclophosphamide	8 (10.0%)	0 (0.0%)
Mycophenolate mofetil	22 (27.5%)	17 (24.3%)
Methotrexate	9 (11.2%)	6 (8.6%)
Cyclosporine A	2 (2.5%)	1 (1.4%)
Azathioprine	24 (30.0%)	15 (21.4%)
GCs	48 (60.0%)	35 (50.0%)
PDN ≤7.5 mg/day	26 (32.5%)	27 (38.6%)
PDN >7.5 mg/day	22 (27.5%)	8 (11.4%)
Biologic agents	0 (0.0%)	14 (20.0%)

†Data in the table are presented as n (%) or median (IQR; Q1-Q3). APS - antiphospholipid syndrome; C3/C4 - C3 complement or C4 complement; CQ - chloroquine; GCs - glucocorticoids; HCQ - hydroxychloroquine; SD - standard deviation; SDI - Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index; SLEDAI-2K - SLE Disease Activity Index 2000.

Systemic Lupus Erythematosus Activity

Tables II and III present demographic and clinical data of patients with DORIS remission and LLDAS.

Over half of patients with SLE fulfilled DORIS remission criteria after 5-year follow-up period. In this group, 53.8% of patients were in remission on-treatment, and 46.1% were in remission off-treatment, considered as complete remission (Table II).

Criteria for LLDAS were fulfilled by a larger cohort (61.4%). The numbers of patients on-treatment and off-treatment were comparable as in the case of patients with DORIS remission (55.8% and 44.2%) (Table III).

Table II. Characteristics of patients with DORIS remission.

Characteristic†	DORIS remission at baseline: 2 patients (2.5% from N=80)	DORIS remission at follow-up: 39 patients (55.7% from N=70)
DORIS on-treatment	2 (100.0%‡)	21 (53.8%)
DORIS off-treatment	0 (0.0%)	18 (46.1%)
Age, years	38.0 (21.2; 29.0-50.2)	43.0 (23.0; 31.0-54.0)
Disease duration, years	5.0 (7.0; 3.0-10.0)	7.0 (8,5; 3.0-11.5)
Immunosuppressants	1 (50.0%)	19 (48.7%)
GCs	2 (100.0%)	9 (23.1%)
Antimalarials	1 (50.0%)	26 (66.7%)
Biologic agents	0 (0.0%)	10 (25.6%)
cSLEDAI=0 points	2 (100.0%)	39 (100.0%)
Elevated ds-DNA	0 (0.0%)	9 (23.1%)
Low C3/C4	1 (50.0%)	7 (17.9%)
cSLEDAI ≤4.0 points	2 (100.0%)	39 (100.0%)
cSLEDAI >4.0 points	0 (0.0%)	0 (0.0%)
PGA ≤0.5 points	2 (100.0%)	39 (100.0%)
PGA >0.5 points	0 (0.0%)	0 (0.0%)
PDN ≤5.0 mg/day	2 (100.0%)	9 (23.1%)
PDN >5.0 mg/day	0 (0.0%)	0 (0.0%)

†Data in the table are presented as n (%) or median (IQR; Q1-Q3). ‡The percentages are derived from the number of patients with DORIS remission unless otherwise specified. C3/C4 - C3 complement or C4 complement; cSLEDAI - clinical SLEDAI; DORIS - The Definition Of Remission In SLE; GCs - glucocorticoids; PDN - prednisone or equivalent; PGA - Physical Global Assessment; SD - standard deviation.

Table III. Characteristics of patients with LLDAS.

Characteristic†	LLDAS at baseline: 6 patients (7.5% from N=80)	LLDAS at follow-up: 43 patients (61.4% from N=70)
LLDAS on-treatment	5 (83.3%‡)	24 (55.8%)
LLDAS off-treatment	1 (16.7%)	19 (44.2%)
Age, years	38.0 (20.5; 29.0-49.5)	43.0 (22.0; 34.5-56.5)
Disease duration, years	5.0 (7.0; 3.0-10.0)	12.0 (7.0; 8.0-15.0)
Immunosuppressants	4 (66.7%)	22 (51.2%)
GCs	2 (33.3%)	10 (23.3%)
Antimalarials	5 (83.3%)	30 (69.8%)
Biologic agents	0 (0.0%)	10 (23.3%)
SLEDAI 2-K ≤4.0 points	6 (100.0%)	43 (100.0%)
Elevated ds-DNA	1 (16.7%)	10 (23.3%)
Low C3/C4	1 (16.7%)	8 (18.6%)
SLEDAI 2-K >4.0 points	0 (0.0%)	0 (0.0%)
PGA ≤1.0 points	6 (100.0%)	43 (100.0%)
PGA >1.0 points	0 (0.0%)	0 (0.0%)
PDN ≤7.5 mg/day	2 (33.3%)	10 (23.3%)
PDN >7.5 mg/day	0 (0.0%)	0 (0.0%)

†Data in the table are presented as n (%) or median (IQR; Q1-Q3). ‡The percentages are derived from the number of patients with LLDAS unless otherwise specified. C3/C4 - C3 complement or C4 complement; GCs - glucocorticoids; PDN - prednisone or equivalent; LLDAS - Low Lupus Disease Activity State; PGA - Physical Global Assessment; SD - standard deviation; SLEDAI-2K - SLE Disease Activity Index 2000.

Half of the patients at follow-up (35) were not treated with GCs at any doses, and only 11.4% (8) were treated with moderate/high GC dose (PDN >7.5 mg/day) compared to 27.5% (22) at baseline (Table I). Notably, among patients that achieved DORIS or LLDAS at follow-up, almost 77.0% were not treated with GCs at any doses (Tables II and III).

At follow-up, 38.6% (27) of patients did not fulfil any remission criteria. In these cases, the analysis revealed life-threatening organ involvement and high percentage of renal (16.0-61.5%) and neuropsychiatric (13.0-50.0%) manifestations (data not shown).

Predictors of Remission

The most important predictor of DORIS remission on-treatment and LLDAS on-treatment was mean SLEDAI-2K score with a cut-off of ≤12.5 points (p=0.004 for DORIS and p=0.002 for LLDAS). The predictor of DORIS remission off-treatment and LLDAS off-treatment was mean SLEDAI-2K score with cut-off of ≤8.0 points (p<0.001 for DORIS and p<0.001 for LLDAS) (Tables IV and V). The mean SLEDAI-2K score was also the predictor for sustained remission according to DORIS and/or LLDAS definitions with a cut-off of ≤12.5 points (p<0.001; OR=28.33; 95% CI: 7.77-103.37). Another predictor for sustained DORIS and/or LLDAS remission was a SLEDAI-2K score of ≤16.0 measured at baseline (p=0.008; OR=4.71; 95% CI: 1.59-13.95).

Immunosuppressive therapy with mycophenolate mofetil (ever) was confirmed as the predictor of DORIS and LLDAS remissions off-treatment (p=0.04). The use of antimalarial drugs was also confirmed as the predictor of DORIS remission off-treatment (p=0.01) and LLDAS remission off-treatment (p=0.009 for antimalarials). Similarly, the age at disease onset above 43 years was a positive predictor of DORIS and LLDAS remission off-treatment (p=0.006) (Tables IV and V).

Table IV. Predictors of DORIS remission on-treatment and off-treatment (univariate regression analysis).

Predictor	DORIS on-treatment	DORIS off-treatment
Age at disease onset, >43 years old	p=0.32[†] OR=2.54 (95%CI 0.51–12.66)	p=0.006[†] OR=6.72 (95% CI: 1.77-25.53)
Mean SLEDAI-2K	cut-off ≤12.5 points p=0.004[‡] OR=7.21 (95% CI: 1.87-27.77)	cut-off ≤8.0 points p<0.001[‡] OR=11.82 (95% CI: 2.97-47.12)
Mycophenolate mofetil therapy (ever)	p=0.51[‡] OR=1.63 (95%CI 0.57-4.64)	p=0.04[‡] OR=0.22 (95% CI: 0.06-0.87)
Antimalarials use (during the study)	p=0.25[‡] OR=2.67 (95%CI 0.68-10.43)	p=0.01[‡] OR=0.21 (95% CI: 0.06-0.67)

CI - confidence interval; DORIS - The Definition Of Remission In SLE; OR - odds ratio; SLEDAI-2K - SLE Disease Activity Index 2000. [†]Fisher exact test; [‡]χ^2 with Yates correction test.

Table V. Predictors of LLDAS remission on-treatment and off-treatment (univariate regression analysis).

Predictor	DORIS on-treatment	DORIS off-treatment
Age at disease onset, >43 years old	p=0.16[†] OR=2.13 (95%CI 0.66-6.87)	p=0.006[†] OR=6.72 (95% CI: 1.77-25.53)
Mean SLEDAI-2K	cut-off ≤12.5 points p=0.002[‡] OR=6.41 (95% CI: 1.89-21.80)	cut-off ≤8.0 points p<0.001[§] OR=11.82 (95% CI: 2.97-47.12)
Mycophenolate mofetil therapy (ever)	p=0.99[§] OR=1.13 (95%CI 0.41-3.11)	p=0.04[§] OR=0.22 (95% CI: 0.06-0.87)
Antimalarials use (during the study)	p=0.12[§] OR=3.44 (95%CI 0.89-13.34)	p=0.009[§] OR=0.21 (95% CI: 0.06-0.67)

CI - confidence interval; LLDAS - Low Lupus Disease Activity State; OR - odds ratio; SLEDAI-2K - SLE Disease Activity Index 2000. [†]Fisher exact test; [‡]χ^2 test; [§]χ^2 with Yates correction test.

The disease duration longer than 16 years was a weak predictor for LLDAS on-treatment only (p=0.049; OR=3.68; 95% CI: 1.02-13.27).

Conclusively, no statistically significant associations were found between DORIS/LLDAS remissions and: lupus nephritis, vasculitis, neuropsychiatric manifestations, APS, SDI at baseline or cyclophosphamide therapy (data not shown).

Discussion

In this study the criteria of DORIS remission and LLDAS were applied taking drug influence (including but not limited to GCs) into account. The aim was to determine the frequency of DORIS remission and LLDAS in the Polish SLE cohort. In the analyzed group, the percentage of patients achieving DORIS remission was relatively high, accounting for 55.7% (Table II). LLDAS, which is less restrictive, as mentioned in the introduction, was achieved by 61.4% of patients. Independently from treatment, the Polish SLE cohort presented a similar proportion of subjects achieving LLDAS like patients with SLE from Italy (69.2%)[18] and Asian-Pacific countries (63.0-74.8%)[19]. Nevertheless, data regarding LLDAS vary, and another multicenter published study from Asian-Pacific countries demonstrated lower proportions of patients with SLE achieving LLDAS (44.0%) than in our study[20].

The final recommendations on remission in SLE published in 2021 indicate DORIS remission as a treatment goal in SLE[4]. LLDAS remains an alternative treatment target in SLE. The treatment goal in clinical practice should be easy to measure, objective in assessment, and devoid of complicated algorithms. Simultaneously, it should perform best in predicting damage progression in SLE[7]. It has been demonstrated that the most attainable definition of remission is cSLEDAI=0[18]. Nonetheless, SLEDAI, in any definition (SLEDAI-2K or cSLEDAI-2K), is not a completely objective tool, especially in terms of skin and joint involvement. Similarly, PGA not always reflects disease activity and following its results may lead to the overtreatment of patients with SLE, especially with GCs[21].

Our analysis demonstrates that the strongest predictor of DORIS remission and LLDAS was the mean SLEDAI-2K score (Tables IV and V). The lower the cut-off according to the mean SLEDAI-2K score (mean SLEDAI≤8.0), the greater the likelihood of achieving complete remission without needing treatment. A systematic review[22] of 41 studies published in the recent 5 years presented proportions of patients achieving remission and predictors of remission in patients with SLE. Based on the analyzed studies, the authors identified that 42.4-88.0% of patients achieved and maintained the remission state for 1 year and 21.1-70.0% for at least 5 years. Like in our study, the lower baseline disease activity and older age at diagnosis were associated with remission (Tables IV and V). Another remission-associated factor indicated in this systematic review was the absence of major organ involvement. What is not surprising, prolonged remission was positively associated with lower damage accrual and better patients' quality of life[22].

When analyzing the effect of treatment on achieving remission, the high percentages of patients who withdrew from GCs or were treated with low doses of GCs during follow-up (PDN ≤7.5 mg/day) draw attention. Interestingly, the total percentage of patients treated with GCs decreased from 60.0% to 50.0% after 5 years of follow-up, which resulted from a double reduction in the number of patients treated with moderate/high GCs doses (PDN >7.5 mg/day). The proportion of patients not treated with any dose of GCs among the groups that achieved DORIS or LLDAS was higher and accounted for nearly 77.0%. This result demonstrates the effectiveness of the treat-to-target therapeutic strategy and reflects current clinical practice consistent with the recommendations on withdrawal of GCs (which may be followed by immunosuppressive therapy withdrawal in case of sustained remission) to protect against organ damage in a long-term perspective[23-25]. The decision to withdraw GCs is a serious step in the process of SLE treatment based on clinical and immunological judgment, the individual risk of disease flare, and especially rheumatologist experience. The frequency of GCs-free patients with SLE in the cohorts reported in literature ranged from 2.4% to 50.0%[26], which is consistent with the frequency we observed. The GCs treatment reduces SLE activity, especially its musculoskeletal and mucocutaneous manifestations, making the objective assessment of the disease activity impossible.

Our results show that relatively many patients used both immunosuppressive and antimalarial drugs. Due to the benefits of long-term use of antimalarials and knowing the problems with patient adherence, almost 73.0% of patients using chloroquine or hydroxychloroquine after 5

years of follow-up can be considered an achievement. Our analysis confirmed that antimalarial treatment is a predictor of DORIS remission and LLDAS off-treatment, similar to mycophenolate mofetil therapy (Tables IV and V).

In our study, the proportion of patients with immunological activity (elevated anti-dsDNA and/or decreased levels of C3 and/or C4 complements) decreased during the 5-year follow-up period from 65.0% to 51.4%, which does not reflect the proportions of patients that achieved DORIS remission or LLDAS (56.0% and 61.0%, respectively). Previous studies[27-29] raised the question of whether immunological SLE activity influences the perception of remission. Patients with prolonged remission, even those with immunological activity have been reported to accrue less damage[30] which, together with our results confirms that the immunological activity does not correlate directly with the clinical activity in SLE[31].

Our study has several limitations that include poor adherence of study patients. During the 5-year follow-up period, only about half of the patients (80 from 168) met the criteria of two visits per year, indicating the significant problem with compliance of patients with SLE in the ambulatory care system. Another limitation is the homogenous, non-multinational, and monoethnic character of the study population which does not allow for demonstrating potential ethnic patterns of SLE expression. These patterns were revealed in Europe, where the most active SLE occurs in Black African descent[32]. Moreover, many studies addressing the problem of remission in SLE present data from multi-ethnic, multinational cohorts, especially Almenara Latin American SLE cohort, Latin American SLE cohort GLADEL or US SLE cohort LUMINA[33-36]. Nevertheless, since studies evaluating patients from Central and Eastern Europe on remission and low disease activity are scarce (contrary to Western European countries and the US[7,18,29,37-40]), our monocentric study presents valuable data. Finally, the study duration, which was difficult to control in ambulatory care, may also be considered a study limitation. We followed-up patients who achieved at least 1 year of remission (which is why we did not evaluate the progress of damage by SDI). Published data showed that the duration of the remission is a crucial factor to consider as significant reduction of organ damage or decrease in flares frequency depend on the degree of remission, but first, on its duration[18,19,27]. In the studies[38,39] on Caucasian patients with SLE, at least 2 consecutive years were protective against damage, but only prolonged remission (over 5 years of maintained remission) was associated with better outcomes in damage accrual. Nonetheless, the study on the largest population assessed so far in terms of SLE remission demonstrated that even a short period of LLDAS on-treatment was associated with a reduced risk of long-term damage[7,18,41].

Conclusions

Presented results demonstrate that remission defined by DORIS and LLDAS are achievable therapeutic goals for SLE treatment of Polish (and, we believe, other) patients in real-life practice, as over half of study patients fulfilled the DORIS remission and LLDAS criteria. The identified predictors for DORIS and LLDAS (lower disease activity, treatment with mycophenolate mofetil or antimalarials) indicate the importance of effective therapy allowing for constant control of disease activity while striving for the maximum reduction of GCs.

Acknowledgements

The authors would like to thank Urszula Skalska, PhD, of Proper Medical Writing Sp. z o. o. for the support in preparation of this manuscript (including text editing and graphical data presentation).

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical Approval

This study was approved by the Bioethical Committee of the Poznań University of Medical Sciences (no. 107/21).

Informed Consent

Patient consent was waived due to the retrospective design of the study.

Authors' Contributions

Pawlak-Buś Katarzyna: conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing - original draft, writing – review and editing, visualization, project administration, funding acquisition.
Schmidt Wiktor: formal analysis, data curation.
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Conflict of Interest
The authors declare that they have no conflict of interest to declare.

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