INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a multisystem disorder of unknown etiology. Abnormalities of immune regulation leading to autoimmune response affecting various organ systems are the hallmark of the disease. Renal involvement is a common complication of SLE and carries significant morbidity and mortality. The renal manifestations are collectively termed as “Lupus Nephritis” (LN).

As per revised classification criteria of The American College of Rheumatology (1997) LN is defined as persistent proteinuria (>0.5 gm / day or >3+ qualitatively) or presence of casts (RBC, hemoglobin, granular tubular or mixed) in urine. Renal involvement usually occurs within first 2 yrs of the diagnosis of SLE and is uncommon after 5 yrs of the onset.

EPIDEMIOLOGY

SLE is predominantly a disease of women with women to men ratio being 8-13: 1. This ratio changes to 2:1 in patients above 45 years of age and in paediatric patients. LN is more common in children than in elderly and men are more likely to be having LN at the diagnosis of SLE. Asians, Hispanics and African Americans are at increased risk of LN than Caucasians with Asians having the greatest risk. As per various studies, women have better survival than men.

PATHOGENESIS

Pathogenesis of SLE is a complex process involving genetic predisposition, environmental & hormonal factors leading to formation of pathogenic autoantibodies and subsequently pathogenic immune complexes leading to persistent inflammation and damage to various organs. These preformed immune complexes and locally formed immune deposits are deposited in kidneys. Positively charged nucleosomes bind to fixed anionic sites in glomerular capillary wall and these autoantigens interact with circulating autoantibodies leading to in situ formation of immune complexes. Monocyte and neutrophil recruitment takes place and monocyte chemoattractant protein type 1 (MCP-1), Interleukin 1 (IL-1), IL-2 receptors, IL-6, interferons (IFN-γ and α), TNF-γ and transforming growth factor (TGF-β) are upregulated resulting in chronic inflammation and chronic oxidative damage with clinical manifestations of the disease.

IMMUNOPATHOLOGY

Immune deposits of Ig G (most common), IgM, IgA, C1, C3 and properdin are deposited in glomeruli, interstitium, tubules and blood vessels with various degrees of severity. In 2003 International Society of Nephrology (ISN) and Renal Pathology Society (RPS) modified WHO classification based on glomerular affection on histopathology (Table I).

Activity and chronicity index by National Institute of Health modified by Austin et al 4 are useful in assessing activity, chronicity and prognosis of LN (Table II). These are scored from 0 to 3 depending on severity and total obtained to get activity and chronicity index. Higher the activity and chronicity index poorer is the outcome.

CLINICAL FEATURES

Renal disease can be asymptomatic especially in patients...
with class I and II and renal symptoms appear when patients are in nephritic stage or develop nephrotic syndrome. Clinical features generally correlate with disease activity and class of LN (Table III).

**DIAGNOSIS**

**Urinalysis**

It is the most important test for detection as well as monitoring of LN. An early morning, midstream, clean catch and non refrigerated specimen is analysed for evidence of proteinuria and active urinary sediments. The characteristic findings on urinalysis are shown in Table IV.

“Telescopic urine sediments” i.e. all types of cells and casts in urine are found in severe proliferative glomerular and tubular disease.

**Renal biopsy**

Information about WHO class, disease activity and prognosis can be obtained by this investigation. Atleast 10 glomeruli should be examined for conclusive results.

Indications of renal biopsy are
A. Nephritic urinary sediments
B. Glomerular hematuria with > 0.5 gm/ day proteinuria
C. Glomerular hematuria with < 0.5 gm/ day proteinuria with reduced C3 and
D. positive Anti-dsDNA
E. Proteinuria > 1 gm/day.

Repeat biopsy indications are
A. Unexplained worsening proteinuria
B. Unexplained worsening renal function (> 30% rise in sr. creatinine)
Table III. Clinical Features

<table>
<thead>
<tr>
<th>Class</th>
<th>Anti-dsDNA</th>
<th>Complement</th>
<th>Urinary Sediments</th>
<th>24 hrs. proteinuria</th>
<th>HT</th>
<th>Creatinine</th>
<th>GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Increased +/-</td>
<td>Reduced -</td>
<td>Inactive</td>
<td>&lt; 1 gm</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Class II</td>
<td>Increased +/-</td>
<td>Reduced -</td>
<td>Inactive</td>
<td>&lt; 1 gm</td>
<td>Infrequent</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Class III</td>
<td>Increased +</td>
<td>Reduced -</td>
<td>Common</td>
<td>&gt; 1 gm</td>
<td>+/-</td>
<td>+/-</td>
<td>N</td>
</tr>
<tr>
<td>Class IV</td>
<td>Increased ++</td>
<td>Reduced -</td>
<td>Active (RBC casts)</td>
<td>&gt; 1 gm</td>
<td>+</td>
<td>+</td>
<td>Reduced -</td>
</tr>
<tr>
<td>Class V</td>
<td>Increased</td>
<td>Reduced -</td>
<td>Active</td>
<td>Nephrotic syndrome</td>
<td>+</td>
<td>+</td>
<td>Reduced -</td>
</tr>
<tr>
<td>Class VI</td>
<td>Usually N</td>
<td>Usually N</td>
<td>Minimal</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>Reduced --</td>
</tr>
</tbody>
</table>

Table IV. Urinalysis in various disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory Glomerular and tubulo- interstitial disorder</td>
<td>Hematuria (Usually microscopic)</td>
</tr>
<tr>
<td>Proteinuric State</td>
<td>Granular and fatty casts</td>
</tr>
<tr>
<td>Nephritic State</td>
<td>RBC, WBC or mixed casts</td>
</tr>
<tr>
<td>Chronic Renal Failure</td>
<td>Broad and waxy casts</td>
</tr>
</tbody>
</table>

C. Persistent glomerular hematuria with > 2 gm/day proteinuria
D. Proteinuria > 3 gm/day
E. Nephritic or Nephrotic flare.

Serological tests

**Anti Nuclear Antibody (ANA)** is useful screening test with sensitivity > 90% in patients with SLE. No correlation between the titers and disease activity has been found.

**Anti-dsDNA Antibody** - These are more specific with SLE and high titers correlate with disease activity, IgG antibodies of high avidity in fixing complement correlate with renal involvement.

**Anti-Sm Antibodies** - Correlate with increased incidence of renal lupus and indicate worse prognosis.

C3 and C4 - Reduction in levels of C3 and C4 on serial monitoring predict flare.

ASSESSMENT OF DISEASE ACTIVITY

Treatment of LN depends upon the severity of disease and WHO class of LN. The assessment of disease activity is as shown in Table V.

Indicators of poor prognosis in LN:
1. Asian, African American race
2. Azotemia (sr. creat. > 2.4 mg/dl)
3. Anemia (hematocrit < 26%)
4. Antiphospholipid antibody syndrome
5. Diffuse proliferative disease
6. Poor response to initial immunosuppressive therapy.
7. Flares with worsening renal function.
8. High activity and chronicity index.
9. Lower education level and low socio economic status.

**TREATMENT OPTIONS FOR LN**

**Corticosteroids (CS)**
Used in induction as well as maintenance therapy in the treatment of LN. IV pulse Methyl prednisolone (MP) is instituted with pulse cyclophosphamide in severe proliferative cases. Oral prednisone in high dose of 1 mg/kg/day followed after 4 to 6 weeks by low dose of < 0.125 mg/kg/day is recommended to avoid corticosteroids toxicity. Adverse effects include hypertension, osteoporosis, dyslipidemia and hypercoagulable status and monitoring for the same should be done.

**Cyclophosphamide (CY)**
Multiple controlled randomized trials have shown effectiveness of pulse Cyclophosphamide therapy in the dose of 0.5 - 1 gm/m² IV diluted in 150 ml of saline infused over 30-60 minutes for 7 pulses followed by quarterly pulses till after 1 year of remission. Monitoring of WBC count, hydration, Inj. Mesna to be given as per NIH protocol for...
Table V. Assessment of disease activity

Proliferative disease

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderately Severe</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Class III without severe histological features</td>
<td>1. Mild disease with partial or no response after initial induction or delayed remission &gt; 12 months.</td>
<td>1. Moderately severe with no remission at 6 to 12 months therapy</td>
</tr>
<tr>
<td>2. Chronicity Index &lt; or = 3</td>
<td>2. Focal proliferative nephritis with adverse histological features or reproducible increase of at least 30% in creatinine</td>
<td>2. Proliferative disease with impaired renal function + fibrinoid necrosis or crescents in &gt; 25% glomeruli</td>
</tr>
<tr>
<td>4. Non nephritic range proteinuria</td>
<td></td>
<td>4. Proliferative nephritis with Cl &gt; 4 or Al &gt; 10 + Cl &gt;3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. RPGN with doubling of creatinine in 2-3 months</td>
</tr>
</tbody>
</table>

Membranous Disease

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non Nephrotic range proteinuria with normal renal function</td>
<td>Nephrotic range proteinuria with normal renal function</td>
<td>Nephrotic range proteinuria with impaired renal function</td>
</tr>
</tbody>
</table>

CY administration. Gonadal toxicity is associated with increasing age and number of pulses which can be reduce by Inj. Leucopride given S.C. 3.75mg 2 weeks prior to pulse.\(^\text{10}\)

Azathioprine (AZA)

Starting dose of 1mg/kg/day increased up to 2-3 mg/kg/day is recommended. Monitoring of sr. creatinine, liver functions with CBC is required. It can produce bone marrow aplasia in patients with deficiency of Thiopurine Methyl Transferase. It has corticosteroid sparing action and is safe in pregnancy.

Mycophenolate mofetil (MMF)

It is reversible inhibitor of inosine monophosphate dehydrogenase and inhibits B & T cell proliferation as well as antibody formation. The starting dose of 1gm/day increased up to 3 gm/day orally has been shown effective in induction as well as maintenance therapy. In study for patients with proliferative LN, short term therapy with IV Cyclophosphamide followed by maintenance therapy with MMF or AZA was found to be more efficacious and safer than long term quarterly pulse therapy with CY.\(^\text{11}\) Adverse effects include leucopenia, nausea, diarrhea and infections.

Rituximab

It is a chimeric murine human monoclonal antibody binding specifically to CD20 antigen. It was found to be effective in some patients with refractory LN in the dose of 375mg/m\(^2\) at 4 wkly infusion with prednisolone.\(^\text{12}\)

Cyclosporine A (CsA)

In low dose of < 5mg /kg/day this drug has been tried in some patients of LN. Evidence of nephrotoxicity should be monitored with RFT every 2 wkly initially followed by once a month. It has a steroid sparing effect.

TREATMENT RECOMMENDATIONS

Depending upon severity of disease and histology of renal biopsy following treatment is recommended.

Indicators of remission

1. Inactive urinary sediments in the absence of extrarenal disease
2. Normalization of complement levels for at least 6 months when patients are off immunosuppressive therapy except low dose CS.

Therapy to be continued for at least 1 year beyond remission

Treatment of renal flare

1. Mild to moderate nephritic flare-High dose CS if no remission treat as severe or CS +AZA/MMF
2. Severe nephritic - Monthly CY pulses plus MP or CS + AZA/MMF
Table VI. Treatment recommendations

<table>
<thead>
<tr>
<th>Histology/severity</th>
<th>Induction</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proliferative-mild</td>
<td>Prednisolone 0.5-1 mg/kg 4-6 weeks gradually taper +/- AZA if no response in 3 months consider treatment for moderately severe disease</td>
<td>Low dose CS &lt; 0.125mg/Kg/day +/- AZA further tapering at the end of each year of remission.</td>
</tr>
<tr>
<td>Moderately severe</td>
<td>MMF 2gm/day or AZA + high dose CS, if no remission 6-12 months pulse IV CY+/- pulse MP for 7 pulses + 0.5mg/Kg/per day CS for 4 weeks and then taper</td>
<td>If remission in 6-12 months taper MMF to 1.5 gm/day for 6-12 months then 1gm per day, further tapering at the end of each year in remission or quarterly pulses of CY or AZA 1-2mg /kg/day</td>
</tr>
<tr>
<td>Severe</td>
<td>Monthly pulses of CY+ MP for 6-12 months, if no response add Rituximab or switch to MMF.</td>
<td>Quarterly pulse of CY for at least one year after remission or AZA 1-2mg /KG/Day or MMF 1-2gm.day</td>
</tr>
<tr>
<td>Membranous- mild</td>
<td>High dose CS +/- AZA</td>
<td>Lose dose CS +/- AZA</td>
</tr>
<tr>
<td>Moderate/severe</td>
<td>By monthly pulse CY for 6 pulses or CsA+/- AZA or high dose CS +MMF</td>
<td>Low dose CS+/-AZA or AZA</td>
</tr>
<tr>
<td>Mesangial</td>
<td>Low dose CS</td>
<td>Low dose CS</td>
</tr>
</tbody>
</table>

Fig.1: Lupus nephritis flare

3. Nephrotic- < 3 gram proteinuria moderate dose CS > 3 gram proteinuria high dose CS. Or AZA/ CsA or CS+ AZA or bimonthly CY/ MMF

Dyslipidemia
It increases risk of atherosclerosis & cardiovascular mortality. Target LDL< 100mg/dl, TG< 150 mg/dl.

Pregnancy
Proteinuria increases due to hyperfiltration in pregnancy.
LN should be suspected in presence of active urinary sediments, increased creatinine & uric acid, reduced C3 with proteinuria. Corticosteroids are safe, add AZA if severe nephritis.

**ESRD**

In patients with rapidly deteriorating renal functions & nephritis pulse MP + CY 8 to 10 hrs before dialysis. Immunosuppressive therapy to be discontinued if creatinine > 5 mg/dl., inactive urinary sediments & renal biopsy suggestive of scarring & atrophy or contracted renal size.

**Renal transplantation**

Patients with active SLE with progressive renal failure are recommended to undergo dialysis for 3-12 months before transplant to achieve reduction in clinical & serological disease activity.\(^{13}\) Anticoagulation is mandatory in patients with APLA for better allograft maintenance and reduced chances of recurrence.\(^{14}\)

**NOVEL THERAPIES IN LN**

High dose immunoablative chemotherapy (high dose CY + MP + Antithymocyte globulin) with autologous haematopoietic stem cell transplant has been tried with marginal improvement in disease activity but 1/3rd patients relapsed.\(^{15}\) Biological response modifiers like anti CD 40 ligand antibodies, CTLA 4 Ig, (Abatacept), anti-TNF-\(\alpha\) chimeric monoclonal antibodies have been tried, but none are showing promising results. Belimumab in two phase III clinical trials have shown promising results in the treatment with SLE.\(^{16}\)

**REFERENCES**