



Management of Systemic Lupus Erythematosus

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Systemic lupus erythematosus (SLE) is a multisystem prototype autoimmune heterogenous illness characterized by myriad of systemic features primarily due to immunodysregulation at multiple levels of the immune cascade with hyperactivation of B-cell activity and diminished T-cell suppressor activity leading to increased tissue specific and non-tissue specific antibodies. Having highly variable features like constitutional symptoms, glomerulonephritis, neuropsychiatric disease and cutaneous manifestations SLE is primarily incurable, but most of the patients experience remission and their survival has improved over the years (Table 1).¹

Table 1: Survival Rates in SLE

| Authors | No. of Patients | 5 years (%) | 10 years (%) | 15 years (%) |
|------------------------------|-----------------|-------------|--------------|--------------|
| Feng PH 1970-80 | 183 | 70 | 60 | - |
| Chen SL 1980-98 | 50 | 98 | 84 | 76 |
| Chandrasekharan 1985-1994 | 330 | 88 | 82 | - |
| Ward MM 1975-93 | 408 | 82 | 71 | 63 |
| Abu Shakra 1980-95 | 665 | 93 | 85 | 79 |

The causes of death in SLE in first 5-10 years are infections, active disease with renal involvement and vasculitis whereas in later years morbidity and mortality are mostly attributed to premature coronary atherosclerosis.^{2,3}

A seemingly constant feature in SLE patients is the accumulation of unusually large amount of apoptotic cells because of defect in the clearance mechanism of phagocytes. Apoptotic cells are non inflammatory but secondary necrotic changes with disintegration and release of cytosolic compounds make them inflammatory. Finally there is activation of autoreactive T & B cells.⁴

PRINCIPLES OF MANAGEMENT

- Early diagnosis and assessment
- Patient education
- Preventive measures
- Control of disease activity
- Organ salvage
- Care of comorbid states and emergencies

After the confirmation of the diagnosis, the disease needs assessment of its activity and extent of organ damage. The various clinical indices of diseases activity include major organ involvement like CNS, CVS, pulmonary, renal and mucocutaneous lesions; laboratory parameters are proteinuria, urinary sediments, serum anti-DS-DNA, platelet count and C₃ & CH₅₀ assay and finally creatinine clearance. In this context disease activity scores have been adopted by different authors in the name of SLEDAI (SLE Disease Activity Index), BILAG (British Isles Lupus Activity Grade), SLAM (Systemic Lupus Activity Measures).

The disease damage of the organs is often irreversible which are exemplified by advanced glomerulosclerosis (WHO VI), cardiomyopathy, progressive interstitial lung disease, stroke and cognitive dysfunction.

Patient education

Patient education is an integral part of comprehensive care. Emotional and psychosocial supports are to be ensured for the success of long term therapy. The counseling about marriage, fertility, contraception need to be addressed.

Preventive measures

Regular evaluation of Lupus activity and damage

Early identification of these will help to diagnose lupus 'flare' or organ damage. The patients are to be informed in this matter before hand.

Photoprotection

The patient is to be advised about ill effects of prolonged exposure to sun and use of sunscreens with protection factor (SPF 15 or above) has to be encouraged.

Vaccination

It is not contraindicated apart from "live" vaccines for patients on more than 10 mg prednisolone a day or other immunosuppressive agents.

Osteoporosis prophylaxis

It is necessary in patient on long term steroids. The supplementation with calcium 1500 mg/day and vitamin D 400 IU/day is advisable. Monitoring with DEXA scan spine for osteopenia/porosis and timely use of Alendronate 70 mg/wk or Risedronate 35mg once a week is necessary.^{5,6}

Table 2 : Treatment Strategy in SLE

| SLE confirmed | | |
|--|---|---|
| Minor organ damage e.g. skin, arthralgia, serositis etc. <ul style="list-style-type: none"> • NSAIDS • Hydroxychloroquine • Low dose steroid 0.25 mg - 0.5 mg/Kg/day | APS <ul style="list-style-type: none"> • Anticoagulant • Low dose Aspirin ± Hydroxychloroquine (HCQS) | Major Organ damage e.g. Renal, CNS, CVS Haematological <ul style="list-style-type: none"> • High dose prednisolone 1-1.5 mg/Kg/day ± Cytotoxics ± "Newer" agents |

Hormones

The traditional high dose oestrogen contraceptives is avoided; the lowest dose oestrogen – progesterone pill or other methods of contraception is encouraged. The use of hormone replacement therapy remains controversial. A multicentric placebo controlled (safety of Estrogen in SLE : National Assessment, SELINA Study) in under way to resolve the controversy. The pregnancy issues need to be discussed with the patient.

Therapeutic Strategy

The broad principle in using various drugs in SLE depends upon extent and severity of organ damage. A special subgroup like antiphospholipid antibody syndrome (APS) has been incorporated in this strategy because of additional therapy with anticoagulants. The approach to therapy is broadly classified (Table 2).

Drug Therapy

The pharmacological treatment of SLE patients consists of four main types of drugs either alone or in combination.⁷

- Non-steroidal anti-inflammatory drugs (NSAID)
- Hydroxychloroquine
- Corticosteroids
- Cytotoxic drugs

The broad selection of drugs depending upon organ damage has been shown to be effective in different subgroups. A new study SLICC (Systemic Lupus International Collaborative Clinics) group is currently aiming to define a drug responder index for SLE patients.⁸

Non-steroidal antiinflammatory drugs

This is advised to control arthralgia and myalgia. Newer COX II inhibitors are preferred than conventional NSAID for safety of stomach and intestine. However nephrotoxicity of all types of NSAIDs is the limitation in elderly and specially in presence of lupus nephritis.

Hydroxychloroquine

This is used as low potency immunosuppressive agent to control fatigue, arthralgia/arthritis and rash; is shown to be effective to prevent 'flares'.⁹ The starting dose is 400mg daily which is

tolerated well. The prevalence of retinal toxicity is approximately 0.5%.^{10,11} Eye examination every 6 months is available. Hydroxychloroquine has also been shown to be effective to help lower plasma total triglyceride, VLDL and apolipoprotein CIII levels.¹²

Corticosteroids

These drugs are recommended in patients with minor and major organ damage in low and high dosage respectively. It is also used as maintenance therapy. In life threatening and vision threatening situation parenteral methyl prednisolone intravenously is prescribed in a dose 500mg - 1000mg daily for three successive days over a period of 3-4 hours each time. It is followed by oral steroids in a dose of 0.75-1mg/kg body weight daily and tailed off over a period of months.

The major side effects of steroids need to be appreciated like osteoporosis, peptic ulceration, hypertension, hyperlipidemia, risk of infection, alopecia, avascular necrosis of bones and accelerated atherosclerosis. Hence gastric protection with proton pump inhibitors, bone protection with weight bearing exercise, calcium, vitamin D and bisphosphonates are essential. It is important to monitor bone mineral density (BMD) every 2 years. The maintenance dose of corticosteroid should not exceed 7.5 mg a day on a long term basis.

Cytotoxic Drugs

The mainstay of treating active lupus with major organ damage is broad spectrum immunosuppression with the ultimate aim of preventing irreversible organ damage. The drugs used are Cyclophosphamide, Azathioprine, Mycophenolate Mofetil either alone or in combination with corticosteroids. Methotrexate is also available option in subsets of SLE patients with predominant joint disease.

Cyclophosphamide

This is given orally (50-100 mg/day) daily or intravenously as "pulse" therapy (15-25mg/kg body weight a day) every 3-4 weeks. The adverse effects include nausea, vomiting, alopecia, haemorrhagic cystitis, infertility in child bearing age and bone marrow suppression. It is important to maintain hydration during 'pulse' therapy. Presumably 'pulse' therapy has lesser side effects than maintenance oral therapy.

Azathioprine

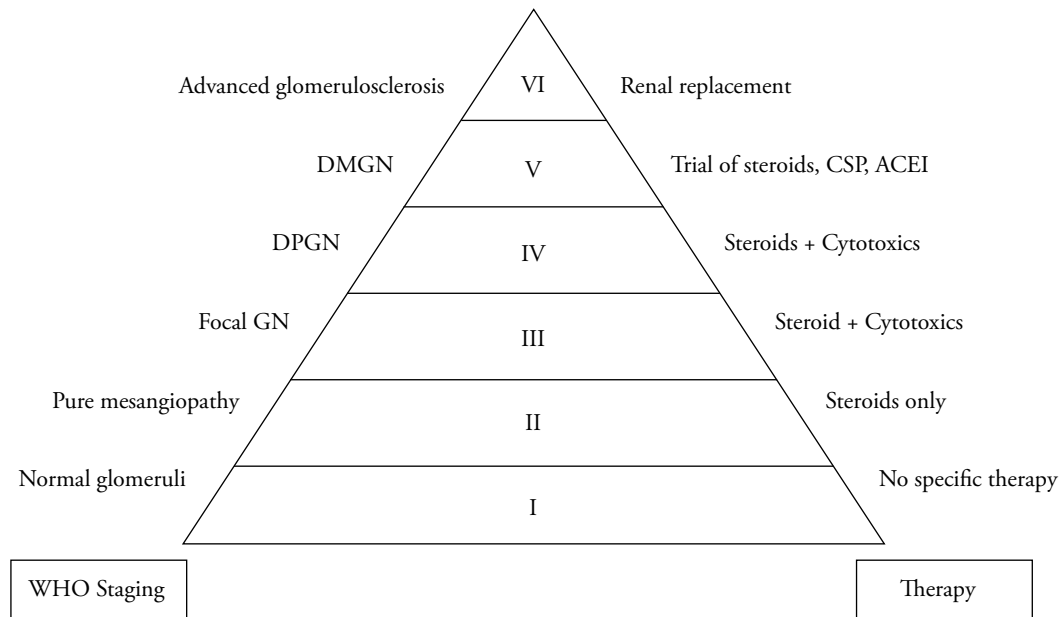
It may be used as steroid-sparing agent in the treatment of renal lupus. The dose is 1.5 – 3 mg/kg/body weight starting with 50mg per day to maximum 150 mg per day. The adverse effects include myelosuppression, hepatic dysfunction and pancreatitis. Regular blood monitoring is essential.

Mycophenolate mofetil

It is a relatively new immunosuppressive agent used in renal lupus refractory to other cytotoxic drugs.¹³ This is given in a dose of 1-2 gm a day in divided dose. Mycophenolate in combination with steroids is equally effective when compared with cyclophosphamide and steroids but with lesser side effects. The adverse effects include nausea, vomiting and myelosuppression.

Cyclosporin A

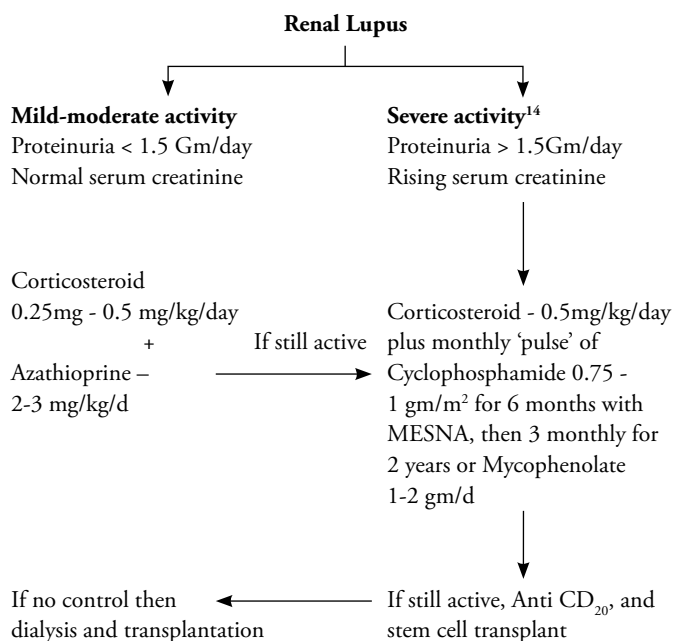
Though it is effective in SLE, it is not often used because of potential risk of nephrotoxicity.



The algorithm of management of Renal Lupus is as below as per protocol of NIH, Bethesda, USA in Table 3.

Fig. 1: Management Pyramid of Lupus Nephritis

Table 3 : Algorithm of Management of Renal Lupus



Management of Lupus related Special Conditions

Renal Lupus

The kidney is the major organ at risk and it is common in Indians. Lupus nephritis may be asymptomatic or may present with nephritis or nephrotic syndrome. It is desirable to have renal biopsy prior to therapy to assess severity, nature and potential reversibility of renal disease. The therapeutic options are matched with WHO histologic staging and classification of renal lupus as in Fig. 1.

Neuropsychiatric Lupus

Intravenous cyclophosphamide is preferred as 'pulse' therapy either alone or in combination with steroids in presence of vasculitis. However it is always important to rule out CNS infection before cytotoxic therapy. Seizures need to be controlled by phenobarbitone, valproate or phenytoin. Cognitive dysfunction needs to be addressed in combination with Psychiatrist. Antiphospholipid syndrome is often associated which requires treatment as below.

Antiphospholipid Antibody Syndrome

About 10% of SLE patients have secondary antiphospholipid antibody syndrome though 25-30% have antiphospholipid antibodies. In patients with thromboembolic features anticoagulation with heparin to keep activated partial thromboplastin time (APTT) 1.5 to 2 times the baseline is advised.¹⁵ This is usually achieved with heparin dose of approximately 1000 units per hour. Simultaneous oral anticoagulation with warfarin 5-10 mg/d is given for 5-7 days by which time INR reaches the therapeutic levels. Heparin is discontinued once warfarin action is optimized and thereafter it is continued as a maintenance dose to keep INR around 2.5 to 3.¹⁶ Concurrent aspirin 75mg/day is also advocated. Immunosuppressives are only needed to control SLE activity.

SLE in Pregnancy¹⁷

Fertility is normal unless the disease is very active. Approximately 25% of patients do not go to full term, well in excess of 10% expected in healthy women. Those with antiphospholipid antibody syndrome are likely to have recurrent miscarriage, still birth and low birth weight babies.¹⁸ Aspirin 75mg a day and/or heparin therapy are advised to salvage foetal wastage. Low dose steroids and azathioprine can be safe during pregnancy but chloroquine, cyclophosphamide and methotrexate are contraindicated. Medical termination of pregnancy is not advocated. Screening

for Anti Ro Ab / Anti La Ab during pregnancy is essential to predict neonatal congenital heart block. Neonatal SLE needs special attention.

Oestrogen containing contraceptives may trigger a 'lupus flare' and should be avoided. Progesterone contraceptives are safe; postmenopausal hormone replacement may be considered under special circumstances.

Infections in SLE

Infections is an important risk in SLE patients on immunosuppressive therapy and it carries considerable morbidity and even mortality. It is difficult to distinguish fever of infection from disease activity. Positive CRP (C-reactive protein) with shift to the left of WBC count predicts infection whereas negative CRP & low C₃ with fever suggest disease activity. Commonly, tuberculosis,¹⁹ candidiasis, *Pneumocystis carinii* are opportunistic infections. Prophylactic antibiotics/immunization are justified in areas of high prevalence. Periodic chest X-ray is useful.

Accelerated Atherosclerosis²⁰

This is considered as one of the delayed complications of SLE. The continuing active vascular inflammation, endothelial dysfunction, antiphospholipid antibody syndrome, abnormal lipids and prolonged steroid therapy are the predisposing factors for such premature, accelerated coronary atherosclerosis with adverse consequences. The management consists of recognition of risk factors and ensuring investigations and treatments. The commonly prescribed options are use of statin, aspirin 75-150mg, clopidogrel 75mg and control of disease with lowest possible dose of Prednisolone 7.5mg to 10mg a day. Often hydroxychloroquine 400mg/day helps control of lipids. Traditional risk factors like hypertension and glucose intolerance need to be controlled. Anticoagulation is indicated if there is antiphospholipid antibody syndrome.

Therapy of Limited Use in SLE

Plasma Exchange

In late 1970 and early 1980 there was great enthusiasm about plasma exchange being used in subsets of renal lupus. However the limitations include "rebound" phenomenon within few weeks, technical difficulties of requiring central venous access with associated complications and patient discomfort with higher cost. Even combination therapy with cyclophosphamide does not offer additional benefit over pulse cyclophosphamide alone.²¹

Role of diet

There is no specific role of any diet in the management of SLE. But a small study in humans has shown beneficial effect of fish oil supplementation over a six month period.²² High saturated fat diet is detrimental for premature coronary atherosclerosis seen in later stage of SLE.

Intravenous high dose gammaglobulins

This therapy has an established role in lupus patients with severe thrombocytopenia or immune neutropenia;²³ splenectomy is advised when there is failure of response to I.V. gammaglobulin.

Cyclosporine therapy

The cyclosporine in low doses of 2.5 - 3 mg/Kg/day may offer reasonable disease control and have steroid-sparing effects.²⁴

Table 4: Potential Novel Therapies for Management of SLE

- Immunosuppressant
 - Leffunomide
 - Tacrolimus
- Blockage of costimulatory pathways
 - Anti-CD₄₀L m Ab
 - CTLA4-1g
- Anticomplement therapy
 - Anti C₃b
- Anticytokine therapy
 - Anti BLYS mAb, Anti IL-10 mAb
- T and B cell tolerance
 - LJP 394
 - Peptide specific vaccination
- Immunoablation
 - High dose immunoablation ±
 - Stem cell transplantation
- Hormonal therapy
 - Dihydroepiandrosterone (DHEA)

However, side effects like hypertrichosis and nephrotoxicity pose practical problems.

Potential Novel Therapies

Rapid developments in biotechnology over the past decade have given the opportunity to develop a greater understanding of immune dysregulation characterising lupus and develop targeted therapy at various levels (Table 4).²⁵

It is expected that novel therapies will have better efficacy and/or better side effect profiles for certain manifestation of lupus. In future these may be considered suitable alternative when standard drugs fail to control the disease.

CONCLUSION

The management of SLE with appropriate use of steroids and other immunosuppressives has improved the outcome over the period of last 20-30 years. The spectrum of illness varies from mild to aggressive disease and hence therapy has to be tailor-made. However appreciation of disease activity and damage, risk-benefit ratio of drug therapy and meaningful patient counselling are keys to the success of management. Many novel targeted therapy are in the horizon which may give some additional benefit in future. The role of accelerated atherosclerosis is a new challenge to be sorted out.

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