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TESI DI LAUREA

Glucocorticoid withdrawal and risk of subsequent flare in Systemic Lupus Erythematosus

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ABSTRACT

Introduction: Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease with a multifactorial pathogenesis. Glucocorticoids (GCs) play a central role in the treatment of active SLE, but their chronic use is linked to well-established side effects and GC discontinuation is a key treat-to-target endpoint in SLE management. However, data on GCs discontinuation in remitted patients are scanty.

Aim: The aim of this study is to evaluate whether GCs can be safely withdrawn in patients in clinical remission and whether GC discontinuation is associated with reduced damage accrual. In addition, another aim is to identify predictors of successful GCs withdrawal, not followed by disease flares.

Materials and methods: A retrospective study was conducted based on the collection of data from 570 SLE patients followed at the Rheumatology Unit of the University Padua Hospital. Patients diagnosed after 1980 and followed-up until 2023 were included in the study. We analysed the characteristics of patients achieving remission on- vs. off- GCs therapy, comparing flare rates in the two groups. Moreover, among remitted patients off-GCs predictors of disease relapse after GC discontinuation were investigated. Disease activity was assessed by the SLE Disease Activity Index-2000 (SLEDAI-2K), with remission defined according to Zen definition: SLEDAI-2K=0, stable background therapy with immunosuppressants and antimalarials, with (remission on-GCs) or without (remission off-GCs) prednisone (PDN) equivalent dose of ≤ 5 mg/day. GC withdrawal was defined as the complete discontinuation of oral GCs. Flares were defined as any increase in clinical SLEDAI-2K>0 or the need for changes in SLE medications. Organ damage was defined according to the SLICC Damage Index (SDI). Outcomes were assessed at two timepoints: last remission and first/first available remission. Kaplan-Meir curve was used to evaluate flare-free survival in on- vs- off-GCs remitted patients. Logistic regression and Cox-regression analyses were used to identify predictors of flare and predictors of flare-free remission, respectively.

Results: Among 570 patients considered for our study, we could analyse data from 484 patients: at last remission, 360 achieved remission off-GCs (74.4%), while 124 on-GCs. During a mean observational time of 87 months (SD 76), 85 flares were observed, 48 in off-GCs remitted patients and 37 in on-GCs remitted patients

(p<0.01). This corresponds to an annual flare rate of 1.65 flare/100 patients/year, and 8.5 flares/100 patients/year in remitted patients off- and on- GCs, respectively (p<0.001). At multivariate logistic regression analysis, flares predictors in off-GCs remission were low C3 levels (OR 0.007, CI 95% 0.00-0.188, p=0.007), arthritis (3.108, 1.096-8.811, p=0.033), leukopenia (2.146, 1.030-4.472, p=0.041), vasculitis (2.650, 1.037-6.773, p=0.042), last remission duration (0.987, 0.980-0.995, p<0.001). By Cox regression analysis, predictors of shorter flare-free remission in remitted patients off-GCs were: thrombocytopenia (HR 2.446, CI 95% 1.106-5.410, p=0.027), vasculitis (3.033, 1.262-7.432, p=0.013), disease duration (0.943, 0.892-0.998, p=0.054), and anti-U1RNP antibody positivity (1.973, 0.988-3.940, p=0.054). As damage is concerned, SDI was lower in remitted patients off-steroids, but similar in patients with or without flares, meaning that prompt restoration of therapy prevented disease-related organ damage.

Conclusion: In patients with SLE in remission, gradual glucocorticoid withdrawal can be safely attempted in the majority of cases, including patients with severe organ involvement (neurological and renal). Withdrawal of GCs improves disease outcomes, reducing accrual of organ damage. According to our results, remission off-GCs is an achievable outcome in SLE, especially in patients without serological activity added to clinical quiescence and in those with less refractory disease.

1. Systemic lupus erythematosus

1.1 Definition

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease with a multifactorial pathogenesis. It is characterized by an abnormally active immune system, resulting in varying clinical symptoms. SLE manifestations are related to the presence of autoantibodies, immune complex formation and deposition and other altered immune processes (1). The clinical presentation of patients with SLE ranges from fatigue and fever, which are common signs, to organ-specific symptoms in the musculoskeletal, skin, gastrointestinal, renal, central nervous and vascular systems. Currently, there is no prevention for SLE, and nonspecific immunosuppressive therapy is used to treat the disease. Glucocorticoids (GCs) are the mainstay of treatment (2), although their prolonged use is associated with side-effects and damage accrual (3).

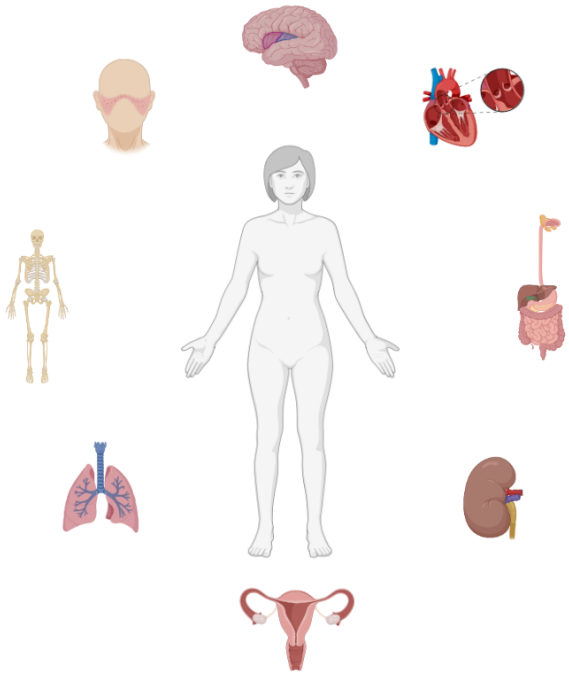


Figure 1.*Systemic lupus erythematosus (SLE): a multisystemic autoimmune disease*

1.2. Epidemiology

Epidemiology of SLE is a complex area of research and there are still many gaps in the delineation of the specific pathogen mechanisms. The global incidence of SLE ranges from 1.5 to 11 per 100,000 person-years, and the prevalence ranges from 13 to 7,713.5 per 100,000 persons. These marked differences in the burden of SLE are

explained by inherent differences in population structure, including gender, ethnicity, and environmental exposures (4).

Mortality rate among SLE patients remains unacceptably high and is two to three times higher than in the general population. The most common causes of death worldwide are infections and cardiovascular disease, which could be reduced by better treatment.

SLE shows marked gender, age, racial, temporal and regional variations, indicating hormonal, genetic and environmental disease triggers. There are gender differences in the development of SLE, with a higher prevalence in women than in men. Recent reports indicate a male-to-female ratio of approximately 12:1 during the childbearing years. The age distribution of SLE cases is usually wide, ranging from children as young as 2 years old.

In women, however, the most common age group is 15-44 years, with the greatest prevalence in the 45-64 age group (5). The reason why women are at greatest risk for SLE during their childbearing years, also suggests that hormones play an important role in the etiology of SLE.

Studies of racial trends have shown that SLE occurs more frequently in non-Caucasians. For example, in the United States, SLE occurs more frequently in African Americans, Hispanics, and Asians than in Caucasians. This suggests that the genetic disposition of SLE is important, but differences in exposure to environmental factors may also explain the excess morbidity from SLE in non-Caucasians (6).

1.3 Etiopathogenesis

The etiology of SLE is still unclear, but the multifactorial nature of the pathogenesis is known: genetic, environmental, and hormonal factors contribute to its development. The pathogenesis involves several cells and molecules involved in apoptosis processes and innate and adaptive immune response.

In SLE patients, the genetic background gives them a predisposition to an exaggerated response to various stimuli, e.g. infections. Thus, after contact with environmental triggers, such as the Epstein Barr Virus (EBV), there is a breakdown of immunological tolerance and immune response against endogenous nuclear antigens develops (2). In addition to this, there are two other important altered cellular mechanisms in SLE: apoptosis and NETosis. Anomalous expression of Fas/Fas Ligand and extrinsic apoptosis pathway play a key role in lymphocytes

apoptosis dysregulation, leading to an increase in apoptotic material. This induces altered clearance of cell debris, leading to altered immunogenicity and an increased autoantigen pool. These are also caused by an altered NEtosis which normally regulates inflammation mechanisms and microorganisms damage (7). However, in addition to these mechanisms, a central role in pathogenesis is played by B and T lymphocytes. B cells generally produce antibodies by means of T lymphocytes activated by secreted cytokines. In addition, recent evidence supports a T-cell-independent mechanism of B-cell stimulation through combined B cell antigen receptor (BCR) and TLR signaling. This situation leads to the production of a wide range of autoantibodies involved in tissue inflammation and damage, with different pathogenetic mechanisms (8).

1.3.1 Environmental factors

The pathogenesis of SLE is still unclear, but risk factors predisposing to the development of the disease have been identified. These can be divided into risk factors that are strongly correlated with the disease and those that are less correlated.

Factors strongly associated with SLE:

- ◊ **Smoking**: Exposure to toxic components of tobacco smoke causes oxidative stress, directly damaging endogenous proteins and DNA, leading to genetic mutations and gene activation that may contribute to SLE. Tobacco stimulates the expression of CD95 on the surface of B cells and CD4 on the surface of T cells, can induce autoimmunity and increases the production of inflammatory cytokines (9).
- ◊ **Alcohol:** low dose of alcohol seems to have a protective role in the risk of developing SLE (10).
- ◊ **Silica:** crystalline silica acts as an immune adjuvant, induces apoptosis and intracellular antigen release, increases inflammatory cytokines, oxidative stress and T-cell response, and decreases the number of regulatory T cells (9).

Factors modestly or weakly associated with SLE

In addition to the factors strongly associated with the risk of developing SLE, other factors have been identified that could be related to SLE. They are: vitamin D, air pollution, obesity, diet, infections, gut microbiome (11,12). However, further confirmatory studies are needed.

1.3.2 Genetic factors

SLE is a multigenic disease caused by the alteration of several genes. Genome-wide association studies (GWAS) have identified more than thirty genes that may be associated with SLE development. These genes are involved in the transcription of proteins that play a key role in the pathogenetic disease processes, such as production of cytokines, chemokines or adhesion molecules, apoptosis, and clearance of apoptotic material or immune complexes (13). Genes most associated with the development of SLE are those of the major histocompatibility complex (MHC). It is a protein complex expressed on antigen-presenting cells (APCs) surface in the case of bacterial infection or in all nucleated cells damaged or infected by intracellular pathogens. MHC class II cell surface molecules present peptides to CD4 T cells to eliminate auto-reactive T cells (negative selection) and induce T regulatory (Treg) cells during T cell development in the thymus, thus shaping the T cell receptor repertoire. In addition to this, peripheral mechanisms of elimination of self-reactive T lymphocytes are required to avoid autoimmune processes (14). Another strongly SLE-associated gene is interferon regulatory factor (IRF5) 5, which induces interferon α (IFNα) production. On the other hand the interferon itself activates IRF5, so it creates a positive feedback loop that results in an aberrant immune response (15). In addition to these, other genes associated with SLE are those encoding for gamma Fc receptors (FcγR). These are on hematopoietic cells surfaces and bind the crystalline fragment of immunoglobulins G by regulating antigen presentation and immune response. The subtype with inhibitory activity is FcγRIIB, expressed on B cells. FcγRIIB has an inhibitive function. Indeed, it restricts cellular functions at several levels in the immune response and alterations of any of these steps is likely to lead to a decrease in tolerance. Multiple signaling abnormalities are present in both T and B cells of SLE patients, which may be at least partially the result of genetic or epigenetic errors, resulting in intrinsic hyperactivity and hyperresponsiveness of T and B cells (16).

Epigenetic mechanisms that cause variation in gene expression (but do not involve changes in the DNA sequence) may be involved in SLE pathogenesis. Such mechanisms are influenced by external stimuli that induce reversible changes in gene expression, but at the same time heritable. Differences in the main epigenetic processes, such as DNA methylation, histone modification and microRNA interference, may partly explain the difference in disease development in

homozygous twins (7,15). These epigenetic mechanisms also explain women's predisposition to developing SLE. This, as an example, in terms of methylation-sensitive genes on the X chromosome, CD40L (CD40 ligand) is overexpressed in women with SLE and may have an impact on SLE susceptibility, since it is crucial for T and B lymphocytes communication regarding antigen stimulation (17).

1.4 Clinical manifestations

SLE affects multiple systems and has a variety of manifestations. Clinical characteristics might range from a relatively mild disease with simply mucocutaneous involvement to a serious, multiorgan threatening illness. In SLE, every organ system may be affected. Sometimes, an autoantibody profile can be used to forecast the progression of a disease and its clinical manifestations. Studies have shown that serological abnormalities might develop years before clinical lupus manifests itself. Pre-clinical lupus refers to a condition when a patient exhibits some clinical symptoms as well as serological abnormalities that are indicative of SLE but does not yet meet the diagnostic criteria for SLE. According to data, a sizable portion of these pre-clinical lupus patients, including those with incomplete lupus or undifferentiated connective tissue disease, may develop clinical lupus and develop other autoimmune diseases (18).

1.4.1 Constitutional Symptoms

The most common SLE constitutional symptoms are fever, weight loss, malaise and fatigue. These are usually the initial presenting symptoms that occur in more than 90% of SLE patients.

1.4.2 Mucocutaneous Manifestations

Mucocutaneous involvement is evident in more than 80% of individuals with SLE and is one of the best-known features. SLE skin lesions can be divided into specific and non-specific lesions:

- ◊ **Specific manifestations**:
    - *Acute cutaneous lupus erythematosus (ACLE):* Its characteristic lesion is malar rash, also known as the butterfly rash, a raised erythematous rash involving the cheeks and nasal bridge. The nasolabial folds are not affected by the rash, which might be macular or papular. It typically starts off acutely but may persist for several

weeks and result in scaling and induration. The lupus disease activity may potentially influence the malar rash (7,18).

- *Subacute cutaneous lupus erythematosus (SCLE):* It can occur in two forms: papulosquamous, similar to psoriasis, or annular-polycyclic with a central clearing and a peripheral flaking. SCLE is a photosensitive rash, diffuse, non-scarring and not hardened. SCLE lesions may persist for several months, however they typically resolve without leaving any scars (18),(7). Up to 90% of patients with a positive Anti-Ro (SSA) antibody experience SCLE rash. Some medications, including hydrochlorothiazide, can potentially contribute to SCLE (19).

- *Chronic cutaneous lupus erythematosus (CCLE):* CCLE lesions include discoid lupus erythematosus (DLE), leucocytoclasic vasculitis, chilblain lupus erythematosus (CHLE), Lupus erythematosus profundus or panniculitis (LEP), lupus tumidus and mucosal lupus erythematosus. DLE is the most common form. It can be localized (limited to the head and neck) or generalized (above and below the neck), and it may occur with or without SLE. These erythematous papules or plaques have a disk-like form, adherent scaling, and center clearing. When DLE involves the scalp, it heals with scarring and may be linked to permanent alopecia. Mucosal DLE lesions are often painful erythematous spherical lesions with white radiating hyperkeratotic striae. Histologically, hypertrophic DLE may resemble squamous cell cancer. Lupus panniculitis is less likely to be related to SLE and can develop above the waist. Secondly, another common finding in patients diagnosed with DLE are mucosal lesions. The oral mucosa is most commonly involved, however the nasal, conjunctival, and genital mucosa may be affected (18). Clinically, the eroded plaques manifest with an irregular white border and radianting striae. On the palate, lesions frequently resemble honeycombs (20).

◊ **Aspecific manifestations**:

- Photosensitivity
- Leucocytoclasic vasculitis
- Diffuse alopecia (“lupus hair”)
- Thrombophlebitis
- Occlusive vasculopathy
- Raynaud phenomenon
- Periungual telangiectasia
- Livaedo reticularis
- Calcinosis cutis
- Papulonodular mucinosis
- Erythema multiforme
- LE non-specific bullous lesions
- Erythromelalgia
- Leg ulcers
- Lichen planus
- Sclerodactyly
- Rheumatoid nodules
- Acanthosis nigricans
- Urticaria

1.4.3 Musculoskeletal manifestations

Musculoskeletal involvement, among the several SLE symptoms, is one of the most frequent manifestation with a prevalence of 80-90% in SLE patients. It may vary from minor arthralgias to deforming arthritis. Muscoloskeletal involvement includes joint pain, polyarthritis, Jaccoud’s arthropathy, rhupus syndrome, tendon inflammation and enthesitis. While up to 50% of SLE patients report having diffuse myalgia, only about 10% of individuals really experience overt inflammatory myositis (21). Important morbidity factors in SLE include osteonecrosis and osteoporosis. Osteomyelitis and septic arthritis are two other potential MSK pathogenic diseases that SLE patients can experience (22).

Lupus arthritis

Lupus arthritis often manifests as a symmetric polyarthritis. Small joints are typically more afflicted than large joints. The joint symptoms might last from a few hours to several weeks or even months. Joint swelling is frequent, and it can occur due to joint fluid or synovial proliferation, even though a physical examination may reveal tender joints with no swelling. In addition, other signs and symptoms of lupus arthritis are joint erythema, pain with joint mobility, and morning stiffness (23). Lupus arthritis mainly affects small joints in the hands (metacarpal phalangeal (MCP), proximal interphalangeal (PIP), distal interphalangeal (DIP)), knees, and wrists and it's typically a non-erosive, symmetrical inflammatory polyarthritis (18).

Jaccoud's arthropathy

Jaccoud's arthropathy (JA) is a kind of lupus arthritis brought on by ligament slackness and subluxation of the joint. However, on X-ray, erosions are typically absent, and physical examination demonstrates reducible joint deformity. This clinical manifestation can mimic rheumatoid arthritis (RA). Deformity in JA ranging from a reducible deviation, such as ulnar reducible deviation, to a more complicated deformity (mutilans-type) with subluxations and fixed joints (24).

Rhupus syndrome

In most cases, lupus arthritis does not have joint erosions, however a small proportion of SLE patients may present eroded joints on X-ray. These are patients with an overlap condition between SLE and RA, also called rhupus syndrome. This erosive arthropathy is associated, as in RA, with anti-cyclic citrullinated peptides antibodies (anti-CCP), rheumatoid factor (RF) and anti-RA33 autoantibody in SLE patients serum (25).

Periarticular involvement

In SLE patients, tendinopathies can also occur. The most frequent of these are tenosynovitis of the hand with a prevalence of 45% in SLE suffers. In addition to this, tendinopathies may manifest as tendonitis or tendon rupture (23).

Muscular involvement

In SLE there may be muscle involvement manifesting as diffuse myalgias. However, in less than 10% of SLE patients, a real inflammatory myopathy occurs. Furthermore, it must be emphasised that lupus patients have a high risk of developing fibromyalgia (18).

Avascular necrosis

Avascular necrosis (AVN) results from impaired bone blood flow, which causes ischemic mortality. It typically occurs in humeral head, tibial plateau, femoral condyles, and femoral head which is the location most frequently afflicted. In SLE patients, AVN can be associated with risk factors such as trauma, alcohol, smoking, chronic glucocorticoid use and antiphospholipid antibodies (APL) (8).

1.4.4 Renal Manifestations

Kidney, with lupus nephritis (LN), is frequently involved in SLE. Typically, within 5 years of diagnosis, LN develops in 40% of SLE patients and still has a 4.3-10.1% probability of progression to end stage renal disease (ESRD). One of the leading causes of death in SLE patients, along with infections, malignancies, and cardiovascular events, is renal failure (26). The prevalence of LN varies by ethnicity and the range of clinical manifestations includes asymptomatic urine anomalies to severely symptomatic nephritic syndrome or quickly progressing renal insufficiency patients. Clinical manifestations may be quiet, with normal 24-hour proteinuria, renal function, and urinalysis results. Furthermore LN signs can be leukocyturia, haematuria, cellular casts and mild proteinuria or more severe manifestations such as nephrotic syndrome, acute nephritic syndrome or rapidly progressing renal failure (27). International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of lupus nephritis and 2018 revision identified six histological classes, defined by specific microscopic lesions and distribution of immune complexes (IC):

- **Class I**: Minimal mesangial LN;
- **Class II**: Mesangial proliferative LN;
- **Class III**: Focal LN (<50% of the glomeruli involved);
- **Class IV**: Diffuse LN (≥ 50% oh the glomeruli involved);
- **Class V**: Membranous LN;

- **Class VI**: Advanced sclerosing LN.

The management of lupus nephritis is based on the results of the biopsy. Each class has a different prognosis, with classes I and II having a good prognosis and classes III and IV having poor prognosis. With the exception of thromboembolism, class V often has a good prognosis. Thrombotic microangiopathy, lupus vasculopathy, interstitial nephritis, vasculitis and arteriolosclerosis are possible additional renal symptoms (18). Renal flares can be influenced by several risk factor: male gender, young age at renal disease onset, delayed treatment or partial response to therapy, high disease activity in other domains, disease with active serology, and African-American ethnicity (27).

1.4.5 Cardiovascular Manifestations

In SLE patients, any layer of the heart, such as pericardium, myocardium, endocardium and coronary arteries, may be affected by disease. The most frequent cardiac symptom is pericarditis with exudative pericardial effusions, furthermore cardiac tamponed is an uncommon condition. Although it is not common, lupus myocarditis represents a major cardiac risk as a result of its effects on the heart's electrical system and function. Development of this condition is influenced by different risk factors including disease activity and ethnicity and generally is associated with anti-Ro (SSA) antibodies (28).

Cardiovascular manifestations also include valvular disorders, notably Libman-sacks endocarditis (LSE). This is a non-infectious lesion targeting largely mitral valve and resulting in valve regurgitation or stenosis (29). LSE occurs frequently in SLE suffers with antiphospholipid syndrome.

Patients with SLE are especially at high risk for coronary artery disease because of coronary vasculitis and atherosclerosis (18). In order to this Myocardial infarction (MI) represents the most important cause of death in young patients.

1.4.6 Pulmonary Manifestations

Pulmonary involvement in SLE is very common and it may represent the first sign of SLE affecting practically any respiratory system part. Pleuropulmonary

involvement has a minimal or absent connection with serological markers, in contrast to what happen in other organs (skin, kidney, nervous system).

The most common thoracic manifestation of SLE is pleuritis. Pleuritic pain is the primary symptom, which is frequently accompanied by fever, coughing, and dyspnea. Sometimes pleural effusion can be asymptomatic and only be found by radiography. Pleuritis are often modest and bilateral, although they might be unilateral (30).

Another important pulmonary manifestation is acute lupus pneumonitis. Its prevalence is between 2% and 9% and it's characterised by a non-specific onset with cough, hemoptysis, dyspnea and fever. Hypoxemia and acute respiratory failure can occur in severe cases. To X-ray images, it appears as unilateral or bilateral alveolar infiltrates at the lung base.

Chronic interstitial lung disease (ILD) usually affected man over 50 years of age with old SLE diagnosis. It can occur after acute pneumonitis and the course may be insidious. Up to 80% of patients with ILD have anti-Ro/SSA in their blood, even if the severity is not related with serological markers (31).

In some cases, SLE patients can have restrictive pattern on spirometry, without any parenchymal alteration. This suggests a shrinking lung syndrome that can manifest with progressive dyspnea (7).

Diffuse alveolar haemorrhage (DAH) is less frequent than other pulmonary manifestations. Women are more affected than man and the main signs and symptoms are dyspnea, decreasing hemoglobin, changing radiographic infiltrates and hemoptysis. It can be a fatal condition (30).

At last, pulmonary hypertension (PAH) can occur in SLE patients. It's associated with antiphospholipid syndrome and Raynaud's phenomenon (18).

1.4.6 Gastrointestinal Manifestations

SLE may affect any portion of the gastrointestinal tract:

Esophagus

The most common manifestations are esophagus dysphagia and dysmotility. This one mainly occurs in the upper one-third of the esophagus, even if can affect also the inferior third esophagus tract.

Stomach

In SLE patients, gastritis and peptide ulcers can occur due to overuse of anti-inflammatory drugs (NSAID) and glucocorticoids (GCs).

Bowel

Lupus enteritis is characterized as either vasculitis or small bowel inflammation. Although presenting symptoms of lupus enteritis vary in kind and intensity, abdominal discomfort is the most frequent one. Intestinal vasculitis cause smooth muscle and enteric nerves damage, leading to intestinal pseudo-obstruction (32).

Pancreas

Pancreatitis is usually more prevalent in the first years after SLE diagnosis. Possible pathophysiologic causes of pancreatitis in SLE include vasculitis resulting in tissue necrosis, intimal thickening with immune complex deposition in the pancreatic arteries and antiphospholipid-associated thrombosis of pancreatic arterioles and arteries (32).

Liver

Increased transaminase levels in SLE patients can be due both disease itself and treatment. If antimitochondrial antibodies and an elevated alkaline phosphatase level are found, autoimmune hepatitis and primary biliary cirrhosis should be taken into consideration. In addition, in SLE patients primary sclerosing cholangitis and autoimmune cholecystitis could be associated (32).

1.4.7 Neuropsychiatric Manifestations

Neuropsychiatric SLE (NPSLE) affect about 50% of SLE patients. It can involve central (CNS) and peripheral (PNS) nervous systems. These are included in the ACR Nomenclature for NPSLE (neuropsychiatric SLE) that defines 19 different neuropsychiatric phenotypes (33).

Central nervous system

Listed below are the most typical central nervous system (CNS) symptoms:

- ◊ *Headaches:* its prevalence is about 50%, however is a non-specific symptom. A lupus-related headache pattern has yet to be found (33).
- ◊ *Cerebrovascular diseases:* they occur in 3–20% of the patients and cause mortality of up to 15%. Main forms of cardiovascular diseases are acute ischemic stroke or transient ischemic attack. These are due to different causes such as a hypercoagulable state secondary to APS, cardioembolic disease secondary to Libman-Sacks endocarditis, arteriosclerosis and CNS vasculitis.
- ◊ *Focal or generalized seizures:* SLE itself or some complications related to disease may cause seizures. Typically, they are isolated episodes; epilepsy is less common. Patients may experience partial simple or complex seizures or tonic-clonic epileptic seizures.

In addition to these there are fewer common manifestations:

- ◊ *Acute confusional state*
- ◊ *Cognitive dysfunction*
- ◊ *Psychiatric manifestations*
- ◊ *Demyelinating disease*
- ◊ *Myelopathy (transverse myelitis)*
- ◊ *Aseptic meningitis*
- ◊ *Cerebral venous sinus thrombosis*
- ◊ *Posterior reversible encephalopathy syndrome (PRES)*
- ◊ *Idiopathic intracranial hypertension*

Peripheral nervous system

Peripheral nervous system involvement is less frequent than CNS involvement; However, it takes several forms (33):

- ◊ *Peripheral neuropathy:* the most prevalent form of PNS manfestations are peripheral polyneuropathies including axonal, demyelinating or mixed type
- ◊ *Cranial neuropathy*

- ◊ *Inflammatory demyelinizing polyradiculoneuropathy*
- ◊ *Autonomic disorder*
- ◊ *Mononeuritis*
- ◊ *Myasthenia gravis*
- ◊ *Plexopathy*

1.4.8 Hematologic manifestations

SLE patients may develop anemia, leukopenia, thrombocytopenia and in some cases lymphadenopathy and splenomegaly.

Anemia

The prevalence of anemia is about 50% in SLE patients. The mainly cause is anemia due to chronic disease. However, there are other forms such as anemia due to iron deficiency, hemolytic anemia in patients with positive Coomb's test or in patients with antiphospholipid antibody syndrome (18).

Leukopenia

Leukopenia develops following neutropenia and lymphopenia. These are caused both by drugs (glucocorticoids) and by disease in its active phase (18).

Thrombocytopenia

Thrombocytopenia can range from mild to severe, and it may be accompanied by autoantibodies against platelets, glycoprotein IIb/IIIa or thrombopoietin receptor, as well as the antiphospholipid antibody syndrome (18).

1.5 Diagnosis

Clinical and physiological examination is frequently insufficient for diagnosing and evaluating SLE pathophysiological processes. A central role is played by immunological and clinical biomarkers, extremely important for improving SLE diagnosis, evaluation and control (34). Clinical signs or symptoms and laboratory biomarkers, that show immune reactivity and inflammation in different organs, are used to identify and categorize patients with SLE. SLE has a major impact on patients' lives and on long-term prognosis, thus it is crucial to diagnose disease as early as possible. Therefore, SLE diagnostic process involves:

- Evaluation of signs and symptoms;
- Aspecific laboratory tests: complete blood count (CBC), urinalysis, liver and renal function test, C-reactive protein (CRP) assay and erythrocyte sedimentation rate (ESR);

- Antibody panel;

1.5.1 Biomarkers and serologic tests

Antinuclear antibodies (ANA)

SLE, as well as other autoimmune diseases, often shows ANA which can be utilized for screening, diagnosis and prognosis. ANA is used as a biomarker of SLE due to its high sensitivity ranging from 95% to 97%. On the other hand, its specificity is about 20%, therefore high levels of ANA are also present in a number of other immunological diseases and in a sizable fraction of the healthy population (35). However, according to EULAR/ACR 2019 classification, a negative ANA serological test excludes SLE classification. ANA can target different autoantigens, thus there are different subgroups of ANA antibodies (18). The main ones are single-stranded DNA antibodies (anti-ssDNA), double-stranded DNA antibodies (anti-dsDNA) and extractable nuclear antigens antibodies (anti-ENA). They can be detected by enzyme-linked immunosorbent assay (ELISA). A positive ANA test needs to be followed by a more specialized autoantibody test, i.e. anti-dsDNA, anti-ENA. Whether these are negative ANA positivity is less likely to indicate disease (36).

Double-stranded DNA antibodies (dsDNA)

Anti-dsDNA antibodies are one of the most distinctive ANA kinds, and they are highly specific (96%) for SLE but are only identified in 60–70% of SLE cases. Therefore, SLE diagnosis is not excluded by a negative anti dsDNA test. Anti-dsDNA antibodies have a strong relationship with disease activity and their concentrations can change over time. As a result, levels may be undetectable throughout treatment and rise during a flare. Anti-dsDNA antibodies only temporarily develop; for this reason, their diagnostic sensitivity is modest (52%). In SLE patients with active nephritis, antibodies can be deposited on the basement membrane, glomeruli and mesangium, so their presence can be considered a predictive marker for the development of lupus nephritis (35).

Extractable nuclear antigen antibodies (ENA)

Anti-ENA associated with systemic lupus erythematosus include:

- ***Anti-Smith Antibodies (anti-SM)***: The positivity of anti-SM is one of the most important criteria in the immunological domain in EULAR/ACR 2019 classification for SLE. Their specificity is very high, about 99%. Anti-SM antibodies correlate with SLE disease activity, but unlike anti-dsDNA antibodies, they have a generally steady expression in peripheral blood. On the other hand, they have a low sensitivity, about 20-30%. Anti-SM antibodies have been linked to lupus nephritis and have been shown to predict silent LN as well as high disease activity, as seen by lymphopenia and hypocomplementemia (37).
- ***Anti-U1-RNP antibodies***: They are often associated with anti-SM antibodies, which can be found in up to 30% of SLE patients. They can be detected in patients with overlap connective tissue disease. However anti- U1-RNP antibodies are not specific for SLE (36).
- ***Anti-Ro (SSA) and Anti-La (SSB) antibodies****:* These antibodies, which have a 90% specificity for Sjögren syndrome, can be used to test for secondary Sjögren syndrome in SLE patients. However, they are also linked to neonatal lupus, photosensitivity, and subacute cutaneous lupus (35).

Further antibodies

- ***Anti-ribosomal P antibodies (anti-P)***: They are highly specific for the disease and they may be associated with its neuropsychiatric symptoms. However, they are uncommon in SLE, less than 5% (36).
- ***Antiphospholipid antibodies (aPL)****:* They are associated with SLE-APS (antiphospholipid syndrome) and represent risk factors for thrombosis and obstetric complications.
- ***Anti-C1q antibodies****:* They are non-specific for SLE and they are associated with impaired apoptotic cell clearance. Even if they are not specific, their levels increase prior to renal flares (38).

Specific urinary biomarkers

Traditional urinary indicators for LN include twenty-four-hour urine protein and protein/creatinine ratio. Detecting renal involvement is important given its contribution to mortality and morbidity in SLE patients. Thus, several urine protein biomarkers have been evaluated as potential SLE biomarkers, particularly for LN: chemokines, cytokines, adhesion molecules and growth factors. Nevertheless, none of these have received authorization for use in clinical settings (35).

Complements C3 and C4

Low levels of C3 or C4, in addition to a positive ANA test, have 94.3% specificity for SLE diagnosis. Therefore, patients with both low C3 and C4 levels and a positive ANA test have 97.6% specificity for an SLE diagnosis (39). However, if C3 and C4 tests are used alone, they lose their specificity. Therefore, they cannot be used as SLE biomarkers. According to recent research, higher plasma complement split products and cell-bound activation products are more accurate diagnostic indicators and strongly correlate with SLE disease activity (39).

1.5.2 Additional examinations

Depending on the organ involved, other examinations can be performed such as (36):

- Chest RX and computed tomography (CT)
- Joint X-rays
- CNS magnetic resonance imaging (MRI)
- Cardiac work-up
- Kidney biopsy
- Skin biopsy

1.5.3 Lupus mimickers and differential diagnosis

The management of a patient with probable SLE necessitates one of the most extensive and thorough clinical workups, given the variability and complexity of this autoimmune disease. Accurate diagnosis of SLE might be challenging and both misdiagnosis and overdiagnosis could be dangerous for patients. The differential diagnosis becomes essential in SLE. Indeed, there are other autoimmune diseases with ANA positivity such as chronic autoimmune hepatitis, dermatomyositis, inflammatory myopathies, juvenile idiopathic arthritis (JIA), primary biliary

cirrhosis, rheumatoid arthritis (RA), Sjögren syndrome (SS) and systemic sclerosis (SSc). The main differential diagnoses are (36,37,39,40):

- **Autoimmune Diseases**
  - Rheumatoid arthritis (RA);
  - Undifferentiated and mixed connective tissue diseases;
  - Sarcoidosis;
  - Fybromialgia;
  - Vasculitis;
  - Behçet disease;
  - Adult-onset Still disease;
  - Undifferentiated polyarthritis;
  - Spondyloarthopaties;
  - Drug-induced lupus (DIL)

- **Infections**:
  - Parvovirus B12
  - Epstein-Barr Virus (EBV)
  - Citomegalovirus (CMV)

- **Neoplasm:**
  - Lymphomas

1.6 Classification criteria

Standardized classifications known as classification criteria are used primarily to produce well-defined, relatively homogeneous cohorts for clinical research. Thus, the intent of diagnostic criteria and the purpose of classification are different. Validated classification criteria are thought to be essential for interpreting study findings and comparing outcomes across investigations (41). For this reason, classification criteria have been drawn up for many years. The first of these were designated, in 1982, by the American College of Rheumatology (ACR) and were based on specific laboratory biomarkers. They were revised by the ACR in 1997 and later in 2012 by the Systemic Lupus International Collaborating Clinics (SLICC) group. To date, the latest classification system used is the one defined by the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR) in 2019. In the table below, the differences between the different classification systems can be seen (34):

Table 1. *Immunological criteria evolution (41).*

	ACR 1982	ACR 1997	SLICC	EULAR
Immunologic disordes	Positive LE cell preparation	-	-	-
	Anti-DNA	Anti-DNA	Anti-DNA	Anti-DNA
	Anti-Sm	Anti-Sm	Anti-Sm	Anti-Sm
	False positive serologic test for syphilis	Anti-phospholipid	Anti-phospholipid	Anti-phospholipid
	-		Low complement	Low C3 and C4
				Low C3 or C4
	-		Positive Coombs test without hemolysis*	-
ANA	Antinuclear antibody		ANA	Entry criterion*

**Definitions apply, §Exclusions apply*

Table 2*. Clinical criteria evolution (41)*

	ACR 1982/1997	SLICC	EULAR/ACR
ACLE	Malar rash	-Malar rash§ -Bullous lupus -Toxic epidermal necrolysis variant -Maculopapular lupus rash -Photosensitive lupus rash -SCLE	-Malar rash -Maculopapular lupus rash
SCLE	-		-SCLE
CCLE	Discoid rash	-Discoid rash* -Hypertrophic lupus -Lupus panniculitis -Mucosal lupus -LE tumidus -Chillblains lupus -Discoid lupus/lichen planus overlap	Discoid lupus
Photosensitivity	Photosensitivity	-	Photosensitivity
Mucosal ulcers	Oral ulcers	Oral ulcers Nasal ulcers	Oral ulcers
Non-scarring alopecia	-	Non-scarring alopecia	Non-scarring alopecia
Arthritis	Non-erosive arthritis*	Arthritis	Joint involvement
Serositis	-Pleuritis* -Pericarditis*	-Pleuritis* -Pericarditis*	Pleural or pericardial effusion*(5)
			Acute pericarditis*(6)
Renal disorder	-Proteinuria* -Cellular casts*	-Proteinuria* -RBC casts*	Proteinuria*
Lupus nephritis histology	-	Compatible with lupus nephritis‡	ISN/RPS III/IV
			ISN/RPS II/V
Neurologic disorder	-Seizures§ -Psychosis§	-Seizures§ -Psychosis§ -Acute confusional state§ -Mononeuritis multiplex§ -Myelitis -Neuropathy§	-Seizures§ -Psychosis§ -Delirium
Hematologic disorder	-Hemolytic anemia* -Leukopenia* -Lymphopenia* -Thrombocytopenia*§	Hemolytic anemia*	Hemolytic anemia*
		-Leukopenia* -Lymphopenia*	Leukopenia*
		Thrombocytopenia*§	Thrombocytopenia*§

**Definitions apply, §Exclusions apply.*
‡Sufficient for classification with positive ANA or anti-dsDNA antibodies.
†Concept survives in definitions. ISN/RPS International Society of Nephrology/Renal Pathology Society classes.

Considering the last Classification criteria, EULAR/ACR 2019, a disease can be classified as SLE if score is ≥10 and entry criterion is fulfilled:

- ◊ **Entry criterion:** positive ANA test result:
  - ANA at a title of ≥1:80 on HEp-2 cells, or an equivalent positive test result (ever);
  - If absent, do not classify as SLE. If present, apply additive criteria.
- ◊ **Additive criteria**:
  - Do not count a criterion if there is a more likely explanation than SLE. Occurrence of a criterion on ≥1 occasion is sufficient.
  - SLE classification requires ≥1 clinical criterion and ≥10 points.
  - Criteria need not occur simultaneously.
  - Within each domain, only the highest weighted criterion is counted toward the total score

Table 3. *European League Against Rheumatism/American College of Rheumatology classification criteria for SLE (1)*

Domains	Criteria	Weight
Constitutional	Fever	2
Hematologic	Leukopenia	3
	Thrombocytopenia	4
	Autoimmune hemolysis	4
Neuropsychiatric	Delirium	2
	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/24 hr	4
	Renal biopsy Class Il or V lupus nephritis	8
	Renal biopsy Class Ill or IV lupus nephritis	10
Antiphospholipid Ab	Anti-cardiolipin Ab or	-
	Anti-ß, GP1 Ab or	-
	Lupus anticoagulant	2
Complement protein	Low C3 or low C4	3
	Low C3 and low C4	4
SLE-specific Ab	Anti-dsDNA Ab or	-
	Anti-Sm Ab	6

1.7 Disease course

Considering the variety of clinical manifestations and laboratory test results, disease activity is highly variable and non-predictable. Disease activity includes both clinical and serological activities. These include inflammatory and non-inflammatory manifestations affecting any area of the body, and serological anomalies such as ANA positivity, low C3 and/or C4, increased gamma globulin serum levels (42). Studies conducted at the University of Toronto Lupus Clinic (UTLC) defined 4 different patterns of disease activity (43):

1. **Prolonged remission (PR):** patients who achieved a clinical SLEDAI- 2K (Systemic Lupus Erythematosus Disease Activity Index) of 0 (serology excluded anti-dsDNA anti-bodies and low complements C3 or C4) within 5 years of enrollment and maintained this status for at least 10 additional consecutive years. Clinical quiescence between visits was ensured by the lack of any new treatment;
2. **Relapsing-remitting (RR):** patients who had at least two periods of clinical remission following periods of activity within the 10 years since enrollment. A remission period was defined as two consecutive visits with a clinical SLEDAI-2K of 0 (serology excluded).
3. **Persistently active (PA):** patients who had never achieved a period (two consecutive visits) of clinical remission within the 10 years since enrollment.
4. **Hybrids:** patients who had only one remission period in the 10 years since enrolment.

1.8 Treatment and Management

Treatment for SLE patients should be multidimensional and start as soon as possible after diagnosis to minimize disease progression, recurrence, damage, and comorbidities. Thus, the likelihood of controlling the disease with a manageable drug regimen in a fair amount of time, increases with earlier treatment. The more timely the treatment, the more the disease is controllable with a manageable drug regimen (44). Therapeutic treatments should attempt to reduce damage accumulation from both active disease and drug-related adverse effects while controlling disease activity. However, the management of SLE is highly diverse, maybe as a result of a lack of agreement on the definitions of remission and/or low

disease activity (LDA), as well as on how SLE should be managed in the long term (44). The pillars on which the management of SLE patients is based, are the following:

- ◊ Early diagnosis
- ◊ Preventive strategies
- ◊ Treat-to-target approach
- ◊ Personalized medicine
- ◊ Tapering and withdrawal

1.8.1 Preventive strategies

Preventive strategies could be distinguished in:

- ◊ **Primary prevention:** preventive strategies for people at risk of developing SLE. The high persistent ANA title (>1:80) and/or the presence of autoantibodies in addition with other risk factors could be useful to identify those at risk of developing SLE and allow their monitoring. Thus, primary prevention is based on the elimination of risk factors and on the treatment with hydroxychloroquine to subjects who have both ANA positivity and complement reduction. Primary prevention also reduces thromboembolic risk in patients with SLE and positive antiphospholipid antibodies, by giving low-dose aspirin (44).
- ◊ **Secondary prevention:** strategies to avoid flares of disease in SLE patients. These strategies are based on primary prevention in addition with appropriate therapy such as mycophenolate mofetil (MMF), methotrexate (MTX), azathioprine (AZA), hydroxychloroquine (HCQ), rituximab (RTX) and cyclophosphamide (CYC).
- ◊ **Tertiary prevention**: strategies to avoid disease progression in patients with SLE. Is a sum of primary, secondary prevention and steroid-sparing strategies.

1.8.2 Treat-to-target approach

The "treat-to-target" approach aims to treat patients toward a goal that can improve the course of their disease (42). The purpose of treatment is to achieve complete symptom management and disease remission, enhance patient long-term outcomes, prevent end organ damage, and improve patient quality of life (35). Therefore, the main target are remission and lupus low disease activity state (LLDAS). The

problem is to give an unambiguous definition of these targets, in fact several studies have been looking at this for many years. To date, the most commonly used definitions of remission are DORIS (45) and Doria-Zen (46), while the currently definition of LLDAS is below in table 5 (47).

Table 4. *DORIS definition of remission in SLE (45)*

DORIS
1. clinical- SLEDAI-2K =0
2. SELENA-SLEDAI physician global assessment (PGA, scale 0–3) ≤0,5
3. Current prednisolone (or equivalent) dose ≤5 mg daily
4. Well tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents, excluding investigational drugs

Table 5*. Doria-Zen definition of remission in SLE (46)*

Remission definition					
	Disease activity		**Treatment**		
Prolonged remission	**Clinical**	**Serological**	**Prednisone**	**Antimalarials**	**IS**
Complete remission	No	No	No	Yes	No
Clinical remission off GCs	No	Yes	No	Yes	Yes
Clinical remission on GCs	No	No/Yes	1-5 mg/day	Yes	Yes
Disease activity was assessed by SLE Disease Activity Index 2000 (SLEDAI-2K)					

Table 6. *LLDAS definition of Franklyn et al (47).*

LLDAS definition
1. SLEDAI-2K ≤4, with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever) and no haemolytic anaemia or gastrointestinal activity
2. No new features of lupus disease activity compared with the previous assessment
3. SELENA-SLEDAI physician global assessment (PGA, scale 0–3) ≤1
4. Current prednisolone (or equivalent) dose ≤7.5 mg daily
5. Well tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents, excluding investigational drugs

Treat-to-target approach can be demonstrated with a simplify flow-chart (figure 2). The first step is achieving and maintaining remission over time. If this is not possible, the goal is to reach an LDA. At this point, after treating patients according to the clinical manifestations, the second step is minimizing and stop glucocorticoids. The third step involves, for patients in remission, a decaling of

immunosuppressive therapy, until discontinuation. For LLDA patients, a decrease in the dose of immunosuppressants is planned.

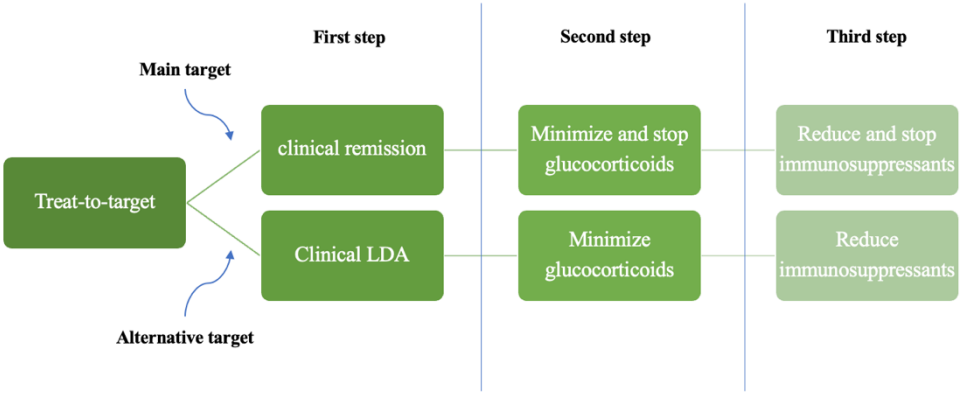


Figure 2. *T2T step by step (44)*

The main treat-to-target drugs are glucocorticoids, antimalarial, immunosuppressive and biologic therapy.

Hydroxychloroquine and antimalarial drugs

They can be used both in mild and severe SLE manifestations and symptoms.

The first line of drug for most patients is hydroxychloroquine. The response to hydroxychloroquine is encouraging, although patient monitoring is necessary due to the possibility of retinal damage with long-term medication (48).

Glucocorticoids

Glucocorticoids are usually given when disease flares-up. They are used in severe manifestations such as lupus nephritis and neuropsychiatric (44). However, the goal is to achieve remission and tapering glucocorticoids. Therefore, glucocorticoids should be replaced by other drugs in the long term, such as immunosuppressive therapy or hydroxychloroquine (49).

Immunosuppressive therapies

The main immunosuppressive drugs are mycophenolate mofetil (MMF), azathioprine (AZA), cyclosporine A, tacrolimus, methotrexate (MTX), and cyclophosphamide (CYC). Immunosuppressive medication choice is influenced by symptoms, age, and family planning. Immunosuppressive drugs are a good choice in patients with relapsing-remitting disease course and in non-responders to

hydroxychloroquine (50). Several studies show that the combination of different drugs is better than the use of a single immunosuppressant (44).

Biologic therapies

Currently biological drugs used in SLE are Rituximab (anti-CD20) and Belimumab (anti- BLyS). These drugs are the first choice for patients with high disease activity including prednisone dosage of 7.5 mg/die or higher, high anti-dsDNA titles and renal symptoms. They are considered when the patient has not responded to optimally tolerated immunosuppressive therapy (35).

In recent years has been created Anifrolumab, a monoclonal antibody against the IFN-I receptor subunit 1 (51). TULIP-1 and TULIP-2 trials demonstrated the efficacy of Anifroluman compared to placebo use. Furthermore, these trials demonstrated the possibility of reducing GCs in patients treated with Anifrolumab, without risk of flare (52).

1.9 Prognosis and complications

Despite improvements in SLE treatment options and a greater understanding of the disease's pathophysiology, SLE patients still have a high death rate and experience severe morbidity. This can be improved by early diagnosis and therapy to minimize organ damage. The main negative prognostic factors are renal involvement, male sex, African American ethnicity, hypertension and high disease activity (53). Complications may be disease process-related, such as renal end-stage disease and atherosclerosis, or medication-induced such as osteoporosis and retinopathy (36).

2. Clinimetric Evaluation

2.1 Disease activity assessment

The assessment of disease activity is crucial for disease management, to prevent long-term effects and to assess patient response to therapy. In addition, the assessment of disease activity is necessary to distinguish real damage related to disease activity from chronic damage or drugs side effects. Clinimetric Evaluation is also necessary to identify patients who may benefit from a specific therapy and enables clinical and longitudinal studies to be compared (54). To date, there is no single system for evaluating disease activity, but guidelines have identified the main ones: BILAG (British Isles Lupus Assessment Group Score), SLEDAI (SLE Disease Activity Index), CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index), ECLAM (European consensus lupus activity measurement) and SLE-DAS (SLE Disease Activity Score). These scores can be classified into two main categories: scores that assess a global measure of activity, such as SLEDAI, and scales that provide an assessment of disease activity in individual organs, such as BILAG index (55). The table below summarises the different disease activity scores (BILAG, SLEDAI, SLE-DAS, ECLAM).

***Table** 7. Differences between disease activity scores*

	BILAG	SLEDAI	SLE-DAS	ECLAM
N° of items	86	24	17	30
N° of organ/systems	8	9	9	10
Review period	28	10		28
Scoring	Individual system	Global	Global	Global
Immunological variables	No	Yes	Yes	Yes
Objective/subjective	Both	Objective	Objective	Both

2.1.1 SLEDAI

The first system for the disease activity evaluation was SLEDAI, in 1985. This score was revised in 2002 to become SLEDAI-2K. It assesses clinical manifestations in 9 organs/systems using 24 items (shown in the table below) (56). The original SLEDAI considered proteinuria, mucosal ulcers, alopecia and skin

manifestations only if these represented the first manifestation or a recurrence, in order to distinguish them from chronic lesions. In the modified SLEDAI-2K version, however, the same manifestations are considered in the score whether they are recurrent or persistent. Anyway, it can have a maximum score of 105, and each item can be scored from 1 to 8 depending on the clinical importance of each particular event. The final score considers the manifestations that occurred in the 10 days prior to the assessment (57).

***Table 8**. Organs/systems assessed in SLEDAI and weight for each item*

Weight	Item
8	Seizure
8	Psychosis
8	Organic brain syndrome
8	Visual disturbance
8	Cranial nerve disorder
8	Lupus headache
8	Cerebrovascular accidents
8	Vasculitis
4	Arthritis (>2 joints)
4	Myositis
4	Urinary casts
4	Proteinuria
4	Haematuria (>5 RBC/HPF)
4	Pyuria (>5 WBC/HPF)
2	New rash
2	Alopecia
2	Mucosal ulcers
2	Pleurisy
2	Pericarditis
2	Low complement
2	Increased DNA binding
1	Fever (< 38.5°C)
1	Thrombocytopenia (<100.000/uI)
1	Leukopenia (<3000/uI)

The final SLEDAI-2K score makes it possible to identify five different categories of disease activity (55):

- No activity (SLEDAI=0),
- Mild activity (SLEDAI=1–5),
- Moderate activity (SLEDAI=6–10),

- High activity (SLEDAI=11–19),
- Very high activity (SLEDAI>20)

It is also necessary to mention the existence of a modified SLEDAI used in pregnant women: SLE-P-DAI (SLE Pregnancy Disease Activity Index). This score is useful for differentiating manifestations caused by the disease from those caused by pregnancy.

2.2 Organ damage assessment

In addition to the disease activity assessment, the assessment of organ damage is also crucial in the clinical evaluation of SLE patients. This evaluation is necessary to assess morbidities caused, not only by the disease, but also by the therapy, particularly GCs. Therefore, it is important to distinguish active disease, from chronic disease damage. To this end, a group of researchers has created a precise score: Systemic Lupus International Collaborating Clinics Damage Index (SLICC). It was approved by the American College of Rheumatology in 1992, so it is also called SLICC/ACR (58). This index uses the evaluation of 12 organs/systems by means of 41 items. Chronic damage is defined as irreversible damage, arising after SLE diagnosis, present for at least 6 months and not attributable to active inflammation. In the case of cardiovascular damage, the presence of an immediate pathological scar, indicative of damage, is sufficient (55). The maximum score is 47 and some events may be counted twice, such as stroke or osteonecrosis in different sites. The most frequent damage includes cataract and retinal damage also caused by the use of hydroxychloroquine, chronic renal insufficiency and musculoskeletal changes, also caused in part by prolonged GCs use.

Table 9. *Organs/systems assessed in SLICC and scores for each item*

Organ/system	Items	Score (maximal)
Ocular	Any cataract ever Retinal change OR optic atrophy	2
Neuropsychiatric	Cognitive impairment OR major psychosis seizures requiring therapy ≥6 months Cerebral vascular accident OR resection not for malignancy Cranial or peripheral neuropathy Transverse myelitis	6
Renal	Estimated or measured GFR <50% Proteinuria >3.5g/24h ESRF (regardless of dialysis or transplantation)	3
Pulmonary	Pulmonary hypertension, Pulmonary fibrosis, Shrinking lung, Pleural fibrosis, Pulmonary infarction OR resection not for malignancy	5
Cardiovascular	Angina OR Coronary artery bypass Myocardial infarction, Cardiomyopathy (ventricular dysfunction) Valvular disease Pericarditis OR Pericardiectomy	6
Peripheral vascular	Claudication, Minor tissue loss (pulp space) Significant tissue loss ever Venous thrombosis with swelling, ulceration OR venous stasis	5
Gastrointestinal	Infarction or resection of bowel below duodenum, spleen, liver or gall bladder ever Mesenteric insufficiency, Chronic peritonitis Stricture OR Upper gastrointestinal tract surgery Pancreatic insufficiency requiring enzyme replacement OR with pseudocyst	6
Musculoskeletal	Muscle atrophy OR weakness Deforming or erosive arthritis (including reducible deformities) Osteoporosis with fracture or vertebral collapse Avascular necrosis, Osteomyelitis	6
Skin	Scarring chronic alopecia Extensive scarring of panniculum other than scalp and pulp space Skin ulceration	2
Gonadal	Premature gonadal failure	1
Endocrine	Diabetes requiring therapy, regardless of treatment	1
Malignancy	Exclude dysplasia	2

3. Glucocorticoids

Glucocorticoids (GCs) have played a central role in SLE therapy for more than 50 years. Their anti-inflammatory and immunosuppressive action is due to two types of mechanisms: non-genomic and genomic pathway. The latter is more responsible for the adverse effects of glucocorticoids, mainly due to their dose and duration of use (3). Evidence of damage in SLE caused by the prolonged use of GCs has been demonstrated by several observational studies, although there are not many studies describing the most effective mode, dose or regimen of administration (59). Glucocorticoids are used to treat severe and moderate symptomatology, ensuring relief of symptoms in a short time. Despite these benefits, the prolonged use of GCs also presents several adverse effects. For this reason, in recent years, efforts have been made to understand how best to manage GC therapy to avoid adverse effects while preventing the reactivation or worsening of the disease. This is also crucial in order to be able to define the disease in terms of remission and low disease activity. Thus, these definitions are also based on the dose of GCs administered to the patient. In accordance with the treat-to-target approach, the main aim is therefore to minimize GC dose as much as possible and, when possible, to discontinue it. To accomplish this goal, it is necessary to understand how withdrawal and tapering of GCs can affect SLE course. To date, several studies gave conflicting results (60,61).

3.1 Glucocorticoid pharmacology

GCs perform their anti-inflammatory and immunosuppressive function by acting on almost all innate and secondary immune cells. Indeed, they primarily reduce the expression of cytokines, adhesion molecules and MHC receptors. They also reduce the circulating number of macrophages and monocytes, while increasing the number of neutrophils. In addition to this, they act by increasing the secretion of inflammatory cytokines such as IL-2, IL-6 and TNF (3).

3.2 Glucocorticoid dose

In agreement with Buttgereit *et al.,* GCs dose may be described as the following (62):

- Low dose ≤7.5 mg prednisone equivalent a day
- Medium dose >7.5 mg, but ≤30 mg prednisone equivalent a day

- High dose >30 mg, but ≤100 mg prednisone equivalent a day
- Very high dose >100 mg prednisone equivalent a day
- Pulse therapy ≥250 mg prednisone equivalent a day for one or a few days.

3.3 Glucocorticoid side effects

It is widely accepted that GCs cause a wide range of negative effects at various organ levels. These effects are connected to dose and time of use and they start to manifest in early stages of disease (63). The major organs involved are:

◊ **Musculoskeletal system:**

- *Osteoporosis*: Bone damage caused by GCs is due to osteoblast inhibition generated by the upregulation of peroxisome proliferator-activated receptor gamma receptor 2 (PPARγ2). This leads to a decrease in bone mineral density (BMD) and increased risk of fracture. The most affected bones are those which present a high trabecular content. In addition with osteoblast inhibition, there is an increase of bone resorption. This is due to an upregulation of RANKL and downregulation of osteoprotegerin (OPG) (64). The damaging action of GCs already starts at the beginning of treatment and reaches the maximum level within 6 months after the beginning of the treatment (3).
- *Osteonecrosis:* GCs cause osteonecrosis changing angiogenetic and apoptotic processes. Several studies show that this damage is associated with high doses and long treatments with GCs (65).

◊ **Endocrine system:**

- *Hyperglycemia:* GCs-related hyperglycemia represents a very frequent finding in both diabetic and non-diabetic subjects. This manifestation occurs with very low doses of GC ranging from 1.5 to 2.5 mg/day of prednisone-equivalent. However, the cumulative dose and duration of treatment are factors that increase the risk of developing GCs-induced diabetes (64).
- *Cushing syndrome:* Cushingoid phenotype may become evident as early as the first months of treatment with low prednisone dose. This manifestation also depends on the dose and duration of therapy (66).
- *Fat redistribution*

- *Suppression of sex hormone secretion*

◊ **Cardiovascular system:** The role of GCs in causing cardiovascular damage is still unclear and current studies present conflicting results.

◊ **Dermatological involvement:** skin changes caused by GCs therapy are particularly related to iatrogenic Cushing's syndrome. These alterations include striae, acne, skin atrophy and purpura (67).

◊ **Ophthalmological involvement:**

- *Cataract:* cortical and subcapsular cataract may develop as a result of long-term use of systemic GC. In particular, it has been shown that taking an average dose of 6 mg/die for a mean of six years can cause cataracts (68).
- *Glaucoma:* glaucoma can cause blindness or at least a loss of visual field. Exposure to ≥7.5 mg/die for a year has been shown to increase the risk of glaucoma (3).

◊ **Psychological involvement:** Short-term GC use can induce euphoria, while prolonged high-dose GC treatment can induce depression and psychosis (3).

Table 10. *Relationship between damage and cumulative dose of GCs (3)*

Adverse effect	Time dependent	Dose dependent	Minimum dose of occurrence, mg
Osteoporosis	Yes (early)	Yes	5
Hyperglycaemia	Yes (early)	Yes	2.5
Cushing syndrome	Yes	Yes	5
Cardiovascular disease	Yes	Yes	7.5
Increased risk of infections	Yes	Yes	5-7.5
Dermatological	Yes	Yes	Undefined
Glaucoma	Yes	Yes	7.5
Cataracts	Yes (delayed)	Yes	6
Psychological and behavioral	Yes (early)	Yes	Undefined

3.4 Accrual damage due to GCs in SLE

Accrual organ damage in SLE is due to both SLE itself and therapy, mostly GCs. Several studies have shown this relationship between global damage in SLE and use of GCs. One of the first studies conducted on GC related damage accrual was carried out at the Toronto Lupus Clinic by Gladman *et al* (69). In this study, patients were followed for 15 years and the damage was assessed with the SLICC/ACR Damage Index (SDI) (70). The average SDI increased over time, from an average of 0.33 in the first 6 months to 1.99 to 15 years. Overall, 87.7% of patients received GC, at an average maximum dose of 37.7 mg/day. After the first year of follow-up, 42% of the damage was considered independent of GCs, 42% likely related to GCs (mainly cardiovascular and neuropsychiatric) and the remaining 16% certainly secondary to the GCs (ocular and musculoskeletal involvement). At the 15th follow-up year, 49% of the damage was definitely associated with the GCs. In this study, the most affected apparatus was found to be the musculoskeletal (69). This confirmed the hypothesis that the prolonged use of GCs increases global organ damage.

In addition to the results from Toronto Lupus Clinic, also research from Hopkins Lupus Cohorts presents relevant data (71). This study analysed the relationship between GCs and organ damage, evaluating four different modes of drug exposure: cumulative GCs dose, cumulative prednisone dose, high-dose prednisone exposure and intravenous (i.v.) pulse methylprednisolone doses. Increased risk of osteoporosis, avascular necrosis, diabetes mellitus, pulmonary fibrosis, cataracts, coronary artery disease and cognitive involvement was associated with the cumulative dose of GC. Damages associated with cumulative dose of prednisone were mainly osteoporosis and cardiovascular involvement. Exposure to high doses of prednisone has been correlated with an increased risk of stroke and osteonecrosis. The type of exposure least involved in organ damage was i.v. pulse administration of methylprednisolone (71).

Additionally to the above-mentioned studies, another study has been conducted on organ damage in patients with early SLE diagnosis. (72). This prospective study showed a significant accumulation of damage in the first year after diagnosis, followed by a steady accumulation of damage in subsequent years. Regarding GCs-related damage, however, the results reported a lower percentage of damage compared to previous researches. This discrepancy was probably due to a shorter

disease duration and a lower dose of prednisone administered to study subjects. Furthermore, these results showed that the cumulative dose of prednisone was independently associated with incident GC-related damage, which increased steadily over time despite the progressive reduction of the daily prednisone dose (72).

Mortality studies were conducted by Sheane *et al.* who compared mortality and morbidity rates between GC-treated and GC-naive patients. The results demonstrated both higher mortality and morbidity in GC-naive patients (73).

Zen *et al*. evaluated the accumulation of organ damage in subjects in remission (74), according to their definition of remission (46). This study showed that in patients in 1,2,3,4-year remission, the accumulation damage is similar in both GCs-free and GCs-treated patients. This emphasises that the duration of remission seems to have a greater impact than the type of remission. This could be explained by showing that patients in remission with GCs therapy take a low dose of GCs. However, when evaluating patients who have been in remission for more than 5 years, the results showed a higher percentage of damage in remitted patients treated with GCs. Therefore, corticosteroids, even at low doses, may contribute to the progression of long-term damage (≥5 years).

The GULP study (subanalysis of the multicentre Early Lupus inception cohort) enrolled patients in concurrent therapy with GCs and HCQs or immunosuppressant within 12 months of SLE classification (63). The aim was to assess success in tapering or discontinuation of GCs without relapsing of disease and assessing organ damage. Core set variables were evaluated at the baseline and every 6 months, including variation in prednisone (PDN) dosage. Of 127 patients selected, 73 managed to tape and maintain PDN <5 mg/day while 17 managed to suspend it. The recurrence rate between the group that maintained a dose of PDN >5 mg/day and the group that scaled the PDN to < 5mg/day was not significantly different. However, there was increased accrual organ damage in subjects that continued GCs therapy > 5mg/day. This study shows that maintaining a PDN dose lower than 5 mg/day could be the middle way to ensure remission without relapse and to ensure less organ damage (63).

3.5 GCs withdrawal risk in patients in long-term remission

As the above studies have shown, the use of GCs is effective in controlling symptoms although being associated with a significant accumulation of organ damage. In accordance with this, the EULAR 2019 guidelines recommend discontinuation of GCs whenever possible. As an alternative to the chronic use of GCs, intravenous pulses administration of GCs or therapy with immunosuppressants or biological therapy is proposed (1,75). However, before decreasing or withdrawing GCs therapy, it is necessary to understand how this will affect disease course and disease activity. Several studies have been conducted over the years evaluating the risk of GCs withdrawal in SLE patients. The results have been mixed.

3.5.1 Studies on GCs withdrawal in lupus nephritis

Although there are not many studies concerning the safety of GCs withdrawal in subjects with SLE, the first studies performed were those covering the suspension of GCs in lupus nephritis (76–78). The first study performed was that of Ponticelli *et al.* in 1988 (77). Data showed that GCs withdrawal was safe in patients with diffuse lupus nephritis but without any clinical disease activity for several months. In addition to this study, a pilot randomised controlled trial was conducted, in which 55 patients were examined over a period of 24 months. Of these, those who had a history of class III or IV LN, who had achieved at least partial remission and who had remained on prednisone treatment were selected. Thus, the eligible patients were divided into two groups: 8 patients were assigned to prednisone continuation and 7 to prednisone discontinuation. The results (table 7) showed that both the number of renal flares and the number of minor flares was lower in patients in whom GCs were discontinued. However, as the study covers a low number of patients, the results must be evaluated considering the limitations of the study (78).

***Table 11**. Primary and secondary outcomes across treatment groups (78)*

Outcome	Prednisone continuation	Prednisone withdrawal	Hazard ratio
Renal flare,s n (%)	3 (38)	1 (14)	2,68
All flares, n (%)	4 (50)	1 (14)	3,35
Minor flares, n (%)	3 (38)	0 (0)	Could not be computed

3.5.2 Studies supporting GCs withdrawal

An observational study (79) assessed the risk of flares after withdrawal of GCs, in SLE patients who had reached remission. The results showed a disease flare in the 20% of patients. Furthermore, this study showed that the percentage of flares tended to be lower in patients whose treatment with GCs and immunosuppressants lasted for several years before GCs withdrawal. In addition to this, the severity of the disease before remission also played an important role, as flares were higher in subjects with major organ involvement.

Another observational study conducted by Tani *et al*. evaluated whether it was possible to withdrawal GCs in patients in remission or with low disease activity. The study followed patients for 6 years and assessed the percentage of flares after discontinuation of GCs (80). Results showed that approximately 20% of subjects experienced a flare after discontinuation. According to this study, disease activity and duration of remission are key aspects that correlate with the rate of flares after withdrawal. Subjects in remission or with LLDA are those who rarely experience flares, while subjects with still active disease have a higher risk of flares. Another key point is that no difference in the percentage of flares was observed between patients in remission and those in LLDA so both situations can be considered as a starting point for tapering GCs (80).

A study confirming the safety of GC withdrawal is the one conducted by Nakai *et al.* This single-center retrospective analysis evaluated the difference in flare risk after GCs suspension in patients who had previous severe organ involvement and those who not had it (81). After 52 weeks from withdrawal of GCs, no significant differences were noted in the flare rate among patients with and without first severe organ involvement (16,7% vs 18.2%, p=1.0). The study also evaluated risk factors for flare after GCs withdrawal: complement reduction, high anti-dsDNA titles more than double upper the laboratory reference, anti- Smith/ anti-ribonucleoprotein positive and the use of any immunosuppressant on the day of GCs discontinuation. On the contrary, the previous involvement of the major organ does not appear to be a risk factor of flare after GCs suspension (81).

In addition to this data, data from the Toronto Lupus Clinic have demonstrated the safety of GCs withdrawal. Patients in clinical remission for two years were selected from the database (60). Those taking low doses of prednisone formed the

maintenance group, those who began GCs tapering formed the group in which GCs were withdrawn. The results (table 8) demonstrated that flares at 12 and 24 months and the accumulation of organ damage were significantly lower in the group in which the GCs were discontinued.

***Table 12**. Flare rates at 12 and 24 months and damage accrual at 24 months (60)*

	Maintenance Group (n = 102)	**Withdrawal Group (n = 102)**	***P* Value**
Flares at 12 months			
Flare (first definition)	30 (29.4)	18 (17.6)	0.023
Flare (second definition)	14 (13.7)	11 (10.8)	0.467
Flare (third definition)	12 (11.8)	7 (6.9)	0.197
Flares at 24 months			
Flare (first definition)	51 (50)	34 (33.3)	0.01
Flare (second definition)	28 (27.5)	15 (14.7)	0.024
Flare (third definition)	27 (26.5)	13 (12.7)	0.013
Damage accrual at 24 months			
Related to glucocorticosteroids	12 (11.8)	3 (2.9)	0.02
Not related to glucocorticosteroids	7 (6.9)	4 (3.9)	0.317
Increase in SDI	18 (17.6)	7 (6.9)	0.022

Furthermore, a prolonged clinical and serological inactivity and concomitant therapy with antimalarials and/or immunosuppressives represent positive predictive factors for a successful GCs withdrawal.

Fasano *et al.* performed an observational study on 154 patients in remission (82). 56 of them formed the GCs withdrawal group, while 98 formed the maintenance group. The percentage of flares in this case was similar in the two groups (10/98 (11.2%) vs 7/56 (12.5%), p=0.81). However, this study was interesting in that it identified which factors influence the risk of flares. These data, in alignment with those already seen, display an increase of flare in subjects with active serological disease, with previous lupus nephritis and with a minor duration of treatment with hydroxychloroquine.

Withdrawal of GCs is also a goal in subjects with long-standing disease. To support this, a cross-sectional study was performed by Sada *et al.* (83). The aim of the study was to show that even in patients with long-standing disease, discontinuation of GCs was associated with less damage accumulation. According to the univariate analysis of patients treated with GCs, patients without GCs had older age, less disease activity, less use of immunosuppressants and hydroxychloroquine, and higher C3 levels. Among patients with a disease duration ≥ 20 years, GC-free status was more frequent in patients without chronic damage (11% vs 4%, p=0.023). Lack of chronic damage was linked to GC-free status after adjusting for age, gender, and disease activity (OR 3.6, 95% CI 1.1 to 11.3) (25).

3.5.2 Studies supporting GCs continuation

As far as the previously mentioned studies are concerned, it is also important to mention that they present contrasts with others. Particularly, the CORTICOLUP trial reports opposite data (61). In this study, 124 patients, in remission for at least one year, have been selected. Sixty-three patients abruptly stopped prednisone, while the others continued the dose of 5 mg/day. The results showed that 7% of the subjects in the maintenance group experienced flares, while in the withdrawal group the percentage was higher, about 27%.
Probably the difference in results compared to those of the Toronto lupus clinic study (60) is given by the fact that in the CORTICOLUP trail, GCs were interrupted abruptly, without a gradual tapering.

A recent meta-analysis evaluated 17 studies on relapse and damage in SLE patients (84). Relapse incidence rates and time to relapse were calculated with their 95% confidence intervals (CI) after discontinuation of GC. The summary risk ratio (RR) and 95% CI of the risk of flare-up/organ damage were calculated using a fixed or random effects model. Of 17 studies, the meta-analysis included 7 studies for the risk of flare after GCs withdrawn and 7 for the assessment of accumulation damage. Results have shown slight increased risk of flare for the withdrawal group RR 1.38 (95% CI 1.01, 1.89), no increased risk of major flares RR 1.77 (95% CI 0.40, 7.83) and borderline risk reduction in damage accrual for the withdrawal group RR 0.64 (95% CI 0.38, 1.09).

3.6 How to withdraw GCs without increasing the risk of flare? Treatment strategies

A recent Japanese study (85) compared two groups of patients treated with different treatment approaches. Group A, consisting of subjects who visited Toho University Ohashi Medical Center between 2013 and 2017, and group B consisting of subjects followed by the center between 1999 and 2003. The first group, unlike the second group, was treated with GCs combined with immunosuppressants. Indeed, immunosuppressants were approved as therapy for SLE after the 2000s. Short-term and intermediate-term results were excellent with some exceptions such as for subjects with pulmonary hemorrhage. However, long-term results remain insufficient due to the accumulation damage caused by GCs. The results demonstrated both a lower flare rate and a lower dose-increase of GCs upon SLE flare in Group A compared to Group B (figure 11). This would demonstrate the efficacy of combining the immunosuppressant with low doses of GCs, up to discontinuation, compared to using high doses of GCs without IS combination (85).

Several studies are still being carried out to ensure the discontinuation of GCs. To date, it is known that the use of HCQ, Belimumab and Rituximab is an excellent alternative to reduce the risk of flare, to reduce accumulation damage and to allow complete withdrawal of GCs (75). Randomised controlled trials of rituximab have been unsuccessful, however subsequent observational studies have suggested that Rituximab in newly diagnosed SLE patients achieves significant clinical responses and minimises the use of GCs. The results for Belimumab were also satisfactory. Indeed, it appears to promote a more rapid reduction of GCs and less organ damage (86). A recent biologic agent approved by FDA and EMA is Anifrolumab (antibody against type I interferon receptor) (87). Its use in patients with SLE has demonstrated lower disease activity and the possibility of GCs reduction.

A new treatment strategy to reduce GCs use and accrual damage due to GCs in SLE patients, could be the early use of biological agents and combination therapy in the first lines of the treatment algorithm.

In light of this, our study aims to demonstrate the possibility of withdrawing GCs in SLE patients in clinical or complete remission

4. Aim of the thesis

The aims of the thesis are:

1. to identify the proportion of patients achieving remission during their disease course;
2. Among remitted patients, to identify the attainability of remission off GCs therapy
3. To estimate flare rate among remitted patients, comparing patients who withdraw GCs versus those who continue GCs;
4. To identify possible predictors of a successful tapering of GCs, i.e. the achievement of stable GCs-free remission;
5. Flare free remission survival in GCs withdrawal-patients and in GCs maintenance-patients
6. To evaluate the following outcomes in patients considered in the analysis:
    a. Chronic organ damage (SLICC);
    b. Cumulative GCs dose;
    c. SLE disease activity (SLEDAI-2k at last follow-up)

5. Materials and Methods

5.1 Patients and method

The lupus database, including 570 SLE patients recruited from the Padua Lupus Cohort between 1980 and 2023, was used for this study. These patients were followed prospectively with serial follow-up every 3 to 6 months. A complete physical examination was performed at each visit, and the outcomes of laboratory tests such as CBC (cell blood count), 24h proteinuria, C3 and C4 assay, anti-DNA title, and others were analysed. In case of disease flare, follow-up was performed earlier than the predetermined times. All patients included in the study satisfied the following inclusion criteria:

- revised ACR Classification Criteria for SLE (88) (table 2);
- diagnosis of SLE between 1980 and 2023;
- previous treatment with GCs;
- being currently in follow-up.

Clinical manifestations were defined using ACR definitions (88). Disease activity was assessed with the SLE Disease Activity Index-2000 (SLEDAI-2K) (SLEDAI table 8, § 2.1.1).

Remission was defined according to Doria-Zen definition: SLEDAI-2K=0, stable background therapy and prednisone (PDN) equivalent dose of ≤ 5 mg/day. Remission without GCs was defined as clinical SLEDA2K=0 without PDN and stable background therapy (47) (Table 4, 5, § 1.8.2) .

Active SLE was defined as clinical SLEDAI-2K > 0 and/or PDN > 7.5 mg/day, regardless of background therapy. GC withdrawal was defined as the complete discontinuation of oral glucocorticoids in patients achieving remission. The start date of GC tapering was identified as the first visit in which steroids were reduced from 5 mg/day to a lower dose. GC stop date was identified as the date in which PDN dose was reduced to zero.

The decision of withdrawing or not steroid therapy was based on expert clinical decision. As for clinical practice in our clinic, the withdrawal was progressively attempted, applying a personalized tapering regimen which took into consideration many clinical and anamnestic characteristics of each single patient, including the type and severity of disease activity, concomitant medications, past history of flares after therapy reduction or discontinuation. Thus, there was not a pre-specified tapering scheme to be applied in all patients. Accordingly, a wide range of duration

of GC discontinuation, from the beginning of GC reduction from PDN 5 mg/day to the complete discontinuation, would be expected. Usually, in our clinic tapering would range from at least 1 months, in patients with mild joint or skin flares, to several weeks or months in patients with life-threatening manifestations. Flare was defined as any increase in clinical SLEDAI-2K>0 or the need for changes in SLE medications, including steroid reintroduction or immunosuppressive therapy modification (89).

Flares occurring in remitted patients kept on 5 mg PDN were considered as flares in remitted patients on-steroids, whereas flares occurring during GC tapering below 5 mg of PDN equivalent and those occurring after discontinuation of GCs were considered as flares in patients off-steroids.

Organ damage was defined according to the Systemic Lupus International Collaborating Clinics (SLICC) Damage Index damage index (SDI) (SLICC table 9, § 2.2). In addition to this, steroid-related organ damage was assessed. According with Gladman *et al.* steroid-related organ damage was categorised into two groups: definitely/possibly related (musculoskeletal, ocular, cardiovascular, diabetes, peripheral vascular disease, neuropsychiatric), unrelated (skin, renal, gastrointestinal, pulmonary, malignancy, premature gonadal failure) (69). The SDI score to define major damage was set at an SDI ≥ 2 (68).

Gladman *et al.* claim that glucocorticoid-related damage is most evident after 15 years of therapy (69). According to this, we divided the cumulative dose of GCs into 5 categories. Considering an average of 5 mg/day, the cumulative dose classes were divided as follows:

- < 1.8 g: < 1 year of GCs therapy
- < 9 g: < 5 years of GCs therapy
- < 18 g: < 10 years of GCs therapy
- < 27 g: < 15 years of GCs therapy
- < 36 g: < 20 years of GCs therapy
- > 36 g: > 20 years of GCs therapy

Data collected included demographic data (age and sex), year of diagnosis, age of SLE onset, disease duration, disease manifestations over the patients disease course date GCs (glucocorticoids) were started, cumulative dose of GCs, current (at the time of remission achievement) and previous therapies (including antimalarials,

immunosuppressants, and biologics), duration of first and last remission, C3 and C4 serum levels and anti-DNA title at GCs withdrawal, time to achieve remission, level of remission (clinical or complete), duration of remission at GC discontinuation, the time between remission achievement and GCs withdrawal (lag time off-GC remission), type of flare (i.e. manifestation requiring a change in therapy, including GC re-introduction, including renal, musculoskeletal, skin, haematological, serosal, neuropsychiatric, and vasculitic flares), flare-free survival (defined as the lag-time between GC discontinuation and a subsequent flare), damage accrual at the end of follow-up. SLICC Damage Index (SDI), SLEDAI-2K, severity [According to Fanouriakis A. *et al.*(1)], and treatment at the last follow-up were also collected.

Patients treated with biologics/investigational drugs were not excluded from the study.

Data collected on clinical manifestations, antibody profile and treatment were collected at three different times: at the first remission/first available remission, at the last remission, and overall.

5.2 Statistical analysis

A retrospective analysis of the prospectively collected data was carried out. Continuous variables were analysed by t-test if normally distributed, Mann-Whitney test if not. Categorical variables were analysed with Chi-square test, with Fisher's correction for samples lower than 5 units.

All data analyses were performed at two different time points:

- Analysis at the last remission
- Analysis at the first/ first available remission

According to our aims, the main outcomes evaluated at univariate analysis were:

- Difference between remitted patients off-GCs compared to remitted patients on-GCs at last remission;
- Difference between remitted patients off-GCs who experienced a flare compared to remitted patients off-GCs who did not have a flare al last remission;
- Difference between remitted patients on/off-GCs who experienced a flare compared to remitted patients on/off-GCs who did not have a flare at last remission;

- Difference of free flare remission survival between remitted patients on-GCs and remitted patients off-GCs;
- Difference in SDI score between remitted patients on GCs and remitted patients off GCs.

In addition to these analyses, the same outcomes were evaluated with two sub-analyses considering two different periods as sensitive analyses:

- patients with SLE diagnosis after 2000
- patients with SLE diagnosis after 2010

Moreover, Kaplan-Meier curve was evaluated for comparing flare-free remission in patients on vs. off-GCs and a Cox regression model was used to explore predictors of flare-free remission.

The association between flare occurrence and GC discontinuation was also assessed in a multivariable logistic regression model with factor associated with flare at univariate analysis (age, disease duration, rash, arthritis/myositis, thrombocytopenia, leukopenia, vasculitis, anti-U1RNP and anti-DNA title, C3 levels) as covariates. In addition, the predictors of flare were also evaluated in remitted patients on and off steroid overall, using the same covariates.

Moreover, predictors of damage accrual among remitted patients were estimated in a multivariable logistic regression model with age, disease duration, HCQ regimen, aPL syndrome, types of organ involvement, use of cyclophosphamide, and GCs status during remission as covariates.

The collinearity of variables was tested before running the multivariate model using Spearman and Pearson correlations for categorical and continuous variables, respectively.

Analyses were performed by the SPSS software (v. 26.0, SPSS, Chicago, IL).

All patients gave informed consent before the inclusion in the study. The study was performed in accordance with the Declaration of Helsinki (90)

6. Results

6.1 Cohort description

Our patients cohort is composed of 570 patients with SLE diagnosis from 1980 to 2023. Description of the cohort is reported in the table below (Table 13):

Table 13. *Cohort description*

	Remission achieved ever *n (%)*	GCs withdrawal ever *n (%)*	GCs withdrawal at last remission *n (%)*	GCs withdrawal at first/first available remission *n (%)*	GCs withdrawal at first/first available remission (+ monophasic patients) *n (%)*	Active disease at last follow-up *n (%)*
Yes	499 (92.2)	401 (75.7)	360 (74.4)	100 (48.3)	323 (66.7)	113 (21)
No	42 (7.8)	129 (24.3)	124 (25.6)	107 (51.7)	161 (33.3)	424 (79)
Total	541(100)	530 (100)	484 (100)	207 (100)	484 (100)	537 (100)
Not available	29	40	86	363	86	33

The main features of these 570 patients were [n,(%)]: women 491 (86.1), men 79 (13.9), mean age in 2023 49.90 years (SD 14.17), mean disease duration in 2023 20.47 years (SD 10.33); as clinical manifestations is concerned, we observed rash in 297 (54.9), alopecia in 68 (12.6), arthritis/myositis in 393 (72.9), serositis in 108 (20.0), renal involvement in 294 (53.4), thrombocytopenia in 106 (19.7), leukopenia in 216 (40.1), neurological in 89 (16.5), vasculitis in 47 (8.7), positive anti-DNA title in 381 (70.7), positive anti-SSA/SSB in 237 (44.7), positive anti-U1RNP 147 (27.7), antiphospholipid syndrome (APL syndrome) in 55 (10.4) patients. Median (IQ range) SLICC at last follow-up was 1 (0-2); median (IQ range) steroid related organ damage was 1 (0-2).

Of the 570 considered patients, it was possible to assess the achievement of remission (ever) in 541 patients (94.9%). Notably, only 21% of patients had an active disease at last follow-up. 499/541 patients (92.2%) achieved remission at least once during the disease course.

As last remission evaluation is concerned, we could analyze data from 484 patients: 360 of them achieved remission off-GCs (74.4%), while the 124 remaining achieved remission on-GCs.,

The mean duration of the last remission in all patients who achieved remission, regardless of their GCs therapy was 87 months (SD 76). Among patients in

remission without GCs and among patients in remission with GCs, mean remission duration was 103 months (SD 79) and 42 months (SD 44), respectively.

In this timeframe, we observed a total of 85 flares, of whom 48 occurred in off-GCs remitted patients and 37 in on-GCs remitted patients.

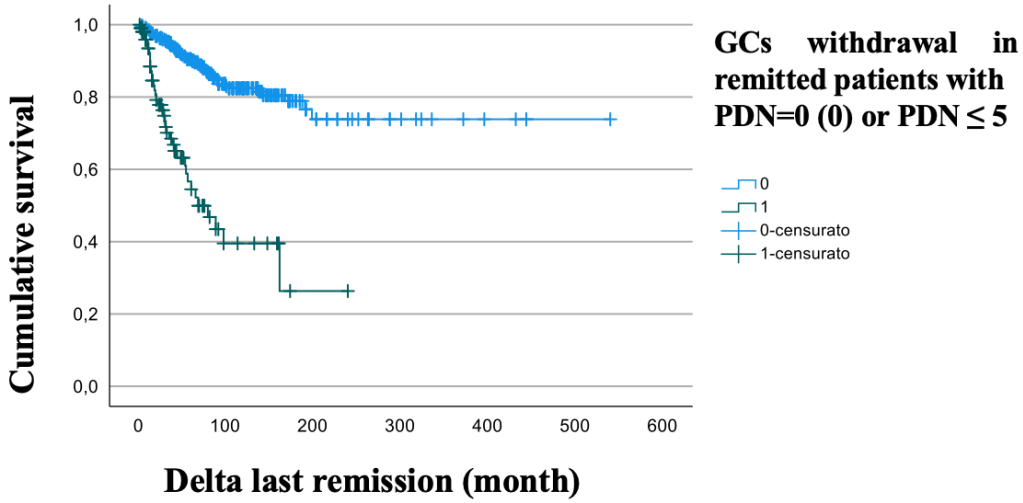
This means that GCs withdrawal was not associated with an increase in the risk of flare.

This corresponds to an annual flare rate of 1.65 flare/100 patients/year, and 8.5 flares/100 patients/year in remitted patients of and on steroids, respectively ($p<0.01$).

In a sensitive analysis where we considered only patients in prolonged stable remission (defined as lasting >2 years as defined in Zen M *et al.* (46) in order to avoid any bias related to the inclusion of patients with early, possibly instable remission, the same trend was observed, with an annual flare rate of 1.36 among off-GCs and 5.9 among on-GCs remitted patients.

6.2 Flare free remission survival

Our study evaluated flare-free survival in remitted patients on-GCs and in those off-GCs. The Kaplan-Meier curve revealed a statistically significant difference ($p=0.002$, confidence interval (CI) 95% 36.302-99.698). Patients in remission who do not take GCs have a higher flare-free survival than patients in remission who continue taking GCs.



By means of a Cox regression it was assessed whether the presence of certain variables could interfere with the survival outcome. The variables considered in the cox regression were patients age, C3/C4 levels and GCs therapy or not in remitted

patients. The results showed that free flare remission survival is influenced by the use of GCs and complement levels.

6.3 Characteristics of patients achieving off-GCs versus on-GCs steroids at last remission

The main differences between remitted patients who were or were not on GCs therapy at last remission are shown in the tables 14,15,16,17. Notably, age at last remission, leukopenia, and anti-SSA/SSB positivity were different between the two groups.

Interestingly, patients who achieved GC-free remission at last remission included a significant proportion of patients who had not been able to maintain remission on-steroid at the first remission (15.9%).

Table 14. *Patients demographic and clinical features*

Characteristics	Remitted patients Off GCs (PDN=0 mg/die) 360 patients	Remitted patients On GCs (PDN≤5 mg/die) 124 patients	P value
Age at last remission *mean ± SD*	41.16 ±13.94	46.54 ±14.89	**< 0.001**
Age in 2023 *mean ± SD*	50.51 ±13.14	50.35 ±15.47	Ns
Female gender *n (%)*	309 (85.8)	106 (85.5)	Ns
Male gender *n (%)*	51 (14.2)	18 (14.5)	Ns
Diagnosis year *mean ± SD*	2002 ±10	2003 ±11	
Rash *n (%)*	189 (54.2)	64 (55.7)	Ns
Alopecia *n (%)*	38 (10.9)	14 (12.2)	Ns
Arthritis/Myositis *n (%)*	257 (74.1)	80 (69.6)	Ns
Serositis *n (%)*	66 (19.0)	28 (24.1)	Ns
Proteinuria *n (%)*	196 (55.7)	58 (48.7)	Ns
Thrombocytopenia *n (%)*	61 (17.6)	26 (22.8)	Ns
Leukopenia *n (%)*	123 (35.3)	56 (48.7)	**0.011**
Neuropsychiatric *n (%)*	54 (15.6)	26 (22.4)	Ns
Vasculitis *n (%)*	34 (9.8)	12 (10.5)	Ns
Anti-DNA *n (%)*	255 (73.5)	77 (67.0)	Ns
Anti-SSA/SSB *n (%)*	140 (40.8)	59 (51.8)	**0.041**
Anti U1RNP *n (%)*	88 (25.7)	39 (33.9)	Ns
APL syndrome *n (%)*	39 (11.5)	11 (9.7)	Ns
Systemic symptoms *n (%)*	103 (28.6)	29 (23.3)	Ns
Renal involvement *n (%)*	166 (53.0)	45 (47.9)	Ns
Anti-DNA at last GCs stop attempt *mean ± SD*	43.29 ±112.54	43.37 ±98.53	Ns
C3 at last remission *mean ± SD*	0.87 ±0.13	0.85 ±0.15	Ns
C4 at last remission *mean ± SD*	0.27 ±0.46	0.22 ±0.09	Ns
Patients On-GCs at first remission *n (%)*	57 (15.9)	20 (16.1)	Ns
Disease duration in 2023 *mean ± SD*	21.36 ±9.93	20.14 ±10.61	Ns

Notably, the proportion of patients treated with azathioprine (AZA), Cyclophosphamide (CYC), Leflunomide (LEF) were different in the two groups of patients. In addition, mean number of GCs withdrawal attempts were significant in the two compared groups. Higher GCs cumulative dose and higher classes of GCs cumulative doses in 2023 were associated with the group of patients continuing GCs. Interestingly, 57.9% of remitted patients on-GCs had never attempted a GCs withdrawal.

***Table 15**. Treatment for SLE ever during the disease course*

Characteristics	Remitted patients Off GCs (PDN=0 mg/die) 360 patients	Remitted patients On GCs (PDN≤5 mg/die) 124 patients	P value
Immunosuppressant n *(%)*	238 (66.7)	87 (70.7)	Ns
Mycophenolate mofetil *n (%)*	158 (64.0)	59 (64.1)	Ns
Azathioprine *n (%)*	96 (38.9)	49 (52.7)	**0.022**
Cyclosporine A *n (%)*	44 (17.8)	20 (22.0)	Ns
Cyclophosphamide *n (%)*	75 (30.2)	18 (19.6)	**0.05**
Methotrexate *n (%)*	59 (23.9)	24 (26.1)	Ns
Leflunomide *n (%)*	2 (0.8)	6 (6.6)	**0.002**
Belimumab *n (%)*	37 (43.6)	24 (49.0)	Ns
Rituximab *n (%)*	16 (20.0)	9 (18.4)	Ns
Tacrolimus *n (%)*	7 (8.8)	6 (12.5)	Ns
Steroid bolus *n (%)*	135 (42.2)	45 (41.3)	Ns
N° immunosuppressants *n (%)*			**0.039**
0	52 (14.4)	11 (8.9)	
1	98 (27.2)	32 (25.8)	
2	71 (19.7)	22 (17.7)	
3	35 (9.7)	18 (14.5)	
4	15 (4.2)	5 (4.0)	
5	1 (0.3)	0 (0.0)	
GCs cumulative dose *n (%)*	22.01 ±16.81	32.16 ± 19.37	**< 0.001**
Withdrawal attempts *n (%)*			**< 0.001**
0	0 (0.0)	66 (57.9)	
1	237 (69.1)	33 (28.9)	
2	81 (23.6)	11 (9.6)	
3	21 (6.1)	3 (2.6)	
4	4 (1.2)	1 (0.9)	
Classes of GCs cumulative dose in 2023 *n (%)*			**< 0.001**
<1.8 g	17 (5.0)	1 (0.8)	
<9 g	72 (21.0)	12 (9.8)	
<18 g	74 (21.6)	17 (13.8)	
<27 g	54 (15.7)	23 (18.7)	
<36 g	43 (12.5)	12 (9.8)	
>36 g	83 (24.2)	58 (47.2)	

The use of Tacrolimus (TCR), methotrexate (MTX), belimumab (BEL), rituximab (RTX) and hydroxychloroquine (HCQ) as a maintenance therapy during

remission, was different in the two considered groups. In particular, HCQ use was associated with off-GCs remission.

Table 16. *Maintenance immunosuppressive treatment during last remission period*

Characteristics	Remitted patients Off GCs (PDN=0 mg/die) 360 patients	Remitted patients On GCs (PDN≤5 mg /die) 124 patients	P value
Mycophenolate mofetil *n (%)*	116 (34.3)	32 (26.9)	Ns
Azathioprine *n (%)*	28 (8)	13 (10.7)	Ns
Cyclosporine A *n (%)*	5 (1.4)	4 (3.3)	Ns
Tacrolimus *n (%)*	4 (1.1)	6 (4.9)	**0.013**
Methotrexate *n (%)*	10 (2.9)	11 (8.9)	**0.006**
Leflunomide *n (%)*	2 (0.6)	2 (1.6)	Ns
Belimumab *n (%)*	38 (10.9)	23 (18.5)	**0.029**
Rituximab *n (%)*	13 (3.7)	10 (8.1)	**0.055**
Hydroxychloroquine *n (%)*	281 (80.7)	85 (68.5)	**0.005**

The SDI was higher, active disease was more common, and mean SLEDAI-2K was higher in remitted patients on-GCs then in patients off-GCs, despite disease severity was similar.

Table 17*. Outcomes at last follow-up: SLICC, SLEDAI-2K, and disease severity*

Characteristics	Remitted patients Off GCs (PDN=0 mg/die) 360 patients	Remitted patients On GCs (PDN≤5 mg/die) 124 patients	P value
SLICC at last follow-up *median (IQR)*	1 (0;2)	1 (0;2)	**0.041**
0	162 (46.0)	50 (41.0)	
1	89 (25.3)	24 (19.7)	
2	47 (13.4)	22 (18.0)	
3	30 (8.5)	12 (9.8)	
4	12 (3.4)	6 (4.9)	
5	4 (1.1)	4 (3.3)	
6	6 (1.7)	1 (0.8)	
7	2 (0.6)	0 (0.0)	
8	0 (0.0)	3 (2.5)	
GCs related organ damage *median (IQR)*	1 (1;2)	1 (1;2)	Ns
0	6 (4.8)	4 (7.8)	
1	88 (69.8)	29 (56.9)	
2	30 (23.8)	15 (29.4)	
3	1 (0.8)	2 (3.9)	
4	1 (0.8)	1 (2.0)	
Active disease at last follow-up *n (%)*	43 (11.9)	28 (22.8)	**0.03**
Disease severity at last follow-up *n (%)*			Ns
Mild	388 (94.7)	110 (90.2)	
Moderate	10 (2.8)	8 (6.6)	
Severe	6 (1.7)	4 (3.3)	
SLEDAI-2K score at last follow-up *mean ± SD*	1.78 ± 2.31	2.53 ± 2.65	**0.006**

Our study also evaluated the overall severity (i.e. the severity of the disease in its entire course), according to Fanouriakis *et al.*, and the pattern of disease activity, according to Tselios et al. (1,91). The overall severity was mild in more remitted patients off-GCs (19%) than in remitted on-GCs (9%) (p=0.05).
Considering the disease activity pattern in remitted patient on-GCs, it was more frequently relapsing-remitted and chronic active then observed in remitted patients off-GCs, who were long quiescent in the almost half per cent of cases (p<0.001).

6.3.1 Analysis of on-GCs vs. off-GCs at first/first available remission

The differences between remitted patients Off-GCs and remitted patients On-GCs were also evaluated at first or first available remission. Data were overlapping with those of the last remission. However, in the first remission, neuropsychiatric involvement (p=0.002), C3 levels (p= 0.021) and immunosuppressive therapy (p=0-045) were also statistically significant.

6.4 Characteristics of Off-GCs remitted patients who had a flare and Off-GCs remitted patients who did not flare at last remission.

The main differences between remitted patients off-GCs who had a flare and remitted patients off-GCs who did not have a flare at last remission are reported in tables 18,19,20,21.

Notably, rash, arthritis/myositis, thrombocytopenia, leukopenia, vasculitis, positive anti-U1RNP and APL syndrome were associated with disease flare.

***Table 18**. Patients demographic and clinical features*

Characteristics	No Flare 290 patients	Flare 49 patients	P value
Age in 2023 *mean* ± *SD*	51.8 ±12.85	45.8 ±11.87	Ns
Female gender *n (%)*	254 (86.7)	39 (79.6)	Ns
Male gender *n (%)*	39 (13.3)	10 (20.4)	Ns
Diagnosis year *mean* ± *SD*	2001 ±10	2003 ±9	
Rash *n (%)*	147 (51.6)	34 (69.4)	**0.021**
Alopecia *n (%)*	28 (9.8)	9 (18.4)	Ns
Arthritis/Myositis *n (%)*	201 (71.0)	44 (89.8)	**0.006**
Serositis *n (%)*	50 (17.6)	14 (28.6)	Ns
Proteinuria *n (%)*	157 (54.7)	32 (65.3)	Ns
Thrombocytopenia *n (%)*	45 (15.9)	12 (28.6)	**0.032**
Leukopenia *n (%)*	94 (33.1)	25 (51.0)	**0.016**
Neuropsychiatric *n (%)*	47 (16.6)	6 (12.2)	Ns
Vasculitis *n (%)*	23 (8.1)	10 (20.4)	**0.008**
Anti-DNA *n (%)*	209 (73.9)	35 (71.4)	Ns
Anti-SSA/SSB *n (%)*	115 (40.9)	18 (38.3)	Ns
Anti U1RNP *n (%)*	66 (23.6)	18 (37.5)	**0.041**
APL syndrome *n (%)*	27 (9.6)	9 (20.0)	**0.040**
Systemic symptoms *n (%)*	87 (27.6)	15 (30.6)	Ns
Renal involvement *n (%)*	134 (52.3)	27 (64.3)	Ns
Anti-DNA at last GCs stop attempt *mean*	42.54	50.2	Ns
C3 at last remission *mean* ± *SD*	0.88 ±0.12	0.82 ±0.16	**Ns**
C4 at last remission *mean* ± *SD*	0.27 ±1.21	0.22 ±0.34	Ns
Patients On GCs at first remission *n (%)*	44 (15.17)	11 (22.44)	Ns
Patients Off GCs at first remission n (%)	249 (85-86)	38 (77.55)	Ns
Disease duration in 2023 *mean* ± *SD*	21.62 ±10.06	19.6 ±8.54	Ns

The proportion of patients who used high dose iv steroids and immunosuppressants were higher in the flare group.

Notably, failure to achieve GCs withdrawal at first remission was not associated with an increase in the risk of flare at last remission, nor the number of previous attempts. GCs cumulative dose and AZA also differed significantly.

***Table 19**. Treatment for SLE ever during the disease course*

Characteristics	No Flare 290 patients	Flare 49 patients	P value
Mycophenolate mofetil *n (%)*	123 (62.8)	31 (73.8)	Ns
Azathioprine *n (%)*	83 (42.3)	10 (23.8)	**0.025**
Cyclosporine A *n (%)*	37 (18.9)	7 (16.7)	Ns
Cyclophosphamide *n (%)*	62 (31.5)	10 (23.8)	Ns
Methotrexate *n (%)*	44 (22.4)	12 (28.6)	Ns
Leflunomide *n (%)*	2 (1.0)	0 (0.0)	Ns
Belimumab *n (%)*	25 (42.4)	11 (64.7)	Ns
Rituximab *n (%)*	9 (15.3)	6 (35.3)	Ns
Tacrolimus *n (%)*	5 (8.5)	1 (5.9)	Ns
Steroid bolus *n (%)*	105 (39.8)	26 (59.1)	**0.016**
Immunosuppressant *n (%)*	188 (64.6)	41 (83.7)	**0.008**
N° immunosuppressant *n (%)*			Ns
0 *n (%)*	47 (16.0)	2 (5.1)	
1 *n (%)*	72 (24.6)	20 (51.2)	
2 *n (%)*	59 (20.1)	10 (25.6)	
3 *n (%)*	28 (9.5)	6 (2.0)	
4 *n (%)*	14 (4.7)	1 (2.6)	
5 *n (%)*	1(0.3)	0 (0.0)	
GCs cumulative dose *n (%)*	21.41±16.57	26.37 ±18.27	Ns
Withdrawal attempts *n (%)*			Ns
1	201 (71.0)	31 (66.0)	
2	62 (21.9)	11 (23.4)	
3	17 (6.0)	4 (8.5)	
4	3 (1.1)	1 (2.1)	
Classes of GCs cumulative dose in 2023 *n (%)*			**0.020**
< 1.8 g	14 (5,0)	2 (4,1)	
< 9 g	66 (23.7)	3 (6.1)	
< 18 g	58 (20.8)	13 (26.5)	
< 27 g	40 (14.3)	10 (20.4)	
< 36 g	39 (14.0)	3 (6.1)	
> 36 g	62 (22.2)	18 (36.7)	

***Table 20.** Maintenance immunosuppressant treatment during remission*

Characteristics	No flare 290 patients	Flare 49 patients	P value
Mycophenolate mofetil *n (%)*	112 (32.3)	27 (33.8)	Ns
Azathioprine *n (%)*	32 (8.9)	7 (8.4)	Ns
Cyclosporine A *n (%)*	6 (1.7)	2 (2.4)	Ns
Tacrolimus *n (%)*	7 (1.9)		Ns
Methotrexate *n (%)*	16 (4.5)	3 (3.7)	Ns
Leflunomide *n (%)*	2 (0.6)	2 (2.4)	Ns
Belimumab *n (%)*	48 (13.4)	10 (12.0)	Ns
Rituximab *n (%)*	15 (4.2)	8 (9.6)	**0.045**
Hydroxychloroquine *n (%)*	273 (76.3)	70 (84.3)	Ns

SDI score, active disease and disease severity at last follow-up were different in the two group of patients.

Table 21. *Outcomes at last follow-up: SLICC, SLEDAI-2K, and disease severity*

Characteristics	No Flare 290 patients	Flare 49 patients	P value
SLICC at last follow-up *median (IQR)*	1 (0;2)	1 (0;2)	**<0.001**
0 *n (%)*	134 (47.0)	19 (38.8)	
1 *n (%)*	71 (24.9)	13 (26.5)	
2 *n (%)*	39 (13.7)	8 (16.3)	
3 *n (%)*	22 (7.7)	6 (12.2)	
4 *n (%)*	10 (3.5)	1 (2.0)	
5 *n (%)*	4 (1.4)	0 (0.0)	
6 *n (%)*	3 (1.1)	2 (4.1)	
7 *n (%)*	2 (2.0)	0 (0.0)	
GCs related organ damage *median (IQR)*	1 (1;2)	1 (1;1)	Ns
0 *n (%)*	2 (2.0)	2 (11.8)	
1 *n (%)*	74 (72.5)	11 (64.7)	
2 *n (%)*	24 (23.5)	4 (23.5)	
3 *n (%)*	1 (1.0)	0 (0.0)	
4 *n (%)*	1 (1.0)	0 (0.0)	
Active disease at last follow-up *n (%)*	3 (1.0)	39 (79.6)	**< 0.001**
Disease severity at last follow-up *n (%)*			**< 0.001**
Mild	286 (97.9)	35 (72.9)	
Moderate	1 (0.3)	9 (18.8)	
Severe	2 (0.7)	4 (8.3)	
SLEDAI-2K score at last follow-up *mean ± SD*	1.25 ±1.51	5.18 ±3.40	**<0.001**
Lag time between remission and GCs withdrawal *mean*	23.41 ±43.08	28.69 ±31.62	Ns

The overall severity and the pattern of disease activity were evaluated. The difference between overall severity in patients who had flare and those who did not have flare was significant: in fact, remitted patients who had a flare, in 67% of cases had a severe disease versus 55% in patients who did not have flare ($p<0.001$). Considering the pattern of disease activity, 73% of patients who had a flare was relapsing-remitting, compared with 37% of patients who did not have a flare ($p< 0.001$).

6.4.1 Sensitive analysis in remitted patients off-GCs with diagnosis after 2000

In a sensitive analysis we evaluated the same differences between remitted patients off-GCs who had a flare or did not have a flare, considering only patients with a

diagnosis after 2000. This made our sample more homogeneous and the significant differences are reported below: age in 2023 (p=.045), age at last remission (p=0.015) rash (p=0.02), arthritis/myositis (p=0.012), serositis (p=0.038), vasculitis (p=.040), C3 level at last remission (p=0.21), organ damage steroid-relates (p=0.041), therapy with Azathioprine (p=.046) and Rituximab (p=0.035), GCs withdrawal (p<0.001), GCs withdrawal attempts (p=0.037), active disease at last follow up (p<0.001), severity at last follow-up (p<0.001), disease course (p<0.001), GCs cumulative dose (p=0.004),

6.4.2 Predictive factors for flare in remitted patients who withdrew GCs

On the basis of the univariate analysis that identified factors associated with disease flares, we evaluated, by means of a multivariate logistic regression analysis, which of these could be considered as predictive factors of flare.

Two multivariate analyses were performed: the first considered serology (C3 values, anti-DNA title), disease duration, clinical manifestations and cumulative steroid dose. In this analysis high C3 levels were protective (OR 0.007, CI 95% 0.00-0.188, p=0.007) against flares. This allows us to state that low C3 levels are an indicator of flare risk.

The second multivariate analysis took into account the same variables excluding serology (C3 and anti-DNA): arthritis (OR 3.108 CI 95% 1.096-8.811 p=0.033), leukopenia (OR 2.146 CI 95% 1.030-4.472 p=0.041), vasculitis (OR 2.650 CI 95% 1.037-6.773 p=0.042) last remission duration (OR 0.987. CI 95% 0.980-0.995, p<0.001) were predictive factor of flare.

6.4.3 Predictive factors of reduced free flare remission survival in remitted patients off GCs

We evaluated, with a cox regression, which factors affect the duration of free flare remission survival in patients who withdrew GCs. The results showed that thrombocytopenia (HR 2.446, CI 95% 1.106-5.410, p=0.027), vasculitis (HR 3.033 CI 95%. 1.262-7.432, p=0.013), disease duration (HR 0.943 CI 95% 0.892-0.998, p=0.054) and anti-U1RNP positivity (HR 1.973, CI 95% 0.988-3.940, p=0.054) can be considered factors that reduce free flare survival remission.

6.4.4 Predictive factor for high organ damage in remitted patients who withdrew GCs

A multivariate analysis was performed to assess predictive factors of major organ damage (SDI≥2). Results identified the following as predictors of high organ damage: vasculitis (OR 4.090, CI 95% 1.585-10.552, p=0.004), antiphospholipid syndrome (APL) (OR 5.290, CI 95% 2.039-13.724, p<0.001), age in 2023 (OR 1.072, CI 95% 1.036-1.110, p<0.001) and cyclophosphamide use (as an indicator of disease severity) (OR 2.025, CI 95% 0.993-4.129, p=0.052) were predictive risk factors. Conversely, hydroxychloroquine proved to be a protective factor (OR 0.505, CI 95% 0.235-1.086, p=0.080).

6.4.5 Off versus on at first/first available remission

The differences between Off-GCs remitted patients who had or did not have a flare were also evaluated at first or first available remission. Data were overlapping with those of the last remission. However, in the first remission, systemic symptoms were more frequent among patients who had a disease flare (p=0.004).

6.5 Characteristics of Off/On-GCs remitted patients who had a flare and Off/On-GCs remitted patients who did not have a flare at last remission

The main differences between remitted patients off-GCs or on-GCs who had a flare and remitted patients off-GCs or on-GCs who did not have a flare, at last remission are reported in the tables below (tables 22,23,24,25). Data were available for 363 patients for group of patients without flare, and for 88 patients for group of remitted patients who had a flare. In our cohort the main flares observed in the group of subjects discontinuing GCs were renal involvement (38.8%), skin manifestations (36%), musculoskeletal manifestations (34%), haematological alterations (25%). Notably, alopecia, arthritis/myositis, thrombocytopenia, leukopenia, positive Anti-U1RNP and level of C3 at last remission were associated with a flare risk.

Table 22. *Patients demographic and clinical features*

Characteristics	No Flare in remitted patients (On/Off GCs) 363 patients	Flare in remitted patients (On/Off GCs) 88 patients	P value
Age in 2023 *mean* ± *SD*	51.3 ±13.43	45.84 ±12.42	**0.011**
Female gender *n (%)*	321 (86.0)	73 (83.0)	Ns
Male gender *n (%)*	51 (14.0)	15 (17.0)	Ns
Diagnosis year *mean* ± *SD*	2002 ±10	2003 ±9	
Rash *n (%)*	183 (52.0)	53 (61.6)	Ns
Alopecia *n (%)*	35 (9.9)	16 (18.6)	**0.025**
Arthritis/Myositis *n (%)*	244 (80.6)	73 (84.9)	**0.005**
Serositis *n (%)*	68 (19.4)	22(25.6)	Ns
Proteinuria *n (%)*	194 (59.4)	47 (54.0)	Ns
Thrombocytopenia *n (%)*	57 (16.3)	25 (29.4)	**0.006**
Leukopenia *n (%)*	124 (35.3)	46 (53.5)	**0.002**
Neuropsychiatric *n (%)*	62 (17.7)	14 (16.3)	Ns
Vasculitis *n (%)*	30 (8.5)	13 (15.3)	Ns
Anti-DNA *n (%)*	225 (72.9)	60 (69.8)	Ns
Anti-SSA/SSB *n (%)*	150 (43.2)	37 (44.6)	Ns
Anti U1RNP *n (%)*	84 (24.2)	33 (39.3)	**0.005**
APL syndrome *n (%)*	34 (9.8)	12 (14.8)	Ns
Systemic symptoms *n (%)*	107 (28.7)	21 (23.9)	Ns
Renal involvement *n (%)*	163 (52.8)	38 (50.7)	Ns
C3 at last remission *mean* ± *SD*	0.88 ± 0.12	0.81 ±8.63	**0.019**
C4 at last remission *mean* ± *SD*	0.27 ±1.11	0.22 ±0.41	Ns
Patients On GCs at first remission *n (%)*	102 (28.1)	44 (50.0)	Ns
Patients Off GCs at first remission n (%)	261 (71.9)	42 (47.8)	Ns
Disease duration in 2023 *mean* ± *SD*	21.3 ±10.22	20.07 ±9.20	Ns

Notably, the rate of patients who withdrew GCs was higher in the group of remitted patients who did not have a flare; therefore GCs do not play a protective role. Patients in flare group had a higher GCs cumulative dose in 2023.

***Table 23**. Treatment for SLE ever during the disease course*

Characteristics	No Flare in remitted patients (On/Off GCs) 363 patients	Flare in remitted patients (On/Off GCs) 88 patients	P value
Mycophenolate mofetil *n (%)*	161 (64.4)	46 (66.7)	Ns
Azathioprine *n (%)*	113 (45.0)	25 (36.2)	Ns
Cyclosporine A *n (%)*	49 (19.6)	14 (20.3)	Ns
Cyclophosphamide *n (%)*	72 (28.7)	12 (17.4)	**0.05**
Methotrexate *n (%)*	58 (23.1)	50 (27.5)	Ns
Leflunomide *n (%)*	4 (1.6)	4 (5.8)	**0.049**
Belimumab *n (%)*	42 (45.2)	17 (58.6)	Ns
Rituximab *n (%)*	15 (16.1)	9 (31.0)	Ns
Tacrolimus *n (%)*	10 (10.8)	2 (7.1)	Ns
Steroid bolus *n (%)*	133 (40.3)	37 (48.7)	Ns
Immunosuppressant *n (%)*	254 (70.4)	69 (79.3)	Ns
N° immunosuppressant *n (%)*			Ns
0	54 (14.88)	5 (5.7)	
1	91 (25.1)	32 (36.4)	
2	71 (19.5)	16 (18.2)	
3	38 (10.5)	13 (14.5)	
4	18 (4.95)	1 (1,1)	
5	1 (0.3)	1 (1.1)	
GCs cumulative dose *mean ± SD*	23.93 ±17.92	28.16 ±17.92	
GCs withdrawal *n (%)*	311 (86.1)	59 (68.6)	**< 0.001**
Withdrawal attempts *n (%)*			**0.044**
0	38 (10,9)	16 (20.0)	
1	223 (63,9)	39 (48.8)	
2	68 (19,5)	16 (20.0)	
3	17 (4,9)	8 (10.0)	
4	3 (0,9)	1 (1.3)	
Classes of GCs cumulative dose in 2023 *n (%)*			**0.004**
<1.8 g	15 (4.3)	2 (2.3)	
<9 g	72 (20.7)	6 (6.8)	
<18 g	68 (19.5)	10 (22.7)	
<27 g	52 (14.9)	18 (20.5)	
<36 g	47 (13.5)	6 (6.8)	
>36 g	94 (27.0)	36 (40.9)	

***Table 24.** Maintenance immunosuppressant treatment during remission*

Characteristics	No Flare in remitted patients (On/Off GCs) 363 patients	Flare in remitted patients (On/Off GCs) 88 patients	P value
Mycophenolate mofetil *n (%)*	112 (32.3)	27 (33.8)	Ns
Azathioprine *n (%)*	32 (8.9)	7 (8.4)	Ns
Cyclosporine A *n (%)*	6 (1.7)	2 (2.4)	Ns
Tacrolimus *n (%)*	7 (1.9)	2 (2.4)	Ns
Methotrexate *n (%)*	16 (4.5)	3 (3.7)	Ns
Leflunomide *n (%)*	2 (0.6)	2 (2.4)	Ns
Belimumab *n (%)*	48 (13.4)	10 (12.0)	Ns
Rituximab *n (%)*	15 (4.2)	8 (9.6)	**0.045**
Hydroxychloroquine *n (%)*	273 (76.3)	70 (84.3)	Ns

Disease severity and proportion of patients with an active disease at last follow up were higher in remitted patients who had a flare achieving remission.

Table 25*. Outcomes at last follow-up: SLICC, SLEDAI-2K, and disease severity*

Disease severity and number of patients with an active disease at last follow up were higher in remitted patients who had a flare achieving remission.

Characteristics	No Flare in remitted patients (On/Off GCs) 363 patients	Flare in remitted patients (On/Off GCs) 88 patients	P value
SLICC at last follow-up *median (IQR)*	1 (0;2)	1 (0;2)	Ns
0 *n (%)*	160 (45.3)	40 (45.5)	
1 *n (%)*	83 (23.5)	21 (23.9)	
2 *n (%)*	54 (15.3)	12 (13.6)	
3 *n (%)*	28 (7.9)	9 (10.2)	
4 *n (%)*	13 (3.7)	3 (3.4)	
5 *n (%)*	7 (2.0)	1 (1.1)	
6 *n (%)*	4 (1.1)	2 (2.3)	
7 *n (%)*	2 (0.6)	0 (0.0)	
8 *n (%)*	2 (0.6)	0 (0.0)	
GCs related organ damage *mean* ± *SD*	1 (1;2)	1 (1;1)	Ns
0	5 (3.8)	3 (10.0)	
1	87 (66.4)	22 (73.3)	
2	35 (26.7)	5 (16.7)	
3	2 (1.5)	0 (0.0)	
4	2 (1.5)	0 (0.0)	
Active disease at last follow-up *n (%)*	3 (0.8)	67 (77.9)	**< 0.001**
Disease severity at last follow-up *n (%)*			**< 0.001**
Mild	354 (98.1)	62 (72,1)	
Moderate	2 (0.6)	16 (18.6)	
Severe	2 (0.6)	8 (9.3)	
SLEDAI-2K score at last follow-up *mean* ± *SD*	1.34 ±1.56	4.83 ±3.33	**<0.05**
Lag time between remission and GCs withdrawal *mean*	23.22 ±47.94	28.66 ±31.24	Ns

The analysis evaluated also the overall severity and the disease activity pattern. The overall severity in this case was not statistically significant. The difference between disease course in remitted patients off/on GCs who had flare and who did not have a flare was statistically significant: 75% of patients who had a flare was relapsing-remitting, compared with 41% of patients who did not have a flare ($p< 0.001$).

The differences between Off/On-GCs remitted patients who had or not did not have a flare were also evaluated at first or first available remission. Data were overlapping with those of the last remission. However, in the first remission, rash, C3 and C4 levels were statistically significant.

6.5.1 Predictive factor for high organ damage in remitted patients who withdrew GCs or did not withdraw it

Table 26. *Predictive factor for high organ damage*

	Range OR (95% CI) for SDI≥2	**p-value**
Age in 2023, years	1.060 (1.030-1.091)	<0.001
Immunosuppressant, yes/no	0.621 (0.079-4.878)	Ns
Vasculitis, yes/no	4.155 (1.591-10.850)	0.004
Neuropsychiatric, yes/no	1.338 (0.645-2.985)	Ns
Antiphospholipid syndrome (APL), yes/no	4.793 (1.844-12.182)	0.001
GCs withdrawal in remitted patients on/off-GCs, yes/no	1.109 (0.536-2.293)	Ns
Disease duration in 2023, years	1.003 (0.963-1.044)	Ns
HCQ therapy at last remission, yes/no	0.387 (0.197-0.759)	0.006
Cyclophosphamide therapy, yes/no	1.583 (0.805-3.111)	Ns

7. Discussion

The main goal in the management of SLE is to achieve remission or LDA (low disease activity), avoiding organ accrual damage caused by the disease itself and by treatment. It is necessary to find the right balance between the benefits of therapy and the potential damage it may cause. Particularly, GCs adverse effects are well known, which is why the guidelines suggest tapering or withdrawing GCs (1). To date, studies about safety of withdrawal of GCs in remitted patients are scanty. Scientific literature is divided into studies supporting or opposing GCs withdrawal (60,61,77–82). In some of them, GCs were discontinued by slow tapering (60), while in others GCs were stopped abruptly without tapering (61).

In our study, we demonstrated that patients discontinuing GCs after remission achievement did not display an increased risk of flare compared to patients who were maintained on 5 mg PDN-equivalent. This is in line with the results of other observational studies (59, 77-82) where GCs were discontinued progressively, during several weeks. In addition, we evaluated mean remission duration, showing that patients on steroid had a shorter mean remission duration than remitted patients off-GCs. This suggest that withdrawal GCs is not a risk factor that exposes patients to an earlier flare occurrence.

The finding that patients kept on-steroids tended to flare more than patients off-steroids should be considered with caution: in fact, in our study the discontinuation of steroids was based on clinical decision and not according to a standardized protocol, which means that the clinicians could decide whether or not to stop steroids. This could have generated a “selection bias”, where more difficult-to-treat patients, i.e. those achieving remission after a period of more severe disease or patients with previous failure in drug tapering, would less likely undertake steroid tapering below 5 mg. To explore this bias, we analyzed the characteristics of patients who did or did not discontinued GCs, i.e. the difference between patients in whom the clinicians were prone to stop steroids and patients in whom the experts decided not to withdraw these drugs.

What distinguishes remitted patients who stopped GCs from those who did not stop GCs?

One of the main endpoints of our study was to understand what differentiates patients in remission who succeed in withdrawing GCs from those who fail it. Results showed that patients who failed to withdraw GCs had a relapsing-remitting

disease course. Furthermore, these patients were shown to have had cutaneous involvement, serositis, or haematological involvement.

These findings are in line with published data, since patients with a relapsing – remitting pattern usually alternates phases of inactive disease to phases with flares, which prevent complete therapy withdrawal. Moreover, skin, serosal, and haematological involvements often display a relapsing-remitting course or are manifestations which can rapidly worsen after steroid discontinuation. This explains why the clinician, knowing the patient clinical history, did not attempt GCs suspension in these patients, because they might reactivate more easily.

Another difference between remitted patients who succeeded in discontinuing GCs and those who failed it, is their different treatment. Cumulative dose of GCs was higher in patients who failed in withdrawing GCs. Indeed, GCs suspension contributes to reducing GCs burden as shown in our results. Patients who succeeded in discontinuing GCs belong to lower classes of cumulative dose than those who failed to withdraw GCs (about 50% had a cumulative GCs dose > 36g). Notably, the proportion of patients who discontinued GCs at least once during their disease course was higher in those who achieved remission without GCs. According to this, 60% of remitted patients on GCs never attempted to withdraw GCs. This reinforces the idea that these patients had particular risk factors, for whom the clinician preferred to maintain GCs. In line with this consideration, the rate of patients using immunosuppressants as maintenance therapy was higher in remitted patients on GCs. This could be related to more severe prior disease in those who maintained GCs.

On the other hand, the percentage of subjects taking hydroxychloroquine (HCQ) as maintenance therapy was higher in remitted patients off-GCs. Indeed, HCQ is used as the main maintenance therapy in SLE, avoiding possible flares (92), and clinicians would be more prone to stop steroids if a patient is on antimalarials, considering the well-known protective effects that this drug has on disease flares (93)

Interestingly, patients who achieved GC-free remission at last remission included a significant proportion of patients (15.9%) who had not been able to maintain remission on-steroid at the time of their first remission. These data showed that, even if an off-GCs remission was not achieved at the first remission, this does not prevent a patient to achieve GC-free remission later on during the disease course.

Thus, a first episode of flare during GC tapering should not discourage further attempts. This is also supported by the fact that organ damage was not higher in patients who experienced a flare during GCs tapering and discontinuation. Indeed, usually these flares were mild, and occurred in patients regularly followed, meaning that therapy was rapidly restarted as soon as the flared was detected. In this context, is important to explain to patients during medical consultations that they should continue the follow-up despite being in remission off-steroid, underlying the importance of adherence to the remaining therapy (HCQ, immunosuppressants) and the importance of regular laboratory testing, in order to identify early signs of a disease relapse.

In our study, we evaluated some key outcome measures in SLE, including the accrual of organ damage, measured by the SDI. Results showed that in remitted patients who withdrew GCs, SDI was lower than in subjects who continued taking GCs despite being in remission. A high level of damage, defined as SDI ≥2, was observed in 15% of remitted patients off GCs and in 40% of remitted patients on GCs. This is in agreement with previous studies showing that even low dose of steroids can contribute to organ damage (69).

The proportion of patients with active disease at the last follow-up was higher in the group of patients who were maintained on GCs during the last remission. This reinforces our main finding that taking low dose GCs does not protect patients from possible subsequent disease reactivation.

What distinguishes remitted patients after GCs withdrawal who had a flare from those who did not have a flare? Flare risk factors

Risk factors for flare were previously identified in studies carried out in patients who withdrew GCs (60,61,77–82). Major organ involvement, LDA (low disease activity) or failure in achieving remission, high anti-DNA title, low C3/C4 and prior short therapy with GCs or immunosuppressants (IS) were the main risk factors observed in these studies.

In our study the main differences between remitted patients off-GCs who had a flare and remitted patients off-GCs who did not have a flare, included clinical features such as cutaneous manifestations, hematological and musculoskeletal involvement and serositis. Interestingly, these are manifestations which typically have a relapsing-remitting course and are sensitive to small changes in steroid dose. It is

worthy to note that, on the other hand, more severe organ involvement such as lupus nephritis and neuropsychiatric SLE were not associated with an increased risk of flare after GC discontinuation. This is a relevant finding of this study, as it demonstrated that GC discontinuation is safe even in patients with severe organ involvement who were able to achieve a stable remission. Thus, our results do not support the use of 5 mg of PDN-equivalent in the long-term maintenance of SLE remission.

On the other hand, another difference between remitted patients off-GCs who had a flare or who did not have a flare is their different treatment. The proportion of patients previously treated with high dose iv steroid and the number of immunosuppressants used were higher in the group of subjects who had a disease reactivation after GC discontinuation. This difference could mean that patients who flared had a refractory disease, which had required more aggressive treatment. Patients with less aggressive treatment, probably, had less disease activity and therefore also a lower risk of flare when they stopped GCs. This is not in disagree with our previous finding regarding the lack of association with severe organ involvement but reinforce the concept that a personalized approach should be applied when facing patients with SLE, based not only on the type of disease manifestation, but also to previous response to therapy.

In our study we also evaluated the off-GCs remission lag time: the time between remission achievement and GCs withdrawal. Results showed that this lag time did not differ significantly between the two groups of patients. This is in contrast with data regarding the discontinuation of immunosuppressants in SLE, showing a strong impact of remission duration upon the risk of flare after immunosuppressant discontinuation (76,93) and also with recent data (81) showing a strong association between the duration of GC tapering and flare occurrence. However, this can be explained by two reasons: in our cohort some patients have a very long disease duration, and before 2000 GCs were not easily discontinued, due to a lower availability of effective drugs able to prevent disease flares. In addition, the minimum duration of GC tapering before discontinuation in our cohort is very rarely shorter than 3 months, which is the cut-off identified by Nakai *et al*. as protective against disease flare after GC discontinuation (81).

As outcome measure is concerned, disease activity at the last follow-up was significantly different in patients who had flare versus those who did not have flare.

Remitted patients off-GCs that experienced a flare had a mild disease activity in 72% of cases versus 99.7% of patients off-GCs who did not have a flare. Moreover, the rate of active disease at the last follow-up was higher in patients who had a flare after GCs withdrawal. In addition, on the basis of the univariate analysis that identified factors associated with disease reactivation (in remitted patients off-GCs), it was evaluated, by means of a multivariate analysis, which of these could be considered as predictive factors of flare. Two multivariate analyses were performed, the first considering clinical manifestations, disease duration, patients age and serological data (C3 levels and anti-DNA title), the second one considering the same variables excluding serological data. In the first analysis, the main flare predictive factor identified was low C3 levels. This is in accordance with other literature data, for example with Nakai *et al.* and Fasano *et al.* (81,82), where serologically active patients (i.e., those in clinical remission) were at higher risk of flare then patients in complete remission (i.e. those with clinical and serological remission). In the second analysis, the main flare predictive factors identified were vasculitis, arthritis, and leukopenia, whereas disease duration was protective against flares. As previously stated, this reinforce the idea that relapsing-remitting manifestations, such as arthritis, haematological involvement, and cutaneous vasculitis, are major risk factors for subsequent relapses. A longer disease duration has been already associated with a low risk of flare in previous study: burden of disease activity is generally higher among young patients and in the first years after diagnosis (59,93).

What distinguishes remitted patients on/off-GCs who had a flare from those who did not have?

Our study also analysed the differences between remitted patients who had a flare and remitted patients who did not have a flare irrespective of being on vs off GCs. As observed in the analysis of flare among off-GCs remitted patients, the main significant differences involved clinical features, use of high dose steroid and IS, and disease severity.

Arthritis/myositis, hematological involvement, alopecia, anti-U1RNP and low C3 were observed in a greater percentage of patients that had a flare after remission achievement. Patients who did not have a flare were able to be off-GCs at last

follow-up in a higher percentage of cases. This confirms that suspending GCs is not a risk factor for disease reactivation.

Regarding disease severity, it was confirmed that patients who relapsed after remission were those who had more severe disease before achieving remission.

Accrual organ damage and steroid-related damage

As far as accrual organ damage is concerned, our findings showed that SDI was lower in patients who withdrew GCs, whereas those who did not withdraw GCs have more damage.

As far as steroid-related damage is concerned, this was not significantly different in our analyses. However, this could be caused by the wide heterogeneity of our cohort in terms of age, year of diagnosis and different therapies during the follow-up. Moreover, median steroid-related damage is quite low in our cohort, reducing the sensitivity of our analysis.

In order to assess the damage in a more homogeneous cohort, a sub-analysis was performed which only considered patients diagnosed from 2010 to 2023. In this case, there was no significant difference between patients in remission taking or not taking GCs and between patients experiencing a flare or not in terms of organ damage. However, a significant difference in the cumulative dose of GCs was observed. These results could be explained considering that newly diagnosed patients have low average cumulative dose of GCs, probably insufficient to cause organ damage at least in the short term.

We performed a multivariate analysis aimed at identifying independent predictive factors for high organ damage (SDI ≥ 2) in remitted patients off GCs. Our results identified vasculitis, APL syndrome, age and cumulative dose as predictive factors. In this multivariate model, GC discontinuation was not a protective factor against damage accrual: a possible explanation resides in the possibility that the association of damage with GC cumulative dose, which is much higher in patients on-GCs, is stronger than the association with current/recent GC dose. Results also showed the protective role of HCQ as maintenance therapy (94,95).

In addition, these results were also confirmed in the multivariate analysis performed on remitted patients on/off GCs irrespective of being on vs. off-GCs.

These results are in agreement with Petri *et al.* who considered GCs cumulative dose, APL syndrome, age, low C3 levels and high anti-DNA title as risk factors (96).

GCs withdrawal is safe in remitted patients

The remission status should be defined in order to identify the patients who can benefit from GCs withdrawal. In our study, we used the definition of remission proposed by Zen *et al.* (74).

On the basis of our study results, it can be stated that GCs withdrawal in remitted patients is safe. Approximately 75% in our cohort achieved clinical or serological remission. This finding is important when correlated with the percentage of patients taking GCs in our cohort (25.6%). There are very few patients taking GCs, which allows to state that GCs withdrawal does not increase flares risk and grants disease inactivity. These data can be compared with the results performed on the Hopkins Lupus Cohort (97). Babaoglu *et al.* evaluated the rate of patients in LLDA in the Hopkins Lupus Cohort. Of all patients in the cohort, 43.2% were in LLDA and 100% of patients were taking doses of GCs < 10 mg/day. Therefore, the percentage of patients on GCs is lower in our cohort than in the Hopkins lupus cohort study. This difference could be due to the different ethnicity. In Babaoglu study, African-Americans had a 36% chance of achieving LLDAS, compared to Caucasians where the chance of achieving LLDAS was 52%. Another reason for this difference could be the healthcare system organisation. In America, the healthcare system is not free of charge as in Italy, therefore patients may not have constant follow-up due to their economic situation; moreover, difference in availability of biological drugs for SLE in US could impact on the possibility of stopping glucocorticoids.

Nossent *et al.* demonstrated that the use of lower doses of GCs can be considered only after achieving a state of stable remission. Therefore, GCs withdrawal can be considered in patients who achieve early remission and who have been in remission for several years (98). According to this, Zen *et al.* conducted a study on SLE patient management, demonstrating the possibility of safe GCs withdrawal in remitted patients, preventing accrual damage (99). Nalotto *et al*. confirmed that in GCs-free remitted patients the flare occurrence is not frequent, being observed in 22% of patients over a mean follow-up of more than 8 years, identifying the most frequent types of flare as renal, articular and cutaneous (100).

In our study, GCs withdrawal safety was confirmed by the assessment of flare free remission survival, which is not shorter in patients who stopped GCs vs. in those how continued 5 mg of PDN. Predictors of decreased flare-free remission survival were thrombocytopenia, vasculitis, shorter disease duration at GCs withdrawal and anti-U1RNP positivity. Notably, anti-U1RNP antibodies are often positive in patients with inflammatory manifestations such as refractory arthritis and subacute skin rash, which respond well to steroid but are less sensitive to other maintenance therapies such as HCQ or MTX.

Flares after GCs withdrawal

Our study showed that patients who withdrew GCs have a low risk of experiencing a flare. In our cohort the main flares observed in the group of subjects discontinuing GCs were renal involvement, skin manifestations, musculoskeletal manifestations, haematological alterations. In the group of patients who continued GCs the types of flare were overlapping with no statistically significant difference.

Our data agree with scientific literature. In Galbraith *et al*. pilot study, in the patients who maintained therapy, renal flare was the most common while severe non-renal flares were rare. In the withdrawal group no patient had a flare.

Goswami *et al.* showed that flares occurred mainly after the first and second year after GCs withdrawal. In order of frequency, the most common flares were renal, musculoskeletal, haematological, mucocutaneous but neuropsychiatric were rare. Major flares occurred in 74.2% of patients, and minor in 25.8% (79).

In Tselios *et al.* study, flares were evaluated at 12 and 24 months. During the 24-month follow-up period, in the GCs withdrawal group mild flares with cutaneous manifestations, hematologic, mild arthritis were observed. In maintenance group and in withdrawal group, the difference in rate of flares was not significant(60).

In Fasano *et al.* study, flares were minor in GCs withdrawal-patients compared with maintenance group. The main flares were: cutaneous manifestations, lupus nephritis and arthritis (82). Hanaoka *et al.* showed that in patients in whom all treatments were withdrawn, the rate of flares was higher than in patients who retained one treatment, even if there was no major organ involvement (101). In our study, the majority of patients who discontinued GC were kept on HCQ, and this could explain the different results we found in terms of flare occurrence.

In a study conducted by Nalotto *et al.*, patients who discontinued GCs experienced various kinds of flares, namely renal, articular, cutaneous, haematological, serositic and neurological (100), in keeping with our results

Table 27. *Summary of scientific literature data*

Author (ref.) Study design	Risk of flare in patients who stopped GCs (%)	Risk of flare in patients who continued GCs (%)	Flare risk factors in GCs withdrawal	Is GCs withdrawal safe?
Ponticelli *et al.* (77)	-	-	-active disease -no diffuse lupus nephritis	Yes
Galbraith *et al.* (78) *randomized controlled trial*	14%	50%	-	Yes
Goswami *et al.* (79) *retrospective longitudinal observational study*	20.9%	-	-Major organs involvement - Previous short-term GCs or IS therapy	Yes
Tani *et al.* (80) *retrospective analysis*	23%	69,8%	LDA or remission not achieved	Yes
Nakai et al. (81) *retrospective observational study*	5%	-	-Young age -High anti-DNA title -low C3/C4	Yes
Tselios *et al. (60)* *observational study*	18% (at 12 months) 31% (at 24 months)	30% (at 12 months) 51% (at 24 months)	-clinical/serological short duration inactivity -no concomitant IS therapy	Yes
Nalotto *et al. (100)* ***observational study***	21,2%	-	-	Yes
Fasano *et al.* (82) *single inception cohort study*	12,5%	11,2%	- active serological disease -previous lupus nephritis -minor duration of HCQ treatment	Yes/No
Mathian *et al.* (60) *randomized controlled trial*	27%	7%	-	No

GCs tapering: mode and timing

In our study tapering time was not calculated, but the lag time between achieved remission and GCs withdrawal was evaluated. Results indicated a mean duration of approximately 22 months. This confirms that tapering in our cohort occurs gradually and not abruptly.

There are few data on the mode and timing of GCs tapering. Moroni *et al*. performed one of the first studies on discontinuation of therapy in patients with lupus nephritis. The study considered withdrawal of other drugs besides GCs,

anyway, they recommended to discontinue therapy gradually and progressively under close supervision. In this study, after complete immunosuppressants withdrawal, GCs were maintained stable for a 2–3 months and then were halved every 2–3 months until complete withdrawal (102).

The results showed that 27.8% of the patients had a flare after withdrawal therapy. Therefore, it was demonstrated that therapy could be safely discontinued in the great majority of patients in stable remission.

Galbraith *et al.* showed in a pilot study that GCs can be safely discontinued with progressive tapering. In this study, GCs were withdrawn according to a precise schedule, for patients taking 15 mg/day GCs were withdrawn in 17 weeks, with progressive tapering, in patients taking 10 mg/day tapering lasted 14 weeks, and for patients taking 7.5 mg/day tapering lasted in 12 weeks (78).

Tselios *et al.* withdrew GCs in a 7-week tapering period. Again, the results demonstrated the safety of suspending GCs *(60)*.

On the other hand, in Mathian *et al.* study, GCs were withdrawn abruptly and probably for this reason GCs withdrawal was not safe (60).

Our study has strengths and limitations. Unlike other studies, it evaluated patients at two different timepoint: last remission and first/first available remission. We considered a high number of patients, with a considerably long follow-up after remission achievement. We evaluated different outcome measures, including damage, disease activity and severity at last follow-up. On the other hand, this is a monocentric study, which includes a low number of non-Caucasian patients; we did not apply a pre-specify protocol in GC tapering. Finally, duration of disease widely varies in our cohort, which could impact on our findings, as SLE management has changed over the last 20 year. Nevertheless, sensitive analyses carried out in patients diagnosed after 2000 confirmed our main findings.

8. Conclusions

Our study results show that GCs use in remitted patients does not protect against the risk of flare and, on the other hand, GC discontinuation did not increase the risk of flare in patients with stable remission. This was observed not only at the last remission, but also in the first/penultimate remission. Predictors of flare after tapering were disease manifestations usually characterized by a relapsing-remitting pattern and sensible to low-dose steroid, including arthritis, skin manifestations, haematological disease, and serologically active disease, in particular in the presence of low C3 levels.

Regarding organ damage (SDI) it is confirmed that the higher the cumulative dose of GCs the higher the SDI score.

Therefore, according to EULAR/ACR 2019 recommendations, it is appropriate to reduce and discontinue GCs when there are suitable conditions to do so, i.e. in remitted patients, especially in those on antimalarials (1). Future studies should evaluate the role of new therapies for SLE, including belimumab, anifrolumab, and other biologics under investigation, in the prevention of flare and in the reduction of damage accrual in remitted patients.

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