Chapter

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Management of Systemic Lupus Erythematosus

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INTRODUCTION

SLE is the commonest connective tissue disease encountered in clinical practice. It is a multisystem disorder which can involve the skin, mucous membranes, joints, lungs, kidneys, central and/or peripheral nervous system, heart, and the gastrointestinal system. Constitutional features of fever, fatigue, anorexia and weight loss are common. Lupus should be suspected in the following clinical settings:

1. Multisystem involvement in a young female
2. Inflammatory polyarthritis with additional features like fever, prominent mucocutaneous involvement, active urine sediment, cytopenias, and neuropsychiatric features
3. FUO (Fever of unknown origin)
4. Unexplained renal failure/nephrotic syndrome
5. Polyserositis
6. Mononeuritis multiplex
7. Psychosis in a young female
8. Picture of ITP (idiopathic thrombocytopenic purpura) with splenomegaly.

SLE is characterized by the presence of antinuclear antibodies (ANA). Indirect immunofluorescence continues to be the gold standard for detection of ANA. Since low titre ANA are seen in nearly 5% healthy young women, interpretation of autoantibody results should always be in context of the clinical picture. Certain ANA subsets such as dsDNA (sensitivity 50-60%) and Sm (sensitivity 30%) are highly specific for SLE. Antibodies to ds DNA should not be used as a screening test for SLE. The major utility is in confirmation of the diagnosis of lupus in ANA positive individuals. Also, dsDNA levels generally correlate with disease activity especially in lupus nephritis. In an occasional patient, the dsDNA levels may not parallel disease activity, the so called "clinico-serologic discordance". In such cases the dictum is to treat the patient and not chase the dsDNA levels.

ASSESSING DISEASE ACTIVITY IN SLE

The aggressiveness of therapy in SLE should match the disease activity. Assessment of disease activity refers to the determination of the extent to which the immunoinflammation of SLE is contributing to the clinical setting at a particular point in time and the likelihood that it will produce lupus related morbidity or mortality. It is analogous to the concept of "tumor burden" in oncologic disease[1]. The change in lupus activity helps a clinician to decide whether SLE is improving or worsening. Disease activity is assessed by a thorough clinical examination and by using laboratory parameters. The single most important laboratory investigation is urinalysis for proteins and sediment (casts and cells). Other laboratory variables used include C3 levels, dsDNA levels, platelet counts and total white cell count (TLC)[2]. ESR, being non-specific, is not very helpful. Repeated ANA testing has no clinical utility as the titers of ANA do not correlate with disease activity. A number of standardized scoring systems have been developed to provide a more reproducible and quantitative assessment of lupus activity. Herein each clinical/laboratory variable e.g. arthritis, alopecia, psychosis, proteinuria is given a weighted score. The commonly employed instruments include SLE-DAI (SLE disease activity index), BILAG (British isles lupus assessment group) and SLAM (systemic lupus activity measure).

DIFFERENTIATING DISEASE ACTIVITY FROM DISEASE DAMAGE

Crucial to the management of SLE is the concept of differentiating 'lupus activity' from 'irreversible damage' due to SLE. 'Disease activity' refers to ***reversible*** manifestations while 'damage' refers to ***non reversible*** charges present for at least 6 months which are not related to active inflammation. The following examples will help to clarify this further. A patient of SLE with interstitial lung disease (alveolitis on bronchoalveolar lavage and high resolution CT) would benefit from high dose steroids and azathioprine/cyclophosphamide. On the other hand in advanced interstitial fibrosis these therapies would be counter productive. It would be best to consider supportive treatment or lung transplantation, if feasible. Similarly myocarditis in SLE would require aggressive immunosuppression while cardiomyopathy, once it has developed, would be best treated with diuretics and vasodilators rather than immunosuppressives. In the same context, lupus nephritis Class III and IV warrant aggressive immunosuppression which is contraindicated in class VI (glomerulosclerosis). Patients in Class VI are best treated with renal replacement therapy (dialysis/transplantation) rather than aggressive immunosuppression. A damage index, reflecting the accumulated damage occurring in patients is available.

GENERAL PRINCIPLES OF MANAGEMENT

Patient education, as in other chronic illnesses, is very important in SLE. Patients should be advised to avoid exposure to sunlight. Some authorities advocate antibiotic prophylaxis before invasive procedures like dental work, genito-urinary instrumentation, etc. Patients on cytotoxics should be advised about contraceptive measures. The conventional wisdom that oral pills are taboo in lupus has been challenged. Recent studies reveal that OCs do not increase the flare rate in mild to moderate lupus[3,4]. However, these drugs need to be used with caution in patients with severe lupus and/or antiphospholipid syndrome.

Associated problems like hypertension, hyperlipidemia, dyselectrolytemias, seizures, anemia, osteoporosis, etc. need as much attention as the primary disease. Tight blood pressure control, use of ACE inhibitors and/or angiotensin receptor blockers, aggressive correction of dyslipidemia, and bone protection with calcium, vitamin D and bisphosphonates if needed are important. Fever in SLE mandates a diligent search and treatment for infection. The presence of leukocytosis and elevated CRP favor the diagnosis of infection while active SLE is usually associated with normal or low white cell counts and a normal CRP level. However, sole reliance on CRP can be misleading.

MAJOR AND MINOR ORGAN INVOLVEMENT IN SLE

Since SLE is a multisystem disorder which can affect any organ it is clinically important to categorize patients into those with ***major organ*** involvement and those with ***minor organ*** involvement. Therapy is directed accordingly. Minor involvement includes serositis, mucocutaneous, musculoskeletal or constitutional symptoms. The major manifestations include lupus nephritis neuropsychiatric SLE, significant cytopenias and interstitial lung disease. In general, patients with minor organ involvement of lupus can be treated with NSAIDs and hydroxychloroquine. Corticosteroids, if needed, are given in relatively small doses (prednisolone 0.25-0.5 mg/kg/day). On the other hand, major organ involvement necessitates use of high dose corticosteroids (prednisolone 1 mg/kg/day or higher) and even cytotoxics (Fig. 1). Patients with minor organ involvement may also require high dose corticosteroids during disease flare. In the same vein, once patients with major organ involvement go into quiescence, the corticosteroids should be tapered to a maintenance dose.

DRUGS USED TO TREAT SLE

The various drugs used to treat SLE include NSAIDs, antimalarials, corticosteroids and cytotoxics (Table 1).

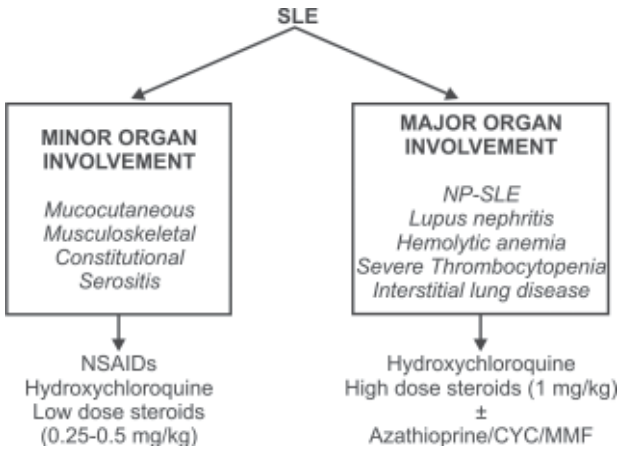

Fig. 1: Approach to management of SLE

NSAIDs = Non steroidal anti-inflammatory drugs
NP-SLE = Neuropsychiatric SLE
MMF = Mycophenolate mofetil
Steroids = Prednisolone
CYC = Cyclophosphamide

Table 1: Drugs used in treatment of SLE

Drug	*Used for*	*Side effects*	*Remarks*
NSAIDs	Mucocutaneous, musculoskeletal, serositis, constitutional	Renal, gastrointestinal blood dyscrasias, neuropsychiatric	Selected patients require gastric protection with proton pump inhibitors
Hydroxychloroquine	Mucocutaneous, musculoskeletal, serositis, constitutional, plasma glucose and cholesterol decreased, aPL decreased	Mainly ocular toxicity. Can cause skin rash, myopathy psychosis	Annual perimetry, Safe in pregnancy
Corticosteroids	Benefit almost all manifestations of SLE	Weight gain, hirsutism, Cushingoid habitus, cataract, hypertension, diabetes, osteonecrosis, osteoporosis, infections	Use minimum possible dose for shortest period of time possible. Taper slowly
Methotrexate	Arthritis, serositis, skin rash, fever	Hepatic toxicity	Monitor LFT. May also be used as a steroid sparing agent
Cyclophosphamide	Lupus nephritis, CNS lupus, refractory thrombocytopenia, ILD	Nausea, vomiting, bone marrow suppression, bladder toxicity, gonadal failure, malignancy	Use reserved for major organ involvement. Intermittent pulses preferable to daily oral
Azathioprine	Major organ involvement	Bone marrow suppression, transaminitis, malignancy	May be used for its steroid sparing effect, safe in pregnancy
Mycophenolate mofetil	Lupus nephritis Class III or IV, Cutaneous lupus	Gastrointestinal toxicity, bone marrow suppression	Emerging as an alternative to cyclophosphamide in severe lupus nephritis

The type and severity of clinical features guide treatment (Fig. 1). A brief outline of the various drugs used is given below:

NSAIDs

Nonsteroidal anti-inflammatory drugs are used to combat musculo-skeletal symptoms, fever, fatigue and mild serositis. In equipotent doses, all NSAIDs are similar in efficacy although side effects differ. Also, in a given patient, the response to an individual NSAID may vary markedly. What is good for one patient may not produce the same benefit in another. So NSAID selection is based on patient preference, dosing frequency and side-effect profile. NSAIDs may cause acute interstitial nephritis, acute tubular necrosis or membranous nephropathy. NSAID induced renal injury in SLE needs to be differentiated from lupus nephritis. Similarly, NSAIDS may be responsible for neuropsychiatric features like headache, dizziness, aseptic meningitis, etc. which need differentiation from neuropsychiatric involvement in SLE.

Antimalarials

Hydroxychloroquine (HCQ) has virtually replaced choloroquine in the treatment of lupus. The therapeutic efficacy of both agents is similar but HCQ is preferred because of greater ocular toxicity with chloroquine. Antimalarials benefit serositis and cutaneous, musculoskeletal and constitutional symptoms of SLE. In addition, HCQ has been shown to favorably alter risk factors for atherosclerotic disease by reducing cholesterol and glucose levels. Titers of antiphospholipid antibodies decline with HCQ treatment. Hydroxychloroquine protects against major disease flares and the current belief is that treatment with this agent needs to be continued indefinitely[5]. Very recently, HCQ has been shown to have benefit for renal remission in membranous lupus nephritis when combined with mycophenolate mofetil[6]. Whether this extends to other forms of renal lupus is not known. Despite being economical and effective, antimalarials are underutilized in the treatment of SLE. All patients with lupus should receive HCQ unless there are specific contraindications.

Corticosteroids

Corticosteroids are beneficial in most of the lupus manifestations. Prednisolone is preferred over long acting steroids such as betamethasone/dexamethasone except in pregnancy with fetal complete heart block where the latter are used since prednisolone does not cross the placental barrier. In emergent and life threatening situations methyl prednisolone pulses may be used (1 gm intravenous infusion daily for 3 days). In most patients steroids can be tapered and even dis-

continued once the disease is quiescent for a prolonged period of time. However, some patients of SLE have a *minimum corticosteroid threshold*—reduction of steroid dose below this threshold leads to a lupus flare. Such patients may need life long corticosteroids.

Cytotoxics in SLE

In general, cytotoxics are indicated in patients with major organ SLE. Intermittent monthly boluses of intravenous cyclophosphamide (CYC) have been the standard treatment for serious lupus especially lupus nephritis. However, side effects including gonadal failure, infection and secondary malignant disease have led to alternative regimens/agents (vide infra). The classical National Institutes of Health (NIH) protocol for severe proliferative lupus nephritis entails use of 6 monthly pulses of intravenous CYC (0.5-1 g/m^2 or 15 mg/kg) followed by subsequent CYC pulses every 3 months for 2-2.5 years (total of 12-14 pulses). The dose of CYC is reduced in renal failure. Hydrocortisone and ondansetron are routinely given prior to administration of cyclophosphamide. Good fluid intake and proper hydration minimize risk of bladder toxicity. MESNA, employed to prevent bladder toxicity, is not easily available in India. Cyclophoshamide has also been shown to result in improvement of a variety of neurological or psychiatric manifestations of SLE. It has to be borne in mind that the onset of action of CYC takes a few days. Corticosteroids are essential to control the immuno-inflammation in emergent situations.

Apart from cyclophosphamide, methotrexate and azathioprine have been used in clinical settings where lupus activity fails to respond completely to steroids or for their steroid sparing effect. Methotrexate given weekly (oral dose ranging from 7.5-25 mg) is used to treat the arthritis of SLE and as a steroid sparing agent in patients requiring large doses. Azathioprine, given orally in doses of 2 mg/KBW, is used to treat major organ lupus especially in young women where gonadal toxicity is a major concern while using cyclophosphamide. In an effort to reduce drug toxicity, azathioprine has also been used as a maintenance agent after induction of remission with cyclophosphamide. Table 2 shows the current recommendations for the management of lupus nephritis.

Intravenous immunoglobulin (IVIG) is occasionally used to control acute bleeding associated with lupus thrombocytopenia or to rapidly increase the platelet count to allow for splenectomy or emergency surgery.

ANTIPHOSPHOLIPID SYNDROME IN SLE

Patients present primarily with arterial/venous thrombosis or pregnancy loss. A host of other clinical features are now recognized. The diagnosis of APS requires the presence of clinical criteria alongwith the presence of moderate to high titer antiphospholipid antibodies (aPL). A single reading of elevated aPL is not enough to diagnose APS. Sustained elevation (positive aPL on at least 2 occasions 6 weeks apart) is a must for diagnosis. This is because transient aPL can be seen with

Table 2: Management of lupus nephritis. (Classes according to the International Society of Nephrology/Renal Pathology Society Classification-2003)

Class I	Minimal mesangial lupus nephritis	No specific treatment
Class II	Mesangial proliferative lupus nephritis	Corticosteroids alone
Class III	Focal lupus nephritis	**Induction (first 6 months)** Corticosteroids (high dose initially) + CYC or MMF
Class IV	Diffuse segmental (IV-S) or global (IV-G) lupus nephritis	**Maintenance** Low dose corticosteroids+Azathioprine or MMF
Class V	Membranous lupus nephritis	Cyclosporin + Corticosteroids ACEI/ARBs to reduce proteinuria
Class VI	Advanced sclerosing lupus nephritis	Renal replacement therapy - dialysis and/or transplantation, maintenance corticosteroids. Avoid high dose corticosteroids/ cytotoxics

Diffuse: A lesion involving most (>50%) glomeruli; **Focal**: A lesion involving < 50% of glomeruli; **Global**: A lesion involving more than half of the glomerular tuft; **Segmental**: A lesion involving less than half of the glomerular tuft (i.e., at least half of the glomerular tuft is spared)

CYC=Cyclophosphamide; MMF=Mycophenolate mofetil;

ACEI=Angiotensin Converting Enzyme Inhibitors; ARB= Angiotensin Receptor Blockers

Tight control of blood pressure mandatory in all patients

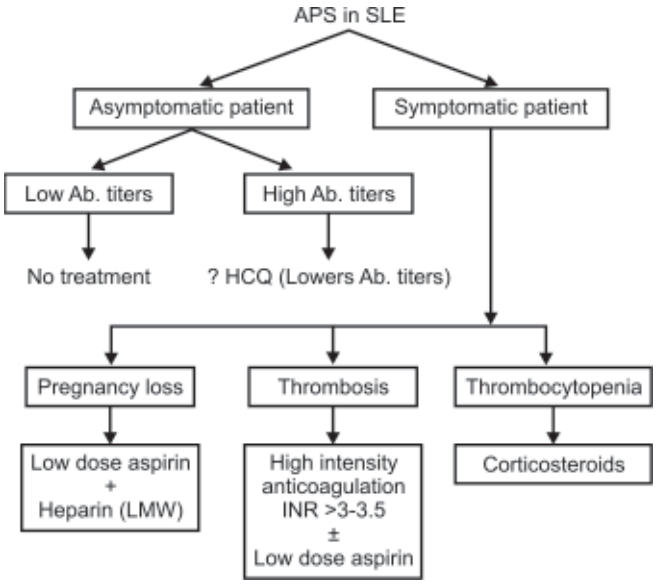

Fig. 2: Approach to antiphospholipid syndrome in SLE

HCQ = Hydroxychloroquine

? = Role not certain

Ab = Antibody

LMN = Low molecular weight

INR = International normalized ratio

several conditions like infections (tuberculosis, mumps), lymphoma, etc. Screening for APS is warranted only if there are clinical pointers suggestive of APS. An algorithmic approach to APS in SLE is presented in Figure 2. Patients of SLE who are asymptomatic for APS but have demonstrable antiphospholipid (aPL) antibodies require no treatment. The routine use of hydroxychloroquine in these patients to lower aPL antibodies is questionable.

SLE AND PREGNANCY

Fertility rates in lupus patients are the same as in the general population but there is a greater incidence of spontaneous abortion, prematurity and intrauterine death in SLE.[7] The issue whether pregnancy induces lupus flare or not is controversial with conflicting reports in the literature. The diagnosis of flare in the pregnant patient can be difficult. Patients with pre-existing lupus nephritis frequently have worsening of hypertension, proteinuria and renal function during pregnancy either because of toxemia or renal flare. Treatment of lupus flare in pregnancy entails use of corticosteroids, vigorous control of blood pressure, and delivery as soon as possible. Hydroxychloroquine and azathioprine are safe during pregnancy. The occurrence and severity of neonatal lupus are unrelated to maternal disease activity or severity. The administration of dexamethasone or betamethasone (not prednisolone) may benefit in utero myocarditis. Infants with a congenital complete heart block require permanent pacing.

SURVIVAL IN INDIAN PATIENTS WITH SLE

Despite tremendous advances in the management of SLE, the survival in India lags behind developed countries. The cumulative percentage survival in India at 1, 5 and 10 years has been reported to be 89%, 77% and 60% respectively with a predicted life expectancy of 13.9 years[8].

EMERGING TRENDS/AGENTS FOR SLE

The recent demonstration of benefit of HCQ in membranous lupus nephritis is an important observation and is bound to pave the way for further studies assessing utility of HCQ in proliferative lupus nephritis and neuropsychiatric lupus.

Of late, the time honored NIH protocol for proliferative lupus nephritis has come under question, largely due to concerns about cyclophosphamide toxicity. The Euro-Lupus Nephritis Trial, a head-to-head comparison of low-dose versus traditional high-dose CYC for severe active lupus nephritis, compared 6 monthly i.v. pulses of CYC 0.5-1 g/m^2 followed by two quarterly pulses to low-dose CYC (fixed i.v. pulses of 500 mg given every 2 weeks for a total of six doses). Azathioprine was used as maintenance therapy after stoppage of CYC in both groups. At 41 months, there were no significant differences in the cumulative probability of treatment failure, renal remissions or renal flares. Patients in the low dose regimen had less toxicity with fewer and less severe infections[9]. The sequential use of CYC and AZA has now been embraced by many rheumatologists and nephrologists.

Another addition to the therapeutic armamentarium in lupus is mycophenolate mofetil (MMF). Mycophenolic acid, the active metabolite of MMF, inhibits inosine monophosphate dehydrogenase, a key enzyme in purine synthesis. As lymphocytes do not possess a salvage pathway, MMF selectively blocks B and T cell proliferation. Other tissues with high proliferative activity like neutrophils, skin, intestine, bone marrow are not affected by MMF because they possess a salvage pathway for nucleotide synthesis. This accounts for the fact that the toxicity profile of MMF is more favorable compared to CYC. The usual dose for induction is 2-3 gms/day while the maintenance dose is 1-2 gm/day. Side effects include vomiting, diarrhea, leucopenia and infections. According to data currently available, MMF may be used in

new cases of mild to moderate lupus nephritis with intact renal function, especially in young patients where fertility is an issue. MMF levels are unpredictable in patients with renal insufficiency. More data is needed in case of patients with rapidly progressive nephritis, recurrent nephritis and moderate renal insufficiency. There are insufficient data to justify use of MMF in pregnant women (Category C). MMF is useful in cutaneous lupus and may also retard development of atherosclerosis[10,11]. The major deterrent to the widespread use of MMF in India is the cost.

Rituximab, a chimeric monoclonal antibody directed against CD20, a membrane-associated glycoprotein present on B-lymphocytes but not on plasma cells, has been used for refractory lupus including lupus nephritis. Other biologic therapies being tried out in lupus are humanised anti-CD20 antibodies, anti-CD22 antibodies, LJP 394 (riquent, abetimus sodium), costimulation blockers, and belimumab, a fully human monoclonal antibody that specifically binds to and neutralises the B-lymphocyte stimulator (BLyS or B-cell-activating factor [BAFF]).

Atherosclerosis has emerged as a major challenge in SLE. According to the current paradigm inflammation plays a major role in atherosclerosis. Lupus being a prototype systemic inflammatory disease is associated with accelerated atherosclerosis and our data, utilizing carotid intimomedial thickness as a surrogate marker for atherosclerosis, reveals that this problem is widespread in Asian Indian patients with SLE[12].

Advances in understanding the pathobiology of lupus have changed the therapeutic landscape of this disease. Several drugs are available and many more are in the pipeline. The need of the hour is to strike a balance between efficacy, availability and cost.

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