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Predictors of Remission in Systemic Lupus Erythematosus

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ABBREVIATION INDEX

ACL	Anticardiolipin
ACR	American College of Rheumatology
Anti-β2GP1	Anti-β2-glycoprotein 1
Anti-DNA	DNA antibodies
Anti-DsDNA	Anti-Double Stranded DNA
Anti-La	Anti-Sjögren's-syndrome-related antigen B. Also called Anti-SSB
Anti-Ro	Anti-Sjögren's-syndrome-related antigen A. Also called Anti-SSA
Anti-Sm	Anti-Smith
Anti-SsDNA	Anti-Single stranded DNA
Anti-U_1 RNP	Anti U1 ribonucleoprotein
APL	Antiphospholipid antibodies
AZA	Azathioprine
BILAG	British Isles Lupus Assessment Group
BSA	Bovine Serum Albumin
CNI	Calcineurin Inhibitors
CNS	Central Nervous System
CYC	Cyclophosphamide
C1q	Complex 1 q
C3	Complement Protein 3

C4	Complement Protein 4
EULAR	European League Against Rheumatism
GC	Glucocorticoids
HCQ	Hydroxychloroquine
IS	Immunosuppressive
IV	Intravenous
LA	Lupus Anticoagulant
LLDAS	Lupus Low Disease Activity State
MMF	Mycophenolate Mofetil
MP	Metylprednisolone
MTX	Methotrexate
PLT	Platelets
RTX	Rituximab
SD	Standard Deviation
SLE	Systemic Lupus Erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
T2T	Treat to Target

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ABSTRACT

Objective: The aim of this study was to identify clinical and therapeutic predictors of prolonged remission in patients from the international longitudinal Cruces-Bordeaux Lupus cohort.

Methods: A total of 203 patients with systemic lupus erythematosus (SLE), 81 from the Bordeaux Lupus cohort and 124 from the Cruces Lupus cohort, were included in the study. We analyzed the relationship between the initial clinical manifestations and treatment with prolonged remission during the 5-year follow-up. The analysis was performed in the whole cohort and then stratified according to the baseline SLEDAI (mild activity 0-5, moderate activity 6-12 and severe activity >12).

Results: Long-term remission was achieved by 54.2% of the patients. In the whole cohort, nephritis, CNS lupus, cutaneous, articular or hematologic diseases conferred a worse prognosis in terms of persistent activity. Regarding therapy, the use of high initial doses of prednisone, oral immunosuppressive drugs and IV CYC were also associated with a lower rate of prolonged remission. On the contrary, a longer duration of HCQ therapy during the follow up was seen among patients achieving prolonged remission.

In the SLEDAI <6 subgroup (remission of 70.5%) longer HCQ therapy was associated with prolonged remission and hematologic manifestations and higher initial doses of prednisone with lack of prolonged remission. In the SLEDAI 6-12 subgroup (remission of 45.2%) cutaneous and serous manifestations and higher initial and cumulative doses of prednisone were associated with lack of prolonged remission. Longer HCQ therapy and the use of methyl-prednisolone pulses were associated with prolonged remission. In the SLEDAI>12 subgroup (remission 20.8%) cutaneous manifestations higher maximum ($p=0.005$) and cumulative doses of prednisone were associated with lack of prolonged remission. Longer HCQ therapy was associated with prolonged remission.

Conclusion: Our study found that deep organ involvement, high initial prednisone doses and cutaneous manifestations, even in the context of multisystemic disease

activity, were related to lack of sustained remission. On the other hand, maintained HCQ therapy and the use of MP pulses, the later in patients with moderate-severe activity, were associated with prolonged remission.

1. INTRODUCTION

1.1. SYSTEMIC LUPUS ERYTHEMATOSUS: MAIN ASPECTS AND GENERAL MANAGEMENT

Systemic Lupus Erythematosus (SLE) is a chronic and potentially fatal autoimmune disorder. It is more common in women between puberty and menopause, and can affect many organs and systems of the body, which can lead to a diversity of presenting symptoms. A delay in the diagnosis can result in more severe damage to vital organs. SLE is also more prevalent in certain racial and ethnic groups, particularly people of African origin living in North America or Europe, who tend to develop the disease at a younger age and have a higher risk of kidney involvement. Autoantibodies are considered to play a significant role in the pathology of SLE, particularly when they form immune complexes. Almost all SLE patients have positive test for antinuclear autoantibodies (1). A large number of specific autoantibodies have been already identified in SLE. Recognizing them not only helps to identify different clinical phenotypes; but also, a specific treatment. The main antibodies and their clinical associations are described in **Table 1**.

Table 1. Autoantibodies in LES. Modified from Kaul et al. Anti-Ro: anti-Sjogren's syndrome-related antigen. Also called Anti-SSA. anti-La: anti-Sjogren's-syndrome-related antigen B. Anti-U_1 RNP: anti U_1 ribonucleoprotein. Anti-Sm: anti-Smith. Also called Anti-SSB. Anti-SsDNA: anti-single stranded DNA. Anti-DsDNA: anti-double stranded DNA. ACL: anticardiolipin. LA: lupus anticoagulant. Anti-β2GP1: anti-β2-glycoprotein 1. C1q: complex 1 q. PLT: platelets. (1)

ANTIBODY	CLINICAL ASSOCIATIONS
Anti-Ro (SSa) / Anti-La (SSb)	• Subacute cutaneous lupus • Secondary Sjögren syndrome • Interstitial lung disease • Shrinking lung syndrome

	• Congenital fetal heart block and neonatal lupus
Anti-U_1 RNP	• Interstitial lung disease • Shrinking lung syndrome
Anti-Sm	• Lupus arthritis and nephritis
Anti-SsDNA	• No specific
Anti-DsDNA	• Clinical activity • Leukocytopaenia • Lupus nephritis
ACL	• Antiphospholipid syndrome
LA	
Anti-β2GP1	
Prothrombin	
Ribosomal-P-proteins and neural antigens	• Neuropsychiatric SLE
C1q	• Lupus nephritis
Red blood cells	• Autoimmune haemolytic anaemia
PLT	• Thrombocytopaenia

The diagnosis of SLE can be difficult due to the wide range of symptoms, which can go from mild joint pains and skin rash to severe complications involving the kidneys, blood, lungs or central nervous system (CNS). A wide variety of manifestations are described in **Table 2**.

Table 2. System affected and main manifestations in SLE. Modified from UpToDate (2).

SYSTEM AFFECTED	MAIN MANIFESTATIONS
Constitutional symptoms	• Fatigue • Fever • Myalgia • Weight loss
Musculoskeletal system	• Arthritis • Arthralgias
Tegumentary system	• Facial eruption (“the butterfly rash”) • Painless oral and/or nasal ulcers • No scarring alopecia
Renal system	• Asymptomatic hematuria and/or proteinuria • Nephrotic syndrome • Rapidly progressive glomerulonephritis • Hypertension
Cardiovascular system	• Pericarditis and verrucous (Libman-Sacks) endocarditis • Coronary artery disease • Thromboembolic disease (arterial and/or venous) • Raynaud phenomenon • Vasculitis of vessels of all sizes
Respiratory system	• Pleuritis • Pneumonitis • Interstitial lung disease • Pulmonary hypertension • Shrinking lung syndrome • Alveolar hemorrhage

Nervous system	• Cognitive dysfunction • Organic brain syndromes • Delirium • Psychosis • Seizures • Peripheral neuropathies
Gastrointestinal system	• Adverse medication reactions • Viral or bacterial infections
Hematologic involvement	• Anemia of chronic disease • Leukopenia (lymphopenia and/or neutropenia) • Mild thrombocytopenia
Ophthalmologic involvement	• Keratoconjunctivitis sicca • Retinal vasculopathy • Optic neuropathy, choroidopathy, episcleritis, scleritis, and anterior uveitis

SLE is a complex disease with a wide variety of symptoms and can be difficult to diagnose. In order to improve the accuracy of SLE identification, only for research purposes, classification criteria have been developed. In 2019, the European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) proposed a set of updated criteria for SLE classification which are more sensitive and specific than previous criteria and help detect early or new-onset SLE (3). These criteria are shown on **Table 3**.

Table 3. EULAR/ACR 2019 Classification Criteria and Weights. ACL: anticardiolipin. Anti-β2GP: anti-β-2-glycoprotein 1. LA: lupus anticoagulant. C3: complement protein 3. C4: complement protein 4. Anti-DsDNA: anti-double stranded DNA. Anti-Sm: anti-Smith. (3)

Clinical domains and criteria	Weight	**Immunology domains and criteria**	Weight
Constitutional:		**Antiphospholipid antibodies:**	
• Fever	2	• ACL OR Anti-β2GP1 OR LA	2
Hematologic:		**Complement proteins:**	
• Leukopenia <4000	3	• Low C3 OR low C4	3
• Thrombocytopenia <100.000	4	• Low C3 AND low C4	4
• Autoimmune hemolysis	4		
Neuropsychiatric:		**SLE-specific antibodies:**	
• Delirium	2	• Anti-DsDNA OR Anti-Sm	6
• Psychosis	3		
• Seizure	5		
Mucocutaneous:			
• Non-scarring alopecia	2		
• Oral ulcers	2		
• Subacute cutaneous OR discoid lupus	4		
• Acute cutaneous lupus	6		

Serosal:	
• Pleural or pericardial effusion	5
• Acute pericarditis	6
Musculoskeletal:	
• Joint involvement	6
Renal:	
• Proteinuria >0.5g/24h	4
• Renal biopsy class II or V lupus nephritis	8
• Renal biopsy class III or IV lupus nephritis	10
Antiphospholipid antibodies:	
• ACL or anti-β2GP1 or LA	2
Complement proteins:	
• Low C3 or low C4	3
• Low C3 and low C4	4
SLE-specific antibodies:	
• Anti-DsDNA or anti-Sm	6

Cardiovascular disease and infections are now the leading causes of death for SLE patients. Both the lack of remission and the extended use of high-dose glucocorticoids (GC) have been associated with adverse outcomes (4).

1.2. TREATMENT OF SLE

The goal of managing systemic lupus erythematosus (SLE) should be to eliminate symptoms, prevent the accumulation of damage, reduce negative side effects of medication and enhance the patient's overall quality of life (5).

The last update of the EULAR guidelines recommends treating SLE as a multisystem disease, diagnosed on clinical grounds with serological abnormalities. Care should be multidisciplinary, with shared decision-making, consider individual, medical and societal costs. Treatment involves high-intensity therapy initially to control disease activity, followed by less intense therapy to maintain response and prevent relapses. Goal is to ensure long-term survival, prevent organ damage, and improve quality of life with the aim of achieving remission or low disease activity and preventing flares (3). In order to achieve this purpose different strategies should be applied.

It is suggested that all individuals with SLE take a dosage of hydroxychloroquine (HCQ) at doses that does not exceed 5 mg/kg based on their actual body weight (6). Research shows that HCQ has several positive effects on individuals with SLE (7).

Immunosuppressive treatments such as methotrexate (MTX), azathioprine (AZA) or mycophenolate (MMF) can help speed up the reduction of GC and may prevent the recurrence of symptoms in the disease (8). The presence of a major flare, the average daily prednisone dosage during the monitoring period and nephrological symptoms at the start of the study are considered the most crucial factors in determining the accumulation of damage (9). Starting these immunomodulatory agents in a timely manner can help to quickly reduce or stop the use of GC (3).

Cyclophosphamide (CYC) can be used for severe or life-threatening cases of SLE and as a last resort therapy for patients who do not respond to other immunosuppressive agents. Biologics such as belimumab or rituximab (RTX) can be used as add-on

treatment for patients who do not respond well to standard treatment (combinations of HCQ and GC with or without immunosuppressive agents). In cases where the disease is severe and does not respond to standard immunosuppressive agents, RTX can be considered as a treatment option (3).

Ultimately, the treatment for SLE is determined by the severity of the disease, and it is necessary to differentiate between different levels of severity (3).

- "Mild: constitutional symptoms/mild arthritis/ rash 9% bovine serum albumin (BSA)/PLT 50-100 X 10^3; Systemic Lupus Erythematosus Disease Activity Index (SLEDAI ≤6); British Isles lupus Assessment Group (BILAG) C or ≤1 BILAG B manifestation"
- "Moderate: RA-like arthritis/rash 9-18% BSA/cutaneous vasculitis≤18% BSA; PLT 20-50x103/mm^3/serositis; SLEDAI 7-12; BILAG B manifestations"
- "Severe: major organ threatening disease (nephritis, cerebritis, myelitis, pneumonitis, mesenteric vasculitis, thrombocytopenia with PLT <20x103/mm^3; TTP-like disease or acute hemophagocytic syndrome; SLEDAI>12; BILAG A manifestations"

It is essential to maintain appropriate control of sun protection, vaccinations, exercise, avoid smoking, maintain a healthy body weight, blood pressure lipids and glucose levels. Recommended treatments for the specific manifestations of SLE and comorbidities are shown in the **Tables 5 and 6.**

Table 5. Treatment for specific manifestations. Modified from Fanouriakis. GC: glucocorticoids. CNI: calcineurin inhibitors. HCQ: hydroxychloroquine. MTX: methotrexate. MMF: mycophenolate mofetil. APL: antiphospholipid antibodies. IV: intravenous. MP: methyl-prednisolone. AZA: azathioprine. RTX: rituximab. CYC: cyclophosphamide. (3)

Skin disease	• "Topical agents (GC, CNI)" • "Antimalarials (HCQ, quinacrine)" • "Systemic GC" • "In non-responsive cases or cases requiring high-dose GC: MTX, retinoids, dapsone or MMF"
Neuropsychiatric disease	• "GC/immunosuppressive for inflammatory process" • "Antiplatelet/anticoagulants for atherothrombotic/APL-related manifestations"
Hematological disease	• "High-dose GC (IV MP) and/or IV immunoglobulin G" • "Immunosuppressive/GC-sparing agents such as MMF, AZA or cyclosporine can be used" • "Refractory cases can be treated with RTX or CYC"
Renal disease	• "MMF" • "Low-dose IV CYC or high-dose IV CYC can also be used (1b/A)" • "For maintenance therapy, MMF(1a/A) or AZA (1a/A) should be used"

Table 6. Treatment for comorbidities. Modified from Fanouriakis. GC: glucocorticoids. (3)

Antiphospholipid syndrome	• "All patients should be screened at diagnosis" • "If high risk, primary prophylaxis with antiplatelet agents" • "For secondary prevention, same as for primary antiphospholipid syndrome"
Infectious diseases	• "Risk factors: Advanced age/frailty, Diabetes Mellitus, Renal involvement, Immunosuppressive therapy, use of GC "
Cardiovascular disease	• Regular assessment for traditional and disease-related risk factors for cardiovascular disease

1.2.1. Use of glucocorticoids

GC can reduce inflammation and suppress the immune system in SLE, but they can also cause nisative side effects. Some of these effects can be temporary, such as weight gain, diabetes, and high blood pressure; but others, like osteonecrosis, osteoporotic fractures and cataracts, are permanent (10).

For a long time, using high doses of oral GC has been the main way to treat active SLE. Many people believe that GC-induced damage is a necessary consequence of controlling lupus activity and preventing damage caused by the disease. However, there is no strong evidence to support this approach. In fact, recent studies in patients with lupus nephritis suggest that using medium doses of prednisone (up to 30 mg/day) in the beginning and quickly reducing the dose to 5 mg/day is just as effective as using high doses (11).

Recent studies have uncovered different mechanisms of action for GC, dependent on the dosage. The genomic pathway, specifically the transactivation mechanism, is

almost fully activated at doses of prednisone above 30 mg/day and is responsible for most adverse effects caused by GC. However, non-genomic pathways, which have more potent and less toxic effects, become active at doses above 100 mg/day, can be utilized for rapid and potent inhibitory effects on immune cells without the adverse effects associated to genomic transactivation (12,13). This is the rationale for the use of MP.

GC can provide relief, but long-term use can lead to irreversible organ damage. Risks increase at doses above 7.5 mg/day. To minimize GC use, two approaches can be considered: use of pulses of IV methyl-prednisolone (MP) and early initiation of immunosuppressive (IS) agents. High-dose IV MP is frequently used for acute, organ-threatening disease (3).

High-dose GC, such as 1 mg/kg/d of prednisone, are commonly recommended to treat severe SLE. However, associated toxicity is very high, and the duration and tapering schedules are largely empirical (13).

The combination of different therapies has allowed for the use of lower doses of oral prednisone, which in turn decreased damage caused by GC and improved cardiovascular outcomes without exacerbating damage caused by SLE. Additionally, supplementing with calcium and vitamin D may be beneficial for patients on long-term glucocorticoid therapy (14).

1.3. REMISSION IN SLE

In order to improve the long-term prognosis of SLE, an international group develop a treat-to-target (T2T/SLE) approach for the management of lupus (4). T2T aims to achieve remission in SLE patients, however the recognition that there is no universally accepted definition for remission, initiated a process to reach consensus on potential definitions for remission in SLE through a large multiparty international task force known as DORIS (Definitions of Remission in SLE) (5,15).

Defining remission in SLE can be difficult. Remission is distinct from a cure and is considered meaningfully different from a state of low disease activity such as the Lupus Low Disease Activity State (LLDAS) that has been developed by the Asia-Pacific Lupus Collaboration (5,6). The achievement of LLDAS state or remission has been linked to a decrease in permanent organ damage accrual (9). However, the concept of remission is more stringent, remarkably it requires a lower dose of prednisone to be achieved (≤5 mg/d vs. ≤7.5 mg/d in LLDAS) (16). Thus, the currently accepted definition for remission according to DORIS is as follows: a score of 0 on the clinical SLEDAI (regardless of serology) and a score of less than 0.5 on the Physician Global Assessment; patients may continue to take antimalarials, low-dose GC (≤5 mg/d of prednisone) or stable immunosuppressives, including biologics, while in remission (15).

Achievement of prolonged remission is a major goal in the management of lupus patients. However, it is infrequently achieved, due both to the failure of controlling lupus activity and of doing so by using long-term prednisone doses >5 mg/d. Therefore, it would be of clinical interest to identify those clinical and therapeutic predictors of prolonged remission in large cohorts of SLE patients.

2. OBJETIVE

The aim of this study is to identify clinical and therapeutic predictors of prolonged remission patients from the international combined Cruces-Bordeaux Lupus cohort.

3. PATIENTS AND METHODS

3.1. STUDY DESIGN AND PATIENTS

This is an observational study of routine clinical care data of the longitudinal Cruces Lupus and Bordeaux Lupus cohorts, as previously described (17).

Eligible patients fulfilled the revised ACR or SLICC criteria for the classification of SLE (18, 19). The point when classification criteria were met was considered time 0 of follow-up. Only patients diagnosed after year 2000 and treated since time 0 at the respective centres (inception patients) were included in the study, in order to avoid bias related with previous therapies administered by referring physicians outside our two Units. All patients were followed during 5 years after the diagnosis, which constituted the time of study.

The study protocol was approved by the institutional review boards and ethic committees of Hospital Universitario Cruces and Bordeaux University Hospital in compliance with the Declaration of Helsinki (17). All participants signed an informed consent form before being included in the databases.

3.2. INDEPENDENT VARIABLES

The database used for this study contained detailed information on demographic information of the patients, autoantibody profiles, lupus activity, long-term therapeutic schedules beyond glucocorticoid use and remission. This database, used in an anonymised way, offered the opportunity to analyse the associations between the different variables and long-term remission.

We used clinical variables at baseline and therapeutic variables within the first year after the diagnosis as the potential predictors of remission. Our rationale to select variables at such time points is that both initial clinical presentation and early therapy of SLE greatly condition the later evolution of the disease.

Also, later therapies are very much conditioned by the achievement (or not) of remission, being thus influenced by the endpoint of the study. The exception was the variable "cumulative months on HCQ during five years", since HCQ should be maintained long-term in all patients with SLE and thus should not be conditioned by the degree of activity during the follow-up.

The baseline clinical profile used for this study included: gender, race, age at diagnosis; anti-Sjögren's-syndrome-related antigen A (anti-Ro), anti-Sjögren's-syndrome-related antigen B (anti-La), anti U1 ribonucleoprotein (anti-U_1RNP), anti-Smith (anti-Sm), DNA-antibodies (anti-DNA) and antiphospholipid antibodies (APL); cutaneous, articular, serous, hematologic, renal and CNS manifestations of SLE and antiphospholipid syndrome. Baseline SLEDAI was also recorded and used to stratify patients for the subgroup analysis (see below).

Therapeutic variables within the first year of follow-up included: cumulative prednisone dose, maximum prednisone dose, use of MP, oral immunosuppressive drugs (AZA, MTX, MMF, CNI) and CYC. In addition, as already explained, we included the cumulative number of months on HCQ during the 5-year follow up.

3.3. ENDPOINT

Prolonged remission according to DORIS definition (5,15) was the endpoint of this study. Remission was assessed yearly (year 1 to 5) after the diagnosis of SLE. Prolonged remission was achieved when patients fulfilled remission criteria during the five consecutive yearly visits.

3.4. STATISTICAL ANALYSIS

Descriptive data were generated, using percentages, means and standard deviations (SD). For a better analysis and interpretation of results, SLE patients were stratified in

3 different subgroups according to the baseline SLEDAI (mild activity 0-5 points, moderate activity 6-12 points and severe activity >12 points).

Factors associated with prolonged remission were analysed by comparing patients who did and did not achieve the main outcome for every candidate variable. The same analysis was performed in each of the 3 SLEDAI subgroups. For the comparisons, Chi-squared, Student's t test and ANOVA were used as indicated according to the type of variable (categorical or continuous). Given the large size of the cohort, non-parametric tests were not necessary to compare non-normally distributed continuous variables. Statistical significance was considered for all the p values <0.05

The JAMOVI (2.3.19 version) was used for all statistical analyses.

3.5. LITERATURE REVIEW

Studies focused on the remission of SLE were retrieved using the combination of terms "Systemic lupus erythematosus" AND "Remission" the PubMed web page (https://pubmed.ncbi.nlm.nih.gov).

4. RESULTS

4.1. DESCRIPTION OF THE COHORT

Two hundred and three patients were included in the study: 122 patients from the Cruces Lupus cohort (60%) and 81 patients from the Bordeaux Lupus cohort (40%). In terms of gender, 84.2% were women and according to race, the percentage of Caucasians reached 91.6%. The mean age at diagnosis was 39 years. With regard to the autoantibody profile, anti-DNA were the most prevalent being present in 63% of the cohort. APL were positive in 28%.

The mean SLEDAI at baseline was 6.8. Articular (78%) and cutaneous (67%) were the most prevalent manifestations, while nephritis was present at diagnosis in 15% patients.

Three out of every 4 patients received prednisone during the first year, with a mean cumulative dose of 4877mg. More than 95% of patients ever received HCQ within the 5-year follow-up, during a mean cumulative time of 52.1 months. MP were given during the first year to 31% of patients. Oral immunosuppressive drugs and CYC were given to 26% and 13% of patients, respectively.

4.2. DESCRIPTION OF THE COHORT BY SLEDAI GROUPS

A description of the cohort by SLEDAI groups is summarized in **Table 7**. As expected, the mean SLEDAI at diagnosis (2.93 vs 8.2 vs 17.9) was significantly increasing among the three groups. There were no other differences among SLEDAI groups regarding demographic variables. However, anti-DNA antibodies were more frequent as the baseline SLEDAI increased (46% vs 73% vs 92%, respectively).

Likewise, lupus nephritis was present in more than 80% of patients with a baseline SLEDAI >12 and in only 13% of those in the SLEDAI group 6-12. As expected, none of the patients in the SLEDAI group 0-5 presented with renal disease. On the other hand, cutaneous and articular involvement were very prevalent in all subgroups, without significant differences.

Regarding treatments, the use and the dose of prednisone progressively increased across the three SLEDAI groups. MP were given to almost 90% of patients in the SLEDAI >12 group, but their use was not limited to this group, with almost one in three patients in the SLEDAI 6-12 group also receiving pulses. Also, marked differences were found regarding therapy with immunosuppressors, both oral and IV CYC.

Table 7. Description of the whole cohort and by SLEDAI groups. SD: standard deviation. Anti-Ro: Anti-Sjögren's-syndrome-related antigen A. Also called Anti-SSA. Anti-La: Anti-Sjögren's-syndrome-related antigen B. Also called Anti-SSB. Anti-U_1RNP: anti U_1 ribonucleoprotein. Anti-Sm: anti-Smith. Anti-DNA: DNA antibodies. APL: antiphospholipid antibodies. CNS: central nervous system. SLEDAI: systemic lupus erythematosus disease activity index. HCQ: hydroxychloroquine. MP: methyl-prednisolone. IS: immunosuppressive. CYC: cyclophosphamide.

Variable	**Total** (n=203)	**SLEDAI 0-5** (n=95)	**SLEDAI 6-12** (n=84)	**SLEDAI>12** (n=24)	**p**
Female, n/N (%)	171/203 (84.2%)	83/95 (87.4%)	68/84 (81%)	20/24 (83.3%)	0.497
Caucasian, n/N (%)	186/203 (91.6%)	88/95 (92.6%)	78/84 (92.9%)	20/24 (83.3%)	0.497
Age of diagnosis (years), mean (SD)	39 (14.7)	39 (13.8)	39.9 (16.1)	35.8 (13.1)	0.436
Anti-Ro, n/N (%)	58/203 (28.6%)	22/95 (23.2%)	29/84 (34.5%)	7/24 (29.2%)	0.243
Anti-La, n/N (%)	23/203 (11.3%)	6/95 (6.3%)	15/84 (17.9%)	2/24 (8.3%)	0.046
Anti-U_1 RNP, n/N (%)	40/203 (19.7%)	21/95 (22.1%)	14/84 (16.7%)	5/24 (20.8%)	0.652
Anti-Sm, n/N (%)	29/203 (14.3%)	10/95 (10.5%)	13/84 (15.5%)	6/24 (25%)	0.179

Anti-DNA, n/N (%)	128/203 (63.1%)	44/95 (46.3%)	62/84 (73.8%)	22/24 (91.7%)	<0.001
APL, n/N (%)	57/203 (28.1%)	29/95 (30.5%)	21/84 (25%)	7/24 (29.2%)	0.708
Cutaneous, n/N (%)	137/203 (67.5%)	62/95 (65.3%)	57/84 (67.9%)	18/24 (75%)	0.658
Articular, n/N (%)	158/203 (78%)	72/95 (75.8%)	64/84 (76.2%)	22/24 (91.7%)	0.221
Serous, n/N (%)	28/203 (13.8%)	3/95 (3.2%)	20/84 (23.8%)	5/24 (20.8%)	<0.001
Hematologic, n/N (%)	16/203 (7.9%)	9/95 (9.5%)	6/84 (7.1%)	1/24 (4.2%)	0.653
Thrombocytopenia, n/N (%)	19/203 (9.4%)	10/95 (10.5%)	8/84 (9.5%)	1/24 (4.2%)	0.632
Lymphopenia, n/N (%)	65/203 (32%)	19/95 (20%)	34/84 (40.5%)	12/24 (50%)	0.002
Nephritis, n/N (%)	31/203 (15.3%)	0/95 (0%)	11/84 (13.1%)	20/24 (83.3%)	<0.001

CNS, n/N (%)	9/203 (4.4%)	1/95 (1.1%)	5/84 (6%)	3/24 (12.5%)	0.035
Hypocomplementemia, n/N (%)	117/203 (57.6%)	42/95 (44.2%)	51/84 (60.7%)	24/24 (100%)	<0.001
Antiphospholipid syndrome, n/N (%)	8/203 (3.9%)	3/95 (3.2%)	3/84 (3.6%)	2/24 (8.3%)	0.495
SLEDAI at diagnosis, mean (SD)	6.8 (5)	2.93 (1.32)	8.2 (2.07)	17.9 (3.23)	<0.001
TREATMENTS					
Prednisone year 1, n/N (%)	63/203(31%)	16/95 (16.8%)	26/84(31%)	21/24(87.5%)	<0.001
Cumulative Prednisone year 1 (mg/d), mean (SD)	4877 (33771)	6195 (49357)	3040 (2513)	6085 (4008)	0.003
Maximum Prednisone Dose year 1, mean (SD)	17.8 (19.2)	9.06 (12.7)	20.5 (18.7)	42.4 (18.0)	<0.001
HCQ years 1-5, n/N (%)	195/203 (96%)	95/95 (100%)	81/84 (96%)	19/24 (79%)	<0.001
Time HCQ years 1-5 (months), mean (SD)	52.1 (17)	54.4 (12.7)	52.7 (16.1)	40.5 (28.1)	0.066

MP year 1, n/N (%)	63/203 (31%)	16/95 (16.8%)	26/84 (31%)	21/24 (87.5%)	<0.001
IS oral year 1, n/N (%)	54/203 (26.6%)	10/95 (10.5%)	24/84 (28.6%)	20/24 (83.3%)	<0.001
CYC year 1, n/N (%)	27/203 (13.3%)	0/95 (0%)	7/84 (8.3%)	20/24 (83.3%)	<0.001
Smoking year 1, n/N (%)	61/203 (30%)	27/95 (28.4%)	25/84 (29.8%)	9/24 (37.5%)	0.720

4.3. ACHIEVEMENT OF REMISSION

Regarding the whole cohort, a total of 110 patients (54.2%) reached long-term remission. According to SLEDAI groups, 67 patients achieved long-term remission (70.5%) in the SLEDAI 0-5 group, vs. 38 patients in the SLEDAI 6-12 (45.2%) and 5 patients (20.8%) in the SLEDAI>12 group.

4.4. FACTORS ASSOCIATED WITH PROLONGED REMISSION IN THE WHOLE COHORT

Among clinical manifestations, those patients presenting with nephritis or CNS lupus were expectedly less likely to achieve prolonged remission. However, milder manifestations such as cutaneous, articular or hematologic (as a whole), also conferred a worse prognosis in terms of persistent activity. Regarding therapy, the use of high initial doses of prednisone, oral immunosuppressive drugs and IV CYC were also

associated with a lower rate of prolonged remission. On the contrary, a longer duration of HCQ therapy during the follow up was seen among patients achieving prolonged remission (**Table 8**).

Table 8. Factors associated with prolonged remission in the whole cohort. SD: standard deviation. CNS: central nervous system. HCQ: hydroxychloroquine. MP: methyl-prednisolone. IS: immunosuppressive. CYC: cyclophosphamide.

Variables	**Prolonged Remission** (n=110)	**No prolonged remission** (n=93)	**p**
DEMOGRAPHICS AND CLINICAL MANIFESTATIONS AT BASELINE			
Female, n/N (%)	91/110 (82.7%)	80/93 (86%)	0.521
Caucasian, n/N (%)	105/110 (95.5%)	81/93 (87.1%)	0.155
Age of diagnosis (years), mean (SD)	40.3 (14.9)	37.5 (14.5)	0.166
Nephritis, n/N (%)	**8/110 (7.3%)**	**23/93 (24.7%)**	**<0.001**
Thrombocytopenia, n/N (%)	9/110 (8.2%)	10/93 (10.8%)	0.531
Lymphopenia, n/N (%)	33/110 (30%)	32/93 (34.4%)	0.502
Hypocomplementemia, n/N (%)	**57/110 (51.8%)**	**60/93 (64.5%)**	**0.068**
CNS, n/N (%)	**2/110 (1.8%)**	**7/93 (7.5%)**	**0.049**

Antiphospholipid síndrome, n/N (%)	5/110 (4.5%)	3/93 (3.2%)	0.630
Cutaneous, n/N (%)	**68/110 (61.8%)**	**69/93 (74.2%)**	**0.061**
Articular, n/N (%)	**79/110 (71.8%)**	**79/93 (84.9%)**	**0.025**
Serous, n/N (%)	16/110 (14.5%)	12/93 (12.9%)	0.735
Hematologic, n/N (%)	**5/110 (4.5%)**	**11/93 (11.8%)**	**0.055**
TREATMENTS			
Cumulative Prednisone year 1 (mg), mean (SD)	5524 (45857)	4111(3385)	0.748
Maximum Prednisone Dose, mean (SD)	**10.1 (13.1)**	**26.8 (21.2)**	**<0.001**
Time HCQ 5 (months), mean (SD)	**56.8 (9.97)**	**46.5 (21.5)**	**<.001**
MP year 1, n/N (%)	32/110 (29.1%)	63/93 (31%)	0.515
IS oral year 1, n/N (%)	**23/110 (20.9%)**	**31/93 (33.3%)**	**0.046**
CYC year 1, n/N (%)	**5/110 (4.5%)**	**22/93 (23.7%)**	**<0.001**

4.5 FACTORS ASSOCIATED WITH PROLONGED REMISSION BY SLEDAI GROUPS

Given that treatments and manifestations are greatly conditioned by the degree of activity, a subgroup analysis of predictors was made stratifying patients by the baseline SLEDAI score.

Among those with mild disease (SLEDAI 0-5), hematologic manifestations were the only associated with a lower chance of prolonged remission. Regarding treatments, longer HCQ therapy was seen among long-term remitting patients; on the other hand, higher initial doses of prednisone were also given to patients not achieving prolonged remission (**Table 9**).

In the subgroup with moderate activity (SLEDAI 6-12), patients with cutaneous and serosal disease were less likely to show long-lasting remission. HCQ therapy was also associated with achieving prolonged remission, in contrast with the use of higher initial and cumulative doses of prednisone. In this subgroup, almost 45% of patients achieving the endpoint were treated with MP, vs. 20% of those who did not attain prolonged remission (**Table 10**).

In the subgroup with severe disease (SLEDAI >12), prolonged remission was achieved by only 5 patients (20%). Despite this low number of responding patients, a number of adverse prognostic variable could be identified: cutaneous disease, higher maximum and cumulative prednisone doses. On the other hand, all patients achieving prolonged remission were treated with HCQ during the complete follow-up period. The use of MP was high in both groups, however all 5 responding patients received this therapy (**Table 11**)

Table 9. Clinical and therapeutic factors associated with prolonged remission in patients with baseline SLEDAI 0-5.

Variables	**Prolonged Remission** (n= 67)	**No prolonged remission** (n=28)	**p**
DEMOGRAPHICS AND CLINICAL MANIFESTATIONS AT BASELINE			
Female, n/N (%)	60/67 (89.6%)	23/28 (82.1%)	0.322
Caucasian, n/N (%)	24/28 (85.7%)	64/67 (95.5%)	0.171
Age of diagnosis (years), mean (SD)	38.7 (15)	39.2 (13.4)	0.888
Nephropathy, n/N (%)	0	0	n/a
Thrombocytopenia, n/N (%)	6/67 (9%)	4/28 (14.3%)	0.440
Lymphopenia, n/N (%)	13/67 (19.4%)	6/28 (21.4%)	0.822
Hypocomplementemia, n/N (%)	29/67 (43.3%)	13/28 (46.4%)	0.778
CNS, n/N (%)	1/67 (1.5%)	0/28 (0%)	0.516
Antiphospholipid syndrome, n/N (%)	3/67 (4.5%)	0/28 (0%)	0.255
Cutaneous, n/N (%)	44/67 (65.7%)	18/28 (64.3%)	0.897
Articular, n/N (%)	48/67 (71.6%)	24/28 (85.7%)	0.144

Serous, n/N (%)	3/67 (4.5%)	0/28 (0%)	0.255
Hematologic, n/N (%)	**4/67 (6%)**	**5/28 (17.9%)**	**0.071**
TREATMENTS			
Cumulative Prednisone year 1 (mg), mean (SD)	7895 (5877)	2127 (2514)	0.606
Maximum Prednisone Dose, mean (SD)	**6.69 (10.9)**	**14.7 (14.9)**	**0.004**
Time HCQ 5 (months), mean (SD)	**55.9 (11.5)**	**50.8 (14.8)**	**0.073**
MP year 1, n/N (%)	10/67 (14.9%)	6/28 (21.4%)	0.440
IS oral year 1, n/N (%)	6/67 (9%)	4/28 (14.3%)	0.440
CYC year 1, n/N (%)	0	0	n/a

Table 10. Clinical and therapeutic factors associated with prolonged remission in in patients with baseline SLEDAI 6-12. SD: standard deviation. CNS: central nervous system. HCQ: hydroxychloroquine. MP: methyl-prednisolone. IS: immunosuppressive. CYC: cyclophosphamide.

Variables	**Prolonged Remission** (n=38)	**No prolonged remission** (n= 46)	**p**
DEMOGRAPHICS AND CLINICAL MANIFESTATIONS AT BASELINE			

Female, n/N (%)	28/38 (73.7%)	40/46 (87%)	0.123
Caucasian, n/N (%)	36/38 (94.7%)	42/46 (91.3%)	0.124
Age of diagnosis (years), mean (SD)	42.1 (17.5)	38.1 (14.9)	0.275
Nephropathy, n/N (%)	4/38 (10.5%)	7/46 (15.2%)	0.526
Thrombocytopenia, n/N (%)	2/38 (5.3%)	6/46 (13%)	0.227
Lymphopenia, n/N (%)	17/38 (44.7%)	17/46 (37%)	0.470
Hypocomplementemia, n/N (%)	23/38 (60.5%)	28/46 (60.9%)	0.974
CNS, n/N (%)	1/38 (2.6%)	4/46 (8.7%)	0.242
Antiphospholipid syndrome, n/N (%)	1/38 (2.6%)	2/46 (4.3%)	0.673
Cutaneous, n/N (%)	**22/38 (57.9%)**	**35/46 (76.1%)**	**0.076**
Articular, n/N (%)	27/38 (71.1%)	37/46 (80.4%)	0.315
Serous, n/N (%)	**13/38 (34.2%)**	**7/46 (15.2%)**	**0.042**
Hematologic, n/N (%)	1/38 (2.6%)	5/46 (10.9%)	0.145
TREATMENTS			

Cumulative Prednisone year 1 (mg), mean (SD)	**1802 (1502)**	**4063 (2726)**	**<0.001**
Maximum Prednisone Dose, mean (SD)	**14.4 (14.8)**	**25.6 (20.2)**	**0.006**
Time HCQ 5 (months), mean (SD)	**57.8 (7.35)**	**48.5 (19.8)**	**0.008**
MP year 1, n/N (%)	**17/38 (44.7%)**	**9/46 (19.6%)**	**0.013**
IS oral Year 1, n/N (%)	13/38 (34.2%)	11/46 (23.9%)	0.298
CYC year 1, n/N (%)	2/38 (5.3%)	5/46 (10.9%)	0.355

Table 11. Clinical and therapeutic factors associated with prolonged remission in patients with baseline SLEDAI >12. SD: standard deviation. CNS: central nervous system. HCQ: hydroxychloroquine. MP: methyl-prednisolone. IS: immunosuppressive. CYC: cyclophosphamide.

Variables	**Prolonged Remission** (n=5)	**No prolonged remission** (n=19)	**p**
DEMOGRAPHICS AND CLINICAL MANIFESTATIONS AT BASELINE			
Female, n/N (%)	3/5 (60%)	17/19 (89.5%)	0.116
Caucasian, n/N (%)	0/5 (0%)	4/19 (21.1%)	0.261

Age of diagnosis (years), mean (SD)	42.6 (12.6)	34 (12.9)	0.223
Nephropathy, n/N (%)	4/5 (80%)	16/19 (84.2%)	0.822
Thrombocytopenia, n/N (%)	**1/5 (20%)**	**0/19 (0%)**	**0.046**
Lymphopenia, n/N (%)	3/5 (60%)	9/19 (47.7%)	0.615
Hypocomplementemia, n/N (%)	0	0	n/a
CNS, n/N (%)	0/5 (0%)	3/19 (15.8%)	0.342
Antiphospholipid síndrome, n/N (%)	1/5 (20%)	1/19 (5.3%)	0.289
Cutaneous n/N (%)	**2/5 (40%)**	**16/19 (84.2%)**	**0.042**
Articular, n/N (%)	4/5 (80%)	18/19 (94.7%)	0.289
Serous, n/N (%)	0/5 (0%)	5/19 (26.3%)	0.197
Hematologic, n/N (%)	0/5 (0%)	1/19 (5.3%)	0.600
TREATMENTS			
Cumulative Prednisone year 1 (mg), mean (SD)	**2040 (865)**	**7150 (3823)**	**0.008**
Maximum Prednisone Dose, mean (SD)	**23.5 (9.94)**	**47.4 (16.3)**	**0.005**

Time HCQ 5 (months), mean (SD)	**60 (0)**	**35.4 (29.7)**	**0.082**
MP year 1, n/N (%)	5/5 (100%)	16/19 (84.2%)	0.342
IS oral Year 1, n/N (%)	4/5 (80%)	16/19 (84.2%)	0.822
CYC year 1, n/N (%)	3/5 (60%)	17/19 (89.5%)	0.116

5. DISCUSSION

This study was focused on identifying clinical and therapeutic predictors of prolonged remission in patients from the international combined Cruces-Bordeaux Lupus cohort.

Prolonged remission was achieved by more than half patients in our cohort. This contrast with lower figures in previous studies. In the cohort by Tsang-A-Sjoe et al, 32.5% of patients had ≥5 consecutive years of remission (9). Ugarte-Gil et al. observed remission in only 11.6% of visits, which was associated with lower risk of new damage (16). In the study by Zen et al. 37.4% of patients had ≥5 consecutive years of remission (20). Factors such as the mean daily dose of prednisone (9), lupus nephritis (9,20), vasculitis, hematological abnormalities and serositis (20) were associated with a decreased odds of remission.

Expectedly, as the baseline activity of our patients increased, the chance for achieving prolonged remission decreased. Most predictors were found both in the whole cohort and in each of the 3 SLEDAI groups. The duration of HCQ therapy during the follow up was the only variable associated with a higher odds of prolonged remission in the whole cohort and in all the SLEDAI subgroups. Furthermore, all patients who achieved prolonged remission in severe SLEDAI subgroup were treated with HCQ during the

complete follow-up period. These data highlight once again the role of HCQ as a basic therapeutic agent in SLE (7).

On the contrary the use of high initial doses of prednisone were associated with a lower rate of prolonged remission in the whole cohort and in each of the three SLEDAI subgroups. Similar results were obtained by Tsang-A-Sjoe et al (9).

An interesting finding of this study was the association of prolonged remission with the use of MP in patients with moderate activity (SLEDAI 6-12). Such therapy did not show a similar effect among patients with mild activity (SLEDAI 0-5). Almost all patients with severe activity (SLEDAI >12) received MP, thus the analysis in this group was not reliable, however, all the patients who did not achieve remission did not receive this therapy.

Our study has a number of limitations. First of all, taking into account its observational design, we can only establish associations but no causality, although most of the associations found make clear clinical sense. It was conducted at two European centers with mostly Caucasian patients, which may limit the generalizability of our results to other populations with different social, demographic and clinical characteristics. The statistical analysis used in the study may not have fully accounted for confounding variables, which could impact the validity of our findings.

On the other hand, our study showed some very consistent results. More severe patients were less likely to achieve prolonged remission; on the other hand, “mild” manifestations, such as cutaneous disease were also associated with reduced rates of remission even in the scenario of moderate-severe disease. Regarding therapy, we confirmed the long-term effects of HCQ in controlling activity in all lupus patients, regardless the degree of activity, the longer the therapy, the better. Also, the use of high initial doses of prednisone made it difficult to achieve remission across all baseline SLEDAI groups, probably due to the failure to reach the required prednisone doses ≤5 mg/d within the end of the first year. This confirms the finding of a multicenter Spanish study showing the predictive value of high initial doses of prednisone on the subsequent GC load (21). Finally, the use of MP within the early

phases of disease results an important tool to achieve remission not only in patients with severe, but also with moderate disease.

Overall, this study provides important insight into factors associated with prolonged remission in SLE, such as organ involvement, initial prednisone dose, use of MP and HCQ therapy. These findings may help guide clinical decision-making and improve outcomes for SLE patients. Further research is needed to confirm these finding and to identify additional predictors of remission, particularly in populations with diverse ethnicity and socio-economic status.

6. CONCLUSIONS

Our study found that deep organ involvement, high initial prednisone doses and cutaneous manifestations, even in the context of multisystemic disease activity, were related to lack of sustained remission. On the other hand, maintained HCQ therapy and the use of MP pulses, the later in patients with moderate-severe activity, were associated with prolonged remission.

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