MINI REVIEW

Systemic Lupus Erythematosus and end-organ damage: A need for low disease activity and less steroid use

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Background

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of unknown aetiology involving many systems that is characterised by a relapsing-remitting course. In the past 40 years, the prognosis for patients with SLE has improved; the 10-year survival is now approximately 90%. Despite improved survival rates, organ damage occurs in 50% of all patients within five years of the diagnosis of SLE.[1]

Up to 40% of patients with SLE develop kidney disease, which represents a major cause of morbidity. Despite an improved prognosis over the last decades, lupus nephritis poses therapeutic challenges and is linked to increased morbidity, mortality and healthcare cost.[2]

SLE and organ damage

Progressive and irreversible damage accumulated with time is associated with the risk of reduced survival of patients with SLE. Persistent disease activity, flare-ups, and accumulating toxicity from chronic use of glucocorticoids (GC) and immunosuppressive (IS) contribute to this risk.[3]

Gladman et al. identified that organ damage, early and late, might be related to corticosteroid therapy in their cohort of patients with SLE followed yearly for 15 years, and most of this damage occurred at 15 years. Thamer et al. also suggested that corticosteroids might have essential mechanisms of action in organ damage apart from anti-inflammatory and immunosuppressive effects in SLE because organ damage varies widely depending on the dose of GC used and the extent of lupus disease.[1]

It is worth mentioning that flares are common in the disease course and contribute hugely to accumulated organ damage and worse outcomes. Young age at disease onset, unuse of antimalarials, persistent generalised disease activity, and positive anti-dsDNA, and low complement are risk factors for higher disease flares.[4]

Goals of SLE treatment

The recently introduced 'treat-to-target' approach in managing the disease has emphasised minimising disease activity as a principal goal of therapy.[3]

There is a consensus that disease remission should be the ultimate goal when treating patients with SLE. In contrast, low disease activity (LDA) could be considered a suitable alternative outcome only when remission cannot be achieved, typically in patients with refractory disease.[5] Remission and LDA have been proposed as targets for the management of SLE. These targets have been associated with a lower probability of mortality, damage, flares, hospitalisation, costs, and cardiovascular events and with a better health-related quality of life.[6]

Despite the heterogeneity of SLE, physicians should try to improve the long-term outcomes by applying all the following goals: **(1)** Control of disease activity, **(2)** Prevent disease

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- Systemic lupus erythematosus is a chronic mutisystemic autoimmune disease of unknown aetiology.
- The message to physicians is to taper prednisolone or introduce other immunosuppressive therapies.
- Hydroxychloroquine (HCQ) is considered the mainstay of SLE treatment.
- SLE is an independent risk factor for cardiovascular disease.

flares, **(3)** minimise irreversible damage accrual **(4)** avoid drug toxicity and **(5)** improve patient's quality of life (QoL). In particular, control of disease activity should aim for the absence of activity in all organs. SLE Disease Activity Index (SLEDAI) close to zero is the target with the lowest possible dose of GC and a non-toxic maintenance dose of IS drugs.

For LDA to be prognostically favourable for minimising future damage, it should be maintained for a substantial period, for example, 12 months. As irreversible damage may be both disease and treatment-related, the challenge in managing a patient with SLE is to use drug therapy judiciously with a careful balance between drug efficacy and harm.[3]

Complete remission, defined as the absence of clinical activity without using GC or IS drugs, is infrequent. The surrogate is to use low disease activity states defined as a SLEDAI score ≤3 on antimalarials, SLEDAI ≤4, or Physician Global Assessment PGA≤1 with GC ≤7.5 mg of prednisone and well-tolerated IS agents. Studies stated that these surrogates have comparable rates in halting the accrual damage (OR 0.5–0.7 for an increase in damage index) and preventing flares compared with remission.[4]

The benefits of CS to induce rapid symptom relief in moderate-severe SLE and to save lives in life-threatening cases are beyond dispute; however, after the acute phase treatment, CS should be maintained at the lowest possible dose or ideally discontinued as soon as possible.

To achieve this goal, two approaches are recommended. The first is to use pulses of intravenous methylprednisolone (MP) 250–1000 mg/day for 1-3 days, reserving higher doses for the most severe disease, after excluding infections followed by prednisolone in a dose rarely higher than 0.5–0.6 mg/kg/day.[4]

This allows a lower starting dose of oral prednisolone with faster tapering. Rigorous efforts should be exercised here to reduce prednisolone to the lowest maintenance dose within six months. The second is the early initiation of IS agents to facilitate and eventually discontinue oral GC. The safe maintenance dose of prednisolone is defined as 7.5 mg / day, with a recommendation to keep it below that after six months. Thamer et al. suggest that low-dose prednisolone does not result in a substantial increase in the risk of irreversible organ damage;[1] however, studies suggested that the risk is there even in doses between 4-6 mg/ day.[3]

The message to physicians treating lupus is to taper prednisone or introduce other immunosuppressive therapies. The threshold of the cumulative prednisolone dose is approximately 540 mg/ month, above this dose patient requires corticosteroid-sparing therapies to control disease activity with minimal organ damage. Zonana-Nacach et al have found that cumulative dose is significantly associated with osteoporosis-induced fractures with a risk ratio (RR) of 2.5, symptomatic coronary artery disease with an RR of 1.7 and cataract with RR of 1.9. And each additional 2-month exposure to high-dose prednisone is associated with a 1.2-fold increase in the risk of both avascular necrosis and stroke.[6,5]

In conclusion, a better understanding of the relationship between corticosteroid therapy, SLE disease activity, and organ damage will hopefully provide a basis for improving the current treatment of SLE.[1]

Steroid therapy in SLE patients

Corticosteroids are the core of therapy for SLE. The route of administration and dosage schedule depend on the severity and distribution of organ involvement. GC have anti-inflammatory and immunosuppressive actions in SLE, and numerous adverse effects result from their use. Some of these adverse effects are reversible, like obesity, diabetes, and hypertension, while others are irreversible, like avascular necrosis, osteoporotic fractures, and cataracts.

Recent studies associate prednisone therapy with permanent organ damage.[1] Several studies have emphasised the risk of accrual damage in a patient with SLE treated with GC, even with as low as 5 or 7.5 mg/day of prednisone or its equivalent.[5]

The efficacy of GC in controlling acute lupus manifestations is well recognised, but their long-term use has numerous issues. Indeed, recent literature highlighted the detrimental effects of chronic use of GC, particularly the increased risk for irreversible organ damage. To this end, there have been attempts to use less GC in therapeutic regimens.[3]

Hydroxychloroquine

Hydroxychloroquine (HCQ) is considered the mainstay of SLE treatment due to its multifaceted beneficial effects, despite the paucity of randomised evidence. Indeed, the use of HCQ has been consistently associated with favourable responses in 'hard' disease outcomes, like irreversible damage, mortality, prevention of congenital heart block and improving metabolic and lipid profile.[3]

HCQ reduces flares and organ damage and improves overall survival. Its recommended daily dose is 5mg/kg with a maximum of 400 mg /day. The risk of retinopathy is higher with higher doses, renal diseases, and old age.[7,8,9] In a study conducted on 189 patients with SLE with a follow-up for a median of 13 years, the addition of HCQ to low-dose aspirin prolonged CV-related event-free survival compared to those using either drug alone. It further reduced the CV risk.[10]

Immunosuppressive (IS) drugs

Immunosuppressive (IS) therapy in SLE is essential for the induction and prevention of remission in patients with organ-threatening lupus. Of these drugs are methotrexate, azathioprine, and mycophenolate. Next to hydroxychloroquine (HCQ), IS drugs are most valuable in the therapeutic armamentarium of SLE. In addition to their immunomodulatory properties, IS allow for a rapid and successful tapering of GC dose and preventing disease flares.[3]

Many drugs are used for this purpose, and their choice depends on the prevailing disease manifestation/s, the patient's age and childbearing potential, safety concerns and cost.[4]

Voclosporin is a novel calcineurin inhibitor (CNI) which has a consistent dose-response and does not need therapeutic drug monitoring, and is more potent than Cyclosporin A.[11] In the AURORA trial, patients were more likely to be in partial remission or have a full kidney response at week 24 and week 52 with voclosporin versus control.[12]

Biological agents

Despite aggressive treatment, approximately 60% of patients with lupus nephritis do not have complete remission, and these patients have poor long-term outcomes. Furthermore, 27 to 66% of patients with lupus nephritis in remission have subsequent flares. Thus, safer therapies that reduce kidney inflammation, prevent flares, and preserve kidney function are needed.

Targeting Interferon pathway

Anifrolumab: Interferon (IFN) system is activated in SLE, and a high IFN level in the serum of a patient with SLE was described 40 years ago that was later identified as type I IFNs.[1, 13] In SLE, interferon (IFN)-regulated genes are prominently expressed, an IFN signature, in blood and tissues.[1]

Observational studies found that patients with malignancy treated with IFN-α may develop a lupus-like disease with autoantibodies to nuclear antigens, concluding that type I IFN

may break the tolerance and induce autoimmune disease.

When genome-wide expression analysis became available, studies showed that 50-70 % of adults and 90 % of children with SLE showed an increased expression of type I IFN-regulated genes (an IFN signature). SLE disease activity correlates with IFN-α levels and the strength of the IFN signature.[13]

In the last decades, the evidence of the important role of type I interferon in the pathogenesis of SLE is remarkably expanded, and this pathway has been targeted as a therapeutic arm in the treatment of SLE. The results of using the first monoclonal antibodies directed against interferon alpha, rontalizumab and sifalimumab, in the treatment of SLE were not promising; however, other agents are proved more successful. The use of anifrolumab, an antibody that inhibits all the five subtypes of I interferon receptors, in the phase II SLE clinical trial gave robust results reaffirming the clinical significance of type I interferons in SLE.[14]

Anifrolumab is a fully human, IgG1κ monoclonal antibody to type I interferon receptor subunit 1 that inhibits the signalling of all types of I interferons. In the TULIP-2 clinical trial,[15] Monthly administration of 300 mg anifrolumab intravenously to patients with active SLE resulted in a higher BICLA response at week 52 than placebo. BICLA response is the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) that needs a reduction in any moderate-to-severe baseline disease activity without worsening in any of the nine organ systems in the BILAG index. The study also showed a reduction in the glucocorticoid dose and the severity of skin disease, which were the secondary endpoints.

Targeting B Cell Therapy

Rituximab: B cells play an essential role in the development of SLE. Blocking of B cells with rituximab, a chimeric mAb against antigen CD20, depletes CD20+ B cells, and this is well established in SLE. It is almost 20 years since B-cell depletion using rituximab was introduced for the treatment of SLE.

The American College of Rheumatology and the European League Against Rheumatology guidelines recommend rituximab for treating lupus nephritis, and NHS England permits its use more widely. Over 50,000 patients with SLE worldwide have been treated with rituximab, and it seems to be very effective for many haematological, musculoskeletal, dermatological and renal aspects of lupus; however, increased risk of infection and hypogammaglobinaemia remain concerns. Rituximab is a chimeric antibody and it causes allergy in about 10 % of patients with SLE. The newer fully-humanised antiCD20 monoclonal antibodies, Ofatumumab and obinutuzumab, are suitable patients who become allergic to rituximab.[16, 17]

Belimumab: Patients with lupus nephrtis produce more B-cell activating factor within the kidney and its level in the serum inreases. Therefore, neutralising B-cell activating factor, with the subsequent down-regulation of B-cell function, decreases in autoantibody production, and inhibition of tertiary lymphoid structure formation in the kidney is a compelling therapeutic approach to lupus nephritis. There is evidence to support beneficial effects of B-cell targeting agents in SLE.

Many observational studies have provided evidence that belimumab is efficacious in reducing disease activity and flare rate, and permitting tapering of GC. Other studies stated that it halts the accumulated damage.[3]

Belimumab is considered for extrarenal disease with inadequate control (ongoing disease activity or frequent flares) to first-line treatments (a combination of HCQ and prednisolone with or without IS agents) and inability to taper GC daily dose to acceptable levels (ie, maximum 7.5 mg/day). Patients who get more benefit from belimumab are those with high disease activity (eg, SLEDAI >10), needs prednisolone dose of more than 7.5 mg/day, have a serological activity (low C3/C4 and high anti-ds DNA titers), mucocutaneous, musculoskeletal and serological manifestations.[4]

Furie and colleagues in their trial on 448 patients with active lupus nephritis showed that belimumab plus standard therapy enhanced

renal responses and lower by 50 % the risk of a renal related event than those who received the standard therapy alone. [18] Combining belimumab with up to 3 grams of mycophenolate mofetil or cyclophosphamide–azathioprine to treat lupus nephritis was not shown to raise the adverse events compared to the results of previous studies.[18]

Wallace and colleagues[19] have studied long-term safety and efficacy of belimumab plus standard of care therapy over 13 years in patiented with active SLE. It is the longest study of belimumab enrolling large number of patients. They found that belimumab was well tolerated with no new safety concerns, and efficacy was maintained in patients who continued the study in consistent with the data from the phase III long-term extension studies. But the relatively low incidence of death in the present study is likely related to the exclusion of patients with active lupus nephritis or central nervous system disease,[4] but the steroid-sparing effect and/or lower rate of organ damage accrual associated with belimumab might also be a contributing factor.[19]

KDIGO 2020 guidelines and ERA_EDTA 2019

The New Kidney Disease Improving Global Outcomes (KDIGO) 2020 and ERA-EDTA 2019 guidelines emphasise lower dose regimens of steroids and immunosuppressive agents to attenuate adverse effects. The recommended dose of intravenous MP is reduced to less than 3 .0 g Recommended initial dose of oral steroids is decreased with more rapid and profound tapering. Also recommended is to use a low dose of Iv cyclophosphamide. The European Renal Association ERA -EDTA has embraced triple therapy of Mycophenolate mofetil (MMF) with CNI and GCs.[2]

SLE and cardiovascular risk

SLE is an independent risk factor for cardiovascular disease (CVD) due to traditional and disease-related risk factors, such as persistent disease activity, lupus nephritis, presence of anti-phospholipid syndrome (aPL), and use of GC. Carotid plaques, carotid intima-media thickness (cIMT), and coronary artery calcium, are measures of atherosclerosis that are frequently used to identify subclinical CVD in SLE. Low-dose aspirin can be used for primary prevention of CVD in patients with SLE as it may reduce the risk for CVD, HR 0.24 in one retrospective study.[4]

It is recommended that patients with SLE should undergo regular assessment for traditional and disease-related risk factors for cardiovascular disease, including persistently active disease, increased disease duration, medium/high titres of aPL, and renal involvement especially, persistent proteinuria and/or GFR <60 mL/min) and chronic use of GC. Based on their individual cardiovascular risk profile, patients with SLE may be candidates for preventative strategies as in the general population, including low-dose aspirin and/or lipid-lowering agents.[4]

The risk of a cardiovascular event in SLE is substantially increased compared to control. In the Hopkins Lupus Cohort, the risk was increased by a factor of 2.661 over the expectation based on the Framingham risk score.[20] Surrogate markers of coronary atherosclerosis are similarly increased, with a prevalence rate of coronary artery calcium of 1.9 over community controls, after adjusting for traditional cardiovascular risk factors.[21]

The pathogenesis of atherosclerosis in SLE is complex and multifactorial. SLE can affect the endothelium of the coronary arteries. Anti-phospholipid antibodies, particularly the lupus anticoagulant, induces a hypercoagulable state increasing cardiovascular events. The usual cardiovascular risk factors can be caused or worsened by SLE, such as lupus nephritis increasing hypertension and hyperlipidaemia, and worsened by treatment with prednisone.[22,23]

Those with higher disease activity are more likely to be prescribed corticosteroids which are associated with an increased risk of cardiovascular events. Finally, the lupus anticoagulant is the anti-phospholipid antibody most strongly associated with thrombosis in SLE, including causing myocardial infarction. The traditional

cardiovascular risk factors of age, male gender, systolic blood pressure, cholesterol, smoking and diabetes were also important in the SLE risk score.[24]

Early mortality in SLE is mainly related to disease activity; however, cardiovascular morbidity and mortality are increased in line with the prolonged overall survival of patients with SLE. Multiple risk factors contribute to this, such as the classical cardiovascular risk factors (CVRF), the disease activity, treatments and complications, and the thrombotic risk due to aPLs.[5]

Data from 1874 patients with SLE vising a single centre from April 1987 to June 2012 were analysed using pooled logistic regression; the authors observed that patient with SLE has 2.66 more times of developing cardiovascular events (CVEs) than in the general population based on Framingham risk scores (95% confidence interval: 2.16, 3.16). After adjustment for age, CVE rates were not associated with the duration of SLE.[20]

The study also found the average level of past SLE disease activity, current levels of circulating anti-double-stranded DNA, and current use of more than 20 mg of prednisolone per day even after adjustment for disease activity, were associated with increased CVEs. The association was insignificant with the history of corticosteroid use. This is consistent with the results of many recent publications that link the current use of corticosteroids with an increased risk of CVEs suggesting a short-term impact of corticosteroids on risk of CVEs.[20]

A key point to emphasise is that in SLE, the scope to modify risk increases through therapy adjustment, especially steroids, and by introducing antimalarials whenever appropriate and therapeutic lifestyle changes. As such, particularly in patients who are deemed to be above their ideal weight, these measures may be beneficial in achieving several targets while avoiding the need for additional drug therapy.[25]

CONCLUSION

In conclusion patients with SLE should not be on high GCs for long periods. We need to minimise GCs exposure while still maintaining adequate control of the disease (remission or low disease activity state). Possible strategies to achieve these goals is to use as lower as possible dose of steroid and the IV pulse MP therapy followed by lower oral doses together with early introduction of concomitant immunosuppressives and biologics. Hydroxychloroquine should be prescribed for every patient with SLE unless it is contraindicated.

*** Parts of this review was delivered to the Iraqi Society of Nephrology on 15 January 2022**

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Abbreviations list: Anti-double-stranded Deoxyribonucleic acid (**Anti-dsDNA**), Anti-phospholipid syndrome (**aPL**), British Isles Lupus Assessment Group (**BILAG**)-based Composite Lupus Assessment (**BICLA**), Calcineurin inhibitor (**CNI**), Cardiovascular (**CV**), Cardiovascular disease (**CVD**), Cardiovascular events (**CVEs**), Cardiovascular risk factors (**CVRF**), Carotid intima-media thickness (**cIMT**), European Renal Association-European Dialysis and Transplant Association (**ERA-EDTA**), Glucocorticoids (**GC**), Hazard ratio (**HR**), Hydroxychloroquine (**HCQ**), Immunosuppressive (**IS**), Interferon (**IFN**), Kidney Disease Improving Global Outcomes (**KDIGO**), Low disease activity (**LDA**), Methylprednisolone (**MP**), Mycophenolate mofetil (**MMF**), Odds ratio (**OR**), Physician Global Assessment (**PGA**), Quality of life (**QoL**), Risk ratio (**RR**), SLE Disease Activity Index (**SLEDAI**), Systemic lupus erythematosus (**SLE**).

Conflict of interest: Authors have nothing to declare.

Funding: None.